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Prognostic Implications of Total Hemispheric Glucose Metabolism Ratio in Cerebro-Cerebellar Diaschisis

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Abstract

Purpose: Diaschisis denotes brain dysfunction remote from a focal brain lesion. We have quantified diaschisis and investigated its prognostic value in glioma.

Methods and material: We compared 50 18F-FDG-PET-CT studies collected prospectively from 14 patients with supratentorial glioma (5 men and 9 women aged 35-77 years) with 10 single scans from healthy controls aged 43-75 years. Dedicated 3D-segmentation software was used to obtain total hemispheric glucose metabolic ratios (THGr) by dividing total hemispheric 18F-fluorodeoxyglucose (FDG) uptake in each diaschitic hemisphere, i.e., the ipsilateral cerebral hemisphere (THGr(Ce)) and the contralateral cerebellar hemisphere (THGr(Cb)), to its respective contralateral side. Receiver operating characteristic (ROC) analysis was performed to determine optimal cut-offs for combinations of THGr(Ce) and THGr(Cb). Two independent observers obtained data for reproducibility analysis, and THGr values were compared with qualitative assessment of diaschisis performed by a PET neuroimaging specialist.

Results: Qualitative analysis confirmed cerebro-cerebellar diaschisis in all glioblastoma PET studies performed within one year of death. Healthy subjects had significantly higher THGr(Ce) values ($p=0.0007$) and THGr(Cb) values ($p=0.02$) than glioblastoma patients. ROC analysis yielded diaschisis thresholds of 0.62 for THGr(Ce) and 0.84 for THGr (Cb). Qualitative assessment demonstrated cerebral diaschisis in 16/17 (94%) of cases with THGr(Ce) below the determined threshold, and cerebellar diaschisis in 25/26 (96%) cases with THGr(Cb) below the determined threshold. When both THGr(Ce) and THGr(Cb) were below ROC threshold, the combined diaschisis measures had a positive predictive value (PPV) for survival above 1 year of 100%. When one parameter was below the threshold, it had a PPV of 75%, and when both parameters exceeded

thresholds, the negative predictive value (NPV) for survival below 1 year was 79%. Median inter-rater variability was 3.3% and 5.9% for THGr(ce) and THGr(Cb), respectively.

Conclusions: The THGr measures demonstrated diaschisis in cerebrum and the cerebellum of patients with glioma. Combined cerebro-cerebellar diaschisis ratios with ROC thresholds for both forebrain and hindbrain had high negative and positive predictive values for survival for less than a year. The THGr method allows comparison of data obtained at different institutions, and is now open for further validation in gliomas and other cerebral diseases.

Keywords: Diaschisis, brain, cerebellum, glioma, quantification, FDG-PET/CT.

Introduction

Diaschisis is an oft-forgotten neurological phenomenon. Introduced in 1914 by von Monakow, the term diaschisis denotes a loss or change of function in regions of the brain remote from the underlying structural (often discrete) lesion due to neuronal connectivity (*1*). With the trillions of connections in the human brain(*2*), diaschisis is a complex entity that is largely unexplored, and conventional structural imaging with computer tomography (CT) and magnetic resonance imaging are inadequate. In a recent review, Carrera et al. suggested four sub-classifications of diaschisis(*3*), that may be more appropriate for mechanistic imaging. Positron emission tomography/computed tomography (PET/CT) with 18F-fluoro-deoxyglucose (FDG) has shown promising results of visual image assessment of diaschisis(*4-9*). Gliomas infiltrate brain parenchyma and destroy healthy brain tissue, which lesions in turn damages other elements of the connectome as manifested by diaschisis. Here, we test a novel method for detection and quantification of diaschisis with 18F-FDG images from PET/CT in patients with gliomas, and we assessed the prognostic value of the presence of diaschisis.

Material and methods

18F FDG images of the brain were obtained with PET/CT in 14 patients (5 men, 9 women; mean age 63 years, range 35-77) who were admitted to the Department of Neurosurgery, Odense University Hospital, with suspicion of cerebral malignancy. Diagnosis based on biopsy and magnetic resonance imaging showed that two patients had diffuse astrocytoma and 12 had glioblastoma. The patients were followed throughout their treatment course for one year, or until death. The FDG images were acquired prospectively at up to six time-points: 1) before treatment 2) after resection or

biopsy, 3) after radiotherapy and/or chemotherapy or no treatment, and 4-6) during chemotherapy or no treatment. Prednisolone was used during the entire treatment course of the glioma patients. Baseline demographic and clinical characteristics of the study population are detailed in Supplementary Table 1. For radiotherapy, either 34Gy/ 10 fractions or 59.4/33 fractions were used. Temozolomide was the standard chemotherapy. The baseline scan was performed a mean of 9 days (range 3-13) after the baseline magnetic resonance images. Follow-up scans were obtained 35 days (range 13-133), 121 days (range: 56 – 263), 339 days (range: 278 –396), and 466 days (range 368 – 536) after the diagnostic magnetic resonance imaging. Tumor volumes were obtained based on volume segmentation of Gadolinium-enhanced T1-weighted images using 3D Slicer Software, Version 4.5 (http://www.slicer.org), an open-source segmentation software program(*10*).

The control group consisted of 10 healthy volunteers (5 men, 5 women; mean age 62.5 years, range 43-75) without neurological disease, severe brain trauma, addiction, or cognitive deficits. These control subjects had a single PET/CT session with the same acquisition protocol as for the patients. All participants gave informed written consent to participate in the study, which was approved by the regional research ethics committee .

