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A Combined Study with 18F-FDG and 11C-Methionine Dynamic PET for the Grading of Brain Gliomas.

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Abstract

Purpose: Conventional MRI based on contrast enhancement and T2/FLAIR is often not sufficient in differentiating grade II from grade III and grade III from grade IV diffuse gliomas. Here we assessed advanced metabolic imaging using two well characterized PET tracers, namely ^{18}F-FDG and ^{11}C-Methionine.

Methods: In this prospective study, 39 patients were enrolled with diffuse gliomas of grades II, III or IV underwent dynamic [^{18}F]-FDF-PET and [^{11}C]-Methionine. The first minutes were taken into account

Results: **T**he use of ^{11}C- Methionine provided significant differences between the different histologic subgroups with a higher number of parameters than did the use of ^{18} F-FDG. The most informative parameter is T/Np (T/N at the peak of the first maximum) with ^{11}C- Methionine.

Conclusion: The study of the first minute passage of ^{18}F-FDG and/or ^{11}C- Methionine through the tumor and healthy tissues in brain gliomas could not only allow improving the identification of the different glioma grades, but also to shorten the time spent by the patients under the camera. In case of using one tracer, methionine still would be the best choice. Otherwise, the use of ^{18}F-FDG and SUVp (SUV at the peak of the first maximum) would provide results likely comparable to methionine T/N index.

Introduction

The attempt to grading brain gliomas by positron emission tomography (PET) started by the early 1980s. Since that time, the most commonly used radiopharmaceuticals were ^{18}FDG (18F-fluorodeoxyglucose, a glucose analog), and ^{11}C-MET (L-methyl-L-methionine, an essential amino acid). The uptake of the former radiopharmaceutical is linked with the tissue demand for glucose [1]. The latter one has several metabolic pathways [2], but its uptake would be mainly related to membrane synthesis and cells growth and proliferation. Comparing the accuracy of both tracers for predicting the histological grade and aggressiveness of the different types of brain gliomas is still rather controversial [3], despite the great number of publications. Most publications relied upon data collected retrospectively. The standardized uptake value (SUV) for FDG, and T/N ratio (tumor to normal tissue ratio) for methionine, were considered as routine clinical quantification methods. The result of each PET investigation usually consisted in one value, measuring the final averaged uptake of the tracer in the region of interest (ROI), over a time period starting several minutes post injection. The aim of our study was to investigate the pharmacokinetics of the first minute of the radiopharmaceutical passing through both the tumor and the healthy tissue, and to compare the results with the histological relevant parameters for grading brain gliomas.

Materials And Methods

This prospective study included patients in whom an MRI examination (T1, T1 with contrast enhancement, T2, and T2-FLAIR) led to suspect the presence of a malignant neoplasm in the brain, before any treatment. Later, the diagnosis was confirmed by stereotaxic biopsy or tumor tissue obtained during open surgery. A total of 39 patients were recruited (20 men, 19 women, age 49 ± 13 years). The study was approved by the institutional review board. All patients provided written informed consent and had agreed on the use of their (anonymized) data for scientific purposes The histological characterization and grading of the tumors are following: glioblastoma n = 14, anaplastic oligodendroglioma n = 5, anaplastic astrocytoma n = 8, oligodendroglioma n = 5, diffuse astrocytoma n = 7. After MRI, each patient underwent two PET examinations (Siemens Truepoint, Siemens Medical Solutions. Knoxville, USA), with ^{18}F-FDG and ^{11}C-MET, lasting 40 and 20 minutes, respectively. Data acquisition started simultaneously with the intravenous administration of the radiotracer. 34 frames were reconstructed for ^{18}F-FDG and 26 frames for ^{11}C-methionine, with a similar duration of 6 * 10 sec, 6 * 20 sec, 6 * 30 sec, 4 * 60 sec and then 12 * 150 sec for ^{18} F-FDG, and 4 * 150 sec for ^{11}C-MET. The OSEM 3D algorithm, with 5 iterations and 8 subsets was used for image reconstruction. No arterial blood sampling was performed.

The images were processed using PMOD software (PMOD v.4.0, Zurich, Switzerland). Dynamic PET series were co-registered with a reference T1 contrast enhanced MR- image. Motion artifacts were compensated. The tumor (T) volume of interest (VOI) was selected on averaged PET images. It included 1 cubic cm of the tissue with the highest tracer uptake. VOI had an arbitrary shape, excluding any internal cavity. The reference (N) volume of interest, a sphere with a diameter of 16 mm, was placed in the healthy part of the brain in the hemisphere contralateral to the tumor, in the frontal cortex if possible. Generated time activity curves (TAC) provided the following parameters: SUV (standardized uptake value) and T/N ratio. Additional parameters have been introduced, which characterize the early tracer uptake and its passage through the tumor during the first minute (see Fig. 1): **T/Nb** (b for bolus) - peak of the first pass (**PFP**) – is the ratio at the moment while tracer is entering the brain, 23 ± 7 sec after the tracer