PET/CT data acquisition

Participants fasted for six hours before undergoing the imaging. They rested supine on the tomograph bed in a darkened and quiet room, with heads immobilized in a dedicated headrest. Participants rested for 10 minutes before the tracer was injected at a dose of 200 MBq 18F-FDG for patients and 4 MBq/kg body weight for control subjects. The images were obtained with the

Generel Electrics Company Discovery 690 PET/CT device with a dynamic acquisition protocol of 60 one-minute frames. Each frame had 47 slices (3.3 mm) and a display field of view of 250x250 mm (matrix 256x256 pixels). A CT-derived attenuation map was applied, and the data were iteratively reconstructed using time-of-flight ordered subset expectation maximizations. The data from 45-60 minutes were summed and used for analysis. Images were quantified as standardized uptake values (SUV), calculated as radioactivity concentration per gram of tissue in predefined volumes of interest relative to injected dose per kg body weight.

PET image analysis

Segmentation

We placed 3D masks around the cerebral and cerebellar hemispheres, both ipsilateral and contralateral to the tumour, using the dedicated software ROVER (ABX, Radeberg, Germany) to segment the volumes of interest. We performed manual correction when a mask clearly included elements outside the brain parenchyma, e.g. parts of the skull or the optic nerve.

We first tested three different cut-off thresholds for the detection of diaschisis: i) a "top-down" procedure with a threshold of either 2 SUVs (2T) or 3 SUVs (3T) below the maximum SUV of the cerebellum or cerebrum, respectively (thus representing the brain parenchyma and neurons with the highest level of FDG accumulation, i.e., the index of functionality), ii) a 40% iterative thresholding algorithm, with either local or global voxel analysis, and iii) a "bottom-up" procedure with a threshold of 0.5 SUV, 2.0 SUV, 3.5 SUV, 4 SUV, or 50% below the maximum SUV. We compared the three methods with respect to THGr and visual assessment of diaschisis, and also tested the level of statistical significance using Kruskal-Wallis equality-of-populations rank test. The "top-down" 3T and 2T approach was found to be most appropriate for quantifying diaschisis in the cerebrum and cerebellum, and included ROVER's built-in partial volume correction feature(*11*).

Individual baseline masks were reused on follow-up PET-scans with the software's fixed co-registration procedure. This co-registration procedure was compared against individual placement of the masks.

Inter-hemispheric glucose metabolism

Image quantification with volumetric (3D) segmentation of malignant tissue is referred to as "total lesion glycolysis"(*12*), as first introduced by Larson et al.(*13*). However, gliomas are known to infiltrate healthy brain tissue and potentially induce regional diaschisis, and we previously observed depressed glucose metabolism in the entire ipsilateral cerebral hemisphere and contralateral cerebellar hemisphere in glioma patients. We thus included non-malignant tissue in the volume of interest and delineated the entire cerebral hemisphere. We refer to the 18F-FDG accumulation in the segmented volumes of interest as "total hemispheric glucose metabolism rate" indices (THG), that are the products of the segmented metabolic volume and the mean SUV in the volume. THG is thus a metabolically segmented parameter, including both malignant and non-malignant tissue, and both white and grey matter.

The hemispheres of likely diaschisis, i.e., the ipsilateral cerebral hemisphere of the supra-tentorial tumour and the contralateral cerebellar hemisphere, were normalized to the respective contralateral hemispheres, providing THG ratio indices (THGr) for cerebrum, THGr(Ce), and cerebellum, THGr(Cb). For assessment of cerebro-cerebellar diaschisis, we constructed a combined THGr index, with cut-off points provided from the area under the curve (AUC) of the ROC analyses of THGr(Ce) and THGr(Cb).

Visual analysis of PET images

The PET images were visually assessed by a nuclear medicine physician experienced in neuroimaging (PG) and blinded to the clinical outcome and the result of the quantitative analysis. Each FDG image was assessed using the following scale. Cerebrum: 0 = normal (symmetric), 1 = probably normal, 2 = unsure, 3 = probably diaschisis (hypometabolism in two lobes in the same hemisphere), 4 = diaschisis (hypometabolism in three lobes), 5 = severe diaschisis (hypometabolism in four lobes). Cerebellum: 0 = normal (symmetric), 1 = probably normal, 2 = unsure, 3 = probably diaschisis, 4 = diaschisis.

Statistical analysis

Survival time was calculated from the day of surgery. The Kruskal-Wallis test was used to identify statistically significant differences of THGr(Ce) and THGr(Cb) between the participant groups. ROC analysis was used to investigate THGr as possible predictor of survival less than one year. AUC of ROC was estimated and the optimal threshold for maximizing classification was found by using the point on the ROC curve closest to the (0,1) corner of the ROC graph(*14*). The optimized ROC thresholds for both cerebrum and cerebellum were applied in a 4x4 table, and the value from each set of PET images was plotted below or above the corresponding threshold. The inter-observer variability of two readers for the quantitative analysis was investigated using the coefficient of variation, i.e. the standard deviation divided by the average of values obtained by the three observers. STATA/IC 13.1 (StataCorp, College Station, Texas 77845 USA) was used for all statistical analyses.

Results

In total, 50 18F-FDG image sets were collected prospectively from the 14 patients. Two patients with low-grade glioma (diffuse astrocytoma) were alive at 3 years, whereas median survival for the 12 patients with glioblastoma was 9 months. Baseline clinical characteristics of the glioma cohort are provided in Supplemental Table 1. Calculation of cerebro-cerebellar diaschisis as THGr was straightforward. Figure 1 shows cerebro-cerebellar diaschisis associated with a glioblastoma, i.e., diaschises in the ipsilateral cerebral hemisphere (THGr <0.62) and the contralateral cerebellar hemisphere (THGr <0.84).

Cerebral diaschisis

Supplemental Table 2 shows the THGr values and results of qualitative diaschisis assessment in the cerebrumfor each patient over time. Figure 2 displays an example of cerebral diaschisis and segmentation with THG. Analysis of the 50 18F-FDG images from the glioma patients revealed median cerebral THGr of 0.62 (range 0.23-4.05) for patients who survived less than one year, 0.71 (0.52-1.73) for patients who survived 1-3 years, and 0.88 (range 0.20-1.06) for patients who survived for more than three years (Figure 3). In comparison, healthy volunteers had a median cerebral THGr of 0.98 (range 0.79-1.54), which statistically was significantly higher than that of all three patient survival groups (p=0.0007).

Glioblastoma patients who survived for more than one year had a median cerebral THGr of 0.93 (range 0.53-1.06) compared to the median of 0.62 (range 0.23-4.05) for patients with survival until one year (p=0.046). The AUC of the ROC was 0.70, and the optimal threshold of THGr(Ce) for predicting survival for more than one year was 0.618.

Cerebral THGr estimates were unusually high for two patients. For the patient with invasive and multifocal hypermetabolism of the entire ipsilateral hemisphere, THGr was estimated at 4.05 post-resection biopsy. For the patient with (visually confirmed) recurrence who died shortly after the scan, THGr was estimated at THGr was estimated at 1.73.

Cerebellar diaschisis

Supplemental Table 3 shows the THGr values and results of qualitative diaschisis assessment in the cerebellum of each patient over time. Supplementary Figure 1 depicts an example of cerebellar diaschisis and segmentation with THG. Analysis of the 50 FDG images from the glioma patients revealed median cerebellar THGr of 0.74 (range 0.16-1.08) for patients who survived for less than one year, 0.88 (range 0.52-1.01) for patients who survived for 1-3 years, and 1.01 (range 0.50-1.18) for patients who survived for more than 3 years (Figure 3). Healthy volunteers had median cerebellar THGr of 0.96 (range 0.79-1.26), which was significantly higher than those of all three patient survival groups ($p=0.02$).

Glioblastoma patients who survived for more than one year had a median cerebellar THGr of 0.93 (range 0.42-1.08) compared to a median of 0.78 (range 0.16-1.01) for patients with survival below one year. The AUC of the ROC was 0.77 and the optimal threshold of THGr(Cb) for predicting survival for more than one year was 0.836.

Cerebellar diaschisis typically involved the cerebellar hemisphere contralateral to the tumour. However, one patient (ID 7) had consecutive cerebellar diaschisis ipsilateral to the glioblastoma, which was located in the occipital lobe above the cerebellar tentorium. As we wanted to calculate the impact of diaschisis using the diaschitic hemisphere as reference point, we switched the cerebellar hemisphere of indexation for this patient.

Comparison of THGr quantification and qualitative assessment

On visual examination, we detected cerebral diaschisis in 78% (39/50) of patient scans, and cerebellar diaschisis in 68% (34/50) (Table 1 and 2). Cerebro-cerebellar diaschisis was seen in all of the 32 PET scans of glioblastomas perfomed less than one year before death and in 42% (5/12) of the 18F-FDG-PET scans performed more than one year before death (including low-grade gliomas). Cerebral diaschisis was seen in 94% (16/17) of cases where cerebral THGr was low (i.e. less than 0.61), and cerebellar diaschisis was seen in 96% (25/26) of cases where cerebellar THGr was low (i.e. less than 0.84).

Prediction by combining THGr for forebrain and hindbrian

For initial differentiation between "glioma brain" and "healthy brain", ROC analysis revealed optimal thresholds of THGr(Ce) at 0.91 and THGr (Cb) at 0.79. THGr estimates below these thresholds in both cerebrum and cerebellum gave 100% sensitivity and 41% specificity of differentiating a patient with glioma from a healthy volunteer.

For prognosis of survival for more than one year after the 18F-FDG-PET scan, in glioblastoma patients, the AUC of ROC revealed thresholds of THGr(Ce) at 0.62 and THGr(Cb) at 0.84. When neither THGr(Ce) and THGr(Cb) value reached the threshold, the combined diaschisis measures had 100% positive predictive value. When only one value failed to reach the threshold, the measure had 75% positive predictive value, and when both test values exceeded the thresholds, the measures had 79% negative predictive value for survival below or above one year for the glioblastoma patients. A positive combined diaschisis test provided 88% sensitivity and 73% specificity for

survival below or above one year after the PET imaging. Table 1 list the results of the AUC of ROC thresholds used in the "combined diaschisis" test.

Inter-observer variability and co-registration follow-up images

The median coefficient of variation for estimates by two independent observers were 3.3% for THGr(Ce) (interquartile range 1.9%-4.2%) and 5.9% for THGR(Cb) (Interquartile range 3.3%-14%) (Supplemental Figure 2). We found the automated reuse of the baseline 3D masks to the patients to be a robust and practical method for segmentation. Taking all time-points together, the mean differences (with 95% confidence intervals) between automated reuse and individual placement of the masks were 0.01 (-0.10 to 0.13) for SUVmax, 0.012 (-0.06 to 0.08) for SUVmean, 0.03 (-0.12 to 0.2) for metabolic volume, 5.77 (-24.7 to 36.3) for THG, -0.19 (-4.2 to 3.8) for cSUVmean, and 12.25 (-30.2 to 54.7) for cTHG. None of these differences were statistically significant ($p>0.05$) (Supplemental Table 4). We also compared reuse of baseline masks stratified to any specific treatment intervention, i.e., post-operation or post chemotherapy; no statistical significant difference was found either (p-value range 0.055-0.96). Automated reuse of the 3D masks allowed excellent delineation of the cerebral and cerebellar structures for visual assessment.

Discussion

The study results showed that estimation of total hemispheric glucose metabolic ratio (THGr) was straightforward and meaningfully could quantify diaschisis in the cerebrum and cerebellum of patients with glioma. Quantitative and visual detection of diaschisis was associated with shorter

survival. THGr estimates had low inter-observer variability despite differences of patient treatments with neurosurgery, radiotherapy, and chemotherapy.

Diaschisis in patients with glioblastoma

Mean age (63 years) and median survival (9 months) for the glioblastoma patients, were similar to those reported in the literature (63.7 years and 9.9 months)(*15*). Glioblastoma patients who survived less than one year had low THGr in most of their cerebral and cerebellar images. Glioblastoma patients surviving for more than one year had a few images with THGr below ROC threshold, but not at the same time in both in cerebrum and cerebellum. The presence of cerebro-cerebellar diaschisis detected with the combined diaschisis test thus had 100% positive predictive value of survival for less than one year. Our findings suggest that an unusually high THGr value may also indicate severe disease (e.g. widespread invasive disease and very short survival), but this is based on only two patients with high values. Note that both these patients either had a biopsy performed (Pt 6) or a partial removal (Pt4); the neurosurgical intervention might be interesting to elaborate further with THGr in patients with glioma and the correlation to diaschisis.

Low-grade gliomas

The two patients with low-grade glioma did not display any significant cerebro-cerebellar diaschisis during the follow-up. Although one-third of the nine images had low cerebral THGr, the cerebro-cerebellar pathways probably were not significantly affected by the neoplasms, as the cerebellar THGr values exceeded the ROC thresholds. The patient with the lowest cerebral THGr values had chronic hearing loss originating in the ipsilateral hemisphere after resection, as well as aggressive

Jackson epileptic seizures, and this was the only patient with low-grade glioma who experienced cancer recurrence. In the light of the THGr results presented for low grade gliomas, one hypothesis is that if a low grade glioma presents with a positive "combined diaschisis" test, this might indicate progression to glioblastoma/ progressive damage to the neuronal connections.

Strengths and weaknesses

This method of quantifying diaschisis improves the understanding of some poorly understood pathophysiological mechanisms in the brain, which may help to improve management strategies for patients with glioma.The study had a small sample size,was exploratory in nature, and time between scans and treatment was heterogeneous. Hence, confounding factors such as age, sex, and treatment intervention was not suitable for a multivariate analysis. However, we systematically and prospectively collected 50 FDG images during the course of treatment of patients for glioma that constitutes a unique material in the literature. The longitudinal study design enabled us to investigate the presence of diaschisis at three to six time-points during a time period of between three months and more than a year, of which validated the reproducibility of the method across heterogeneous treatment interventions. The combined estimation of THGr values in the ipsilateral cerebrum and the contralateral cerebellum provided a way of quantifying cerebro-cerebellar diaschisis that would allow comparison of results between institutions, with less interference from misinterpretation of SUV, and differences in tracer dose, device brand, and acquisition times(*16*).

The method presented here may be relevant also for other brain diseases. FDG imaging has suggested the presence of diaschisis in multiple sclerosis(*17*), Lyme's disease(*18*), thalamocortical lesions(*5*), traumatic diffuse brain injury(*19*), and dementia(*20*). Baron and colleagues found that a cerebral hemispheric ratio below 0.85 in thalamocortical lesions consistently was associated with

cognitive impairment(*5*). Psychological disorders can also display decreased regional or global glucose metabolism, wich can be speculated to also be caused by diaschisis, e.g. chronic fatigue syndrome(*21*), post-traumatic stress disorder(*22*), major depressive disorder(*23*), and chronic depression syndromes(*24*).

Moreover, diaschisis has been suggested to represent a reversible neurological phenomenon by Sobesky and colleagues(*25*). They found that "reversal" of diaschisis along the treatment trajectory was associated to better clinical outcome in stroke patients. In this respect, the THGr method presented might be a means of monitoring quantitatively treatment effects in stroke patients or other brain diseases with diaschisis."

In the glioma material, a 3T and 2T "top-down" cut-off provided the best prognostic information by revealing the extent of diaschisis. However, other brain diseases may require different algorithms, and the specific cut-off points require validation by comparison with a suitable reference. Glioblastomas normally are recognized by their hypermetabolism(*26*). However, we observed that some or all of the ipsilateral hemisphere of glioblastoma patients had lower glucose metabolism than the contralateral hemisphere. This observation is sensitive to the potential effects of oedema surrounding the tumour, which may create a false impression of hypometabolism as demonstrated by Alavi and colleagues(*27*). Future studies of diaschisis in gliomas will need to take this into account by supplementing with information obtained by CT or preferably MRI.

Conclusions

The THGr measures demonstrated cerebral and cerebellar diaschisis in patients with glioma. ROC analysis demonstrated cerebro-cerebellar diaschisis ratios to have significant PPV for survival above one year, and NPV for survival below one year. The THGr method allows comparison of data

obtained at different institutions, and is now open for further validation in gliomas and other cerebral diseases.

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Competing financial interests

The authors declare that they have no competing financial interests.

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Fig. 1 Detection of cerebro-cerebellar diaschisis with fluorodeoxyglucose positron emission tomography (FDG-PET).

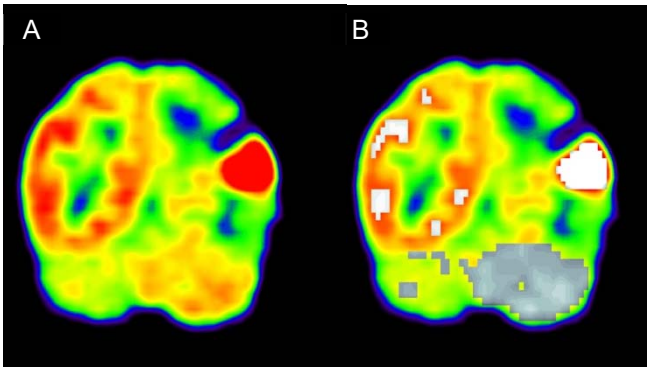


Figure 1 Coronal view of (**a**) the FDG-PET scan, and (**b**) quantification of the glucose metabolic rate. Widespread diaschisis is seen in the ipsilateral cerebral hemisphere and the contralateral cerebellar hemisphere, to the supratentorial glioblastoma. The cerebro-cerebellar diaschisis was confirmed by a lower total hemispheric glucose metabolic ratio (THGr) in the cerebrum (<0.61) and the cerebellum (<0.84). Tumour had recurred after resection, and the patient died 30 days after the scan was performed.

Fig. 2 Quantification of diaschisis in the cerebrum of a patient with glioblastoma.

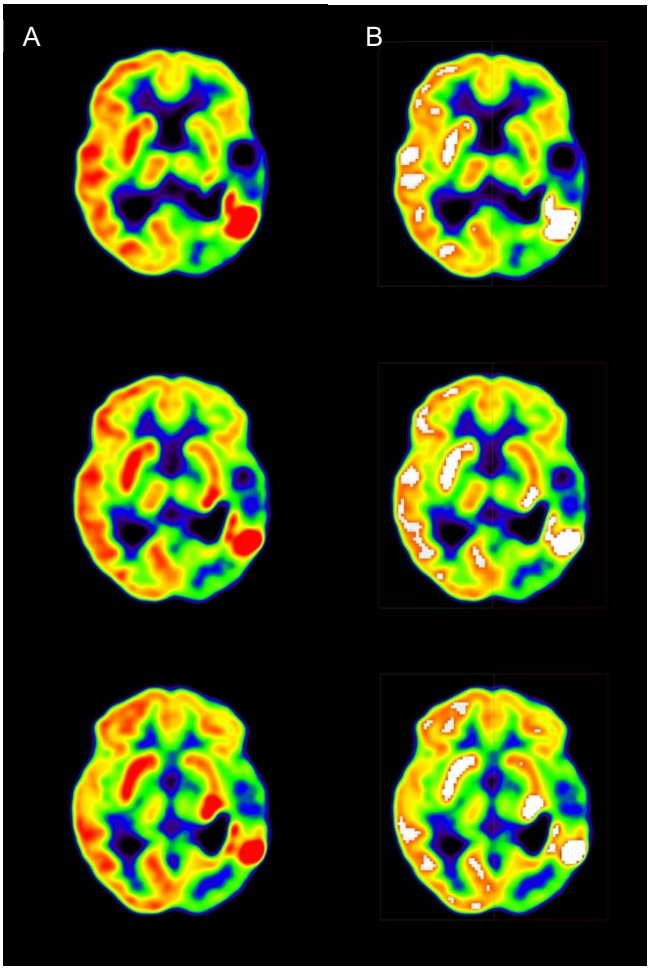
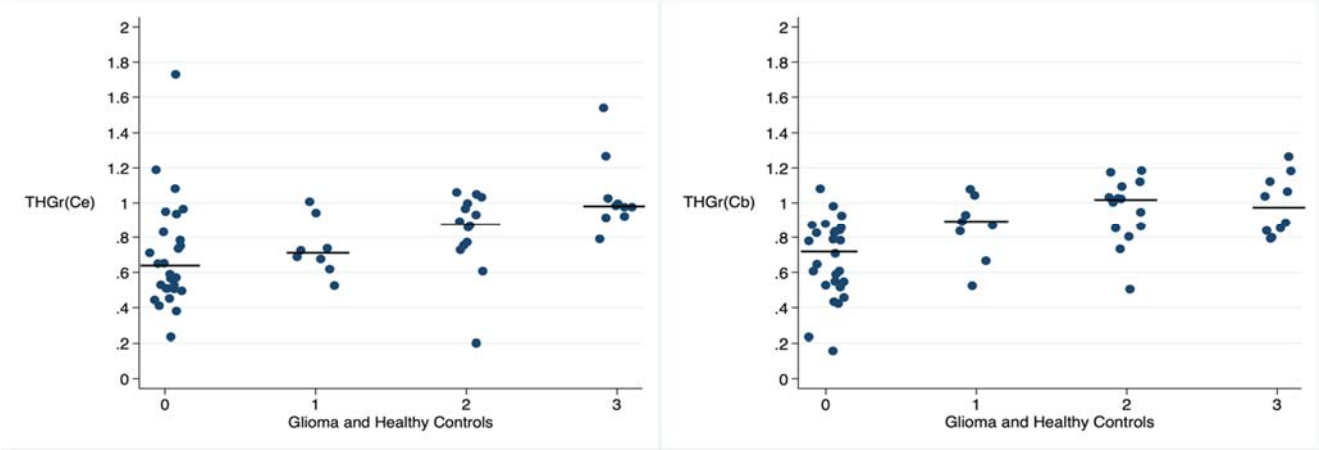


Figure 2 FDG-PET scan and three consecutive trans-axial images. The glioblastoma was located 4 slices (13.2 mm) above. (a) Diaschisis seen in the ipsilateral frontal lobe, reaching back to the occipital lobe and likely also the basalganglia and thalamus. Total hemispheric glucose metabolism ratio (THGr) in the diaschitic cerebral hemisphere was 0.38 (b), which was significant lower than in healthy controls.

Figure 3 Scatter plot of total hemispheric glucose metabolism ratio (THGr) in cerebrum (Ce, left) and cerebellum (Cb, right) in 14 glioma patients and 10 controls.



0= Patients surviving <1 year (8 glioblastomas), 1= Patients surviving 1-3 years (3 glioblastomas), 2= Patients surviving >3 years (1 glioblastoma, 2 low-grade gliomas), 3= Healthy controls. Grey bars display median values.

Table 1. Indexation of "Combined diaschisis" : Total hemispheric glucose metabolism ratio (THGr) for glioblastoma patients in both cerebrum and cerebellum and the prognostic implications.

Test Interpretation		Test* Cerebrum	Test* Cerebellum	Short survival (<1y) †	Longer survival (>1y)	Total	Prognostic implication
Negative	Both tests exceeded threshold	+	+	3	11	14	Negative predictive value 79%
Positive	One test below threshold	-	+	3	1	4	Positive predictive value 75%
		+	-	9	3	12	
	Both tests below threshold	-	-	11	0	11	Positive predictive value 100%
Total				26	15	41	
Prognostic implication				Sensitivity 88%	Specificity 73%		

* The cut-off points for THGr in cerebrum and cerebellum, was provided from AUC-ROC analysis, respectively dichotomization for cerebral THGr; + = > 0.62 and – = < 0.62 . Dichotomization for cerebellar THGr; + = >0.84 and - = < 0.84 † PET- scan performed less than or more than 12 months before death.‡ Healthy individuals (n=10) had n=8 FDG-PET scans in the Negative Test (-/-) and two in the likely positive test (+/-)

Table 1. Cerebro-cerebellar diaschisis was assessed by a combined THGr index using cut-off points derived from the area under the curves (AUC) of Receiver Operating Characteristic (ROC) analysis of THGr(Ce) and THGr(Cb). In patients with glioblastoma, low THGr in both regions (Ce<0.62 and Cb<0.84) had 100% positive predictive value for glioblastoma survival <1 year after the FDG-PET scan. If both THGr(Ce) and THGr(Cb) were above the thresholds, the negative predicitive value was 78.6% for survival with glioblastoma of more than one year.

Supplemental Table 1. Baseline clinical characteristics of the glioma cohort.

Patient	Survival	Sex	Age	Diagnosis	Tumor location*	Tumor Size†	Growth pattern‡	METH	IDHI	Resection
1	>3y	F	35	LGG	I	37	H	/	/	Partial
2	>3y	F	38	LGG	P	35	H	/	+	Full
3	>3y	F	58	HGG	O	56	N	+	–	Partial
4	23 mo.	F	69	HGG	P T	14	N	–	/	Partial
5	19 mo.	M	64	HGG	F	194	Inv.+N	–	–	Radical
6	12,5 mo.	F	69	HGG	P O	70	Inv.+N	–	–	Partial
7	11 mo.	F	77	HGG	T	34	Inv.+N	–	–	Radical
8	10 mo.	F	71	HGG	P O	60	Inv.+N	/	–	Radical
9	9.5 mo.	M	72	HGG	T	170	Inv.+N	+	–	Biopsy
10	7.5 mo.	F	73	HGG	P F	59	Inv.+N	+	–	Radical
11	6 mo.	M	66	HGG	O	92	Inv.+N	+	–	Partial
12	5 mo.	F	69	HGG	P	43	Inv.+N	–	–	Biopsy
13	3 mo.	M	60	HGG	T	62	Inv+N	–	–	Partial
14	3 mo.	M	61	HGG	T M	13	Inv.+N	–	–	Data unknown

y = year, mo. = months, LGG = low-grade glioma (diffuse astrocytoma, grade II glioma), HGG = high-grade glioma (glioblastoma, grade III+IV glioma), MGMT = Methylated, IDHI = isocitrat dehydrogenase

*Tumour location, I = insula, P = parietal lobe, O = occipital lobe, T = temporal lobe, F = frontal lobe

†Tumour volume in cc was determined using 3D Slicer 4.5, an open-source segmentation software platform (http://www.slicer.org). ‡ Growth pattern, H = hypometabolic, Inv. = invasive growth with only hotspots, N = hypometabolism representing necrosis in centre of tumour.

+ Present, - Not present, /Missing data

Supplemental Table 2.
Total hemispheric glucose metabolic ratio values and results of visual diaschisis assessment in the cerebrum for each patient with glioma

Survival	Patient ID	Pre-treatment		Post-operative		After radio- or chemotherapy, or no treatment		After chemotherapy or no treatment		After chemotherapy or no treatment		After chemotherapy or no treatment	
		THGr	Visual	THGr	Visual	THGr	Visual	THGr	Visual	THGr	Visual	THGr	Visual
>3y	1	0.87	/	0.73	++	0.86	++	0.60	+	0.20	/		
>3y	2	0.97	/	0.75	+	0.77	+	†		0.89	/		
>3y	3	1.00	+	1.06	-	0.93	+	1.00	+	1.05	/	0.83	+
23 mo.	4	0.74	++	0.68	+	0.73	/	0.52	+	1.73	+		
19 mo.	5	0.62	/	0.94	+	0.69	++	0.95	++	0.45	++		
12,5 mo.	6	1.00	-	1.19	-	0.94	-						
11 mo.	7	0.74	+	0.78	+	0.51	++						
10 mo.	8	0.57	+	0.53	+	0.51	+						
9.5 mo.	9	0.23	++	0.59	++	0.65	++						
7.5 mo.	10	0.50	++	0.65	++	0.38	++						
6 mo.	11	1.08	++	*4.05	++	0.97	++						
5 mo.	12	0.51	+	0.57	++	0.44	++						
3 mo.	13	0.53	++	0.41	++								
3 mo.	14	0.71	+	*0.75	++								

* Only biopsy was performed. † PET scan missing due to technical error in the session. Visual assessment of diaschisis: - = Normal (symmetric), / = Equivocal, + = Probably diaschisis (hypometabolism in 2-3 lobes in the same hemisphere), ++ = Confirmed diaschisis (hypometabolism in four lobes).

Table 1 shows a high prevalence of cerebral diaschisis in gliomas, especially in patients with shorter survival, and it was associated with low THGr (<0.62). Visual assessment of diaschisis was subjective, time-consuming, and challenging, whereas THGr estimation was straightforward

Supplemental Table 3.
Total hemispheric glucose metabolic ratio values and results of visual diaschisis assessment in the cerebellum for each patient with glioma

Survival	Patient ID	Pre-treatment		Postoperative		After radio- or chemotherapy, or no treatment		After chemotherapy or no treatment		After chemotherapy or no treatment		After chemotherapy or no treatment	
		THGr	Visual	THGr	Visual	THGr	Visual	THGr	Visual	THGr	Visual	THGr	Visual
>3y	1	1.18	-	0.73	++	0.80	++	0.86	++	0.85	-		
>3y	2	1.19	-	0.50	++	1.09	-	†		1.12	-		
>3y	3	1.02	-	1.03	-	1.00	-	1.03	-	0.95	-	1.08	-
23 mo.	4	0.87	+	1.04	-	0.84	-	1.08	+	0.55	++		
19 mo.	5	0.52	+	0.89	-	0.67	-	0.98	-	0.16	+		
12,5 mo.	6	0.93	+	0.42	+	0.23	+						
11 mo.	7	0.83	+	0.85	+	0.65	+						
10 mo.	8	0.87	+	0.88	+	0.84	+						
9.5 mo.	9	0.53	++	0.43	++	0.61	++						
7.5 mo.	10	0.78	++	0.52	++	0.71	++						
6 mo.	11	0.61	+	*0.55	++	0.46	++						
5 mo.	12	0.83	+	0.78	++	0.83	+						
3 mo.	13	0.59	++	0.83	++								
3 mo.	14	0.93	+	*0.79	+								

* Only biopsy. was performed .† PET scan missing due to technical error in the session. Visual assessment of diaschisis. - = Normal (symmetric), / = Equivocal, + = Probably diaschisis (hypometabolism in 2-3 lobes in the same hemisphere), ++ = Confirmed diaschisis (hypometabolism in four lobes).

Table 2. The table shows a high prevalence of diaschisis in in gliomas, especially in patients with shorter survival, and it was associated with low

THGr (<0.84)

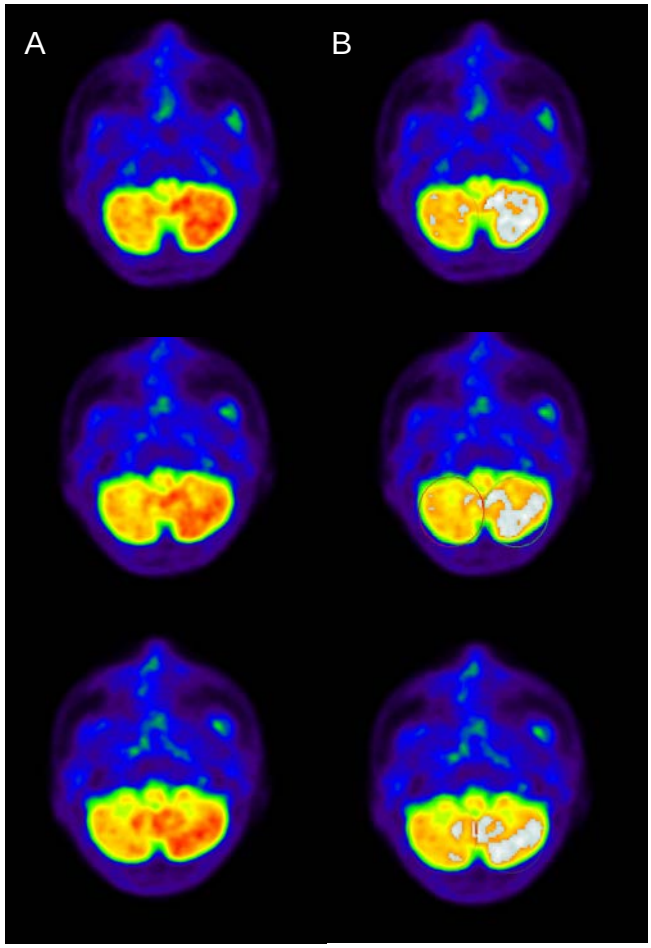
Supplemental Table 4. Variability due to reuse of the baseline mask in follow-up PET scans.

Parameter	Mean difference (95% CI)	P value
SUVmax	0.01 (-0.10 to 0.13)	0.80
SUVmean	0.012 (-0.06 to 0.08)	0.73
PVc SUVmean	0.03 (-0.12 to 0.2)	0.63
Metabolic volume	-0.19 (-4.2 to 3.8)	0.92
THG (Metabolic volume x SUVmean)	5.77 (-24.7 to 36.3)	0.71
THG PVc	12.25 (-30.2 to 54.7)	0.57

SUVmax = maximum standardized uptake value, SUVmean = mean standardized uptake value; PVc = partial volume corrected, THG = total hemispheric glucose metabolism rate.

Automated reuse of the baseline mask in follow-up PET scans can result in serious deviations in the outcome SUV variables. For validation of this automated procedure, 21 FDG-PET scans (chosen due to heterogeneity in patient movement between scans) were also segmented independently, i.e. the operator manually aligned the baseline mask to the follow-up PET scan. The Wilcoxon matched-pairs signed-ranks test was used to compare the two methods. Visual analysis was also performed for validation of the location of the interpolated masks. The results in the table show that the software could provide reliable automated reuse of cerebral hemispheric and whole cerebellar baseline masks. We also compared reuse of baseline masks stratified to any specific treatment intervention (i.e. postoperative or post-chemotherapy), but no statistically significant difference was found (p values ranged from 0.055 to 0.96). The large mask size and the relatively fixed anatomical shape of the target structures could explain these good results, which indicate that the automated reuse of cerebral hemispheric and cerebellar masks provided in the ROVER software is applicable for routine clinical use.

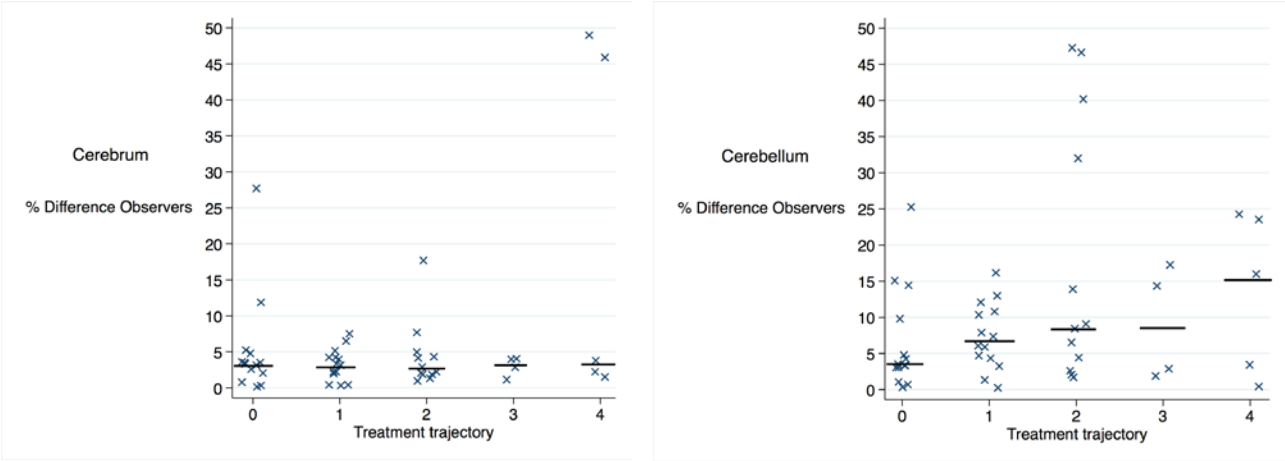
Supplemental Figure 1: Quantification of diaschisis in the cerebellum of a patient with glioblastoma.



ab

FDG-PET scan and three consecutive trans-axial images. (A) Diaschisis seen in the contralateral cerebellar hemisphere to the supratentorial tumour. (B) Total hemispheric glucose metabolic ratio (THGr) in cerebellum was 0.65, which was less than in healthy controls and patients surviving > 1 year.

Supplemental Figure 2. Inter-rater variability for total hemispheric glucose metabolism ratio (THGr) for cerebrum and cerebellum.



0= Before any treatment intervention, 1= After resection or biopsy, 2= After radio- or chemotherapy, 3= After chemotherapy, 4= During chemotherapy/No treatment.

Two independent observers independently used the THGr method in the glioma cohort. The scatter plot and median illustrate the coefficient of variation as percentage difference between two independent observers of THGr outcome in cerebrum and cerebellum . In total, 50 PET scans were independently analysed by two observers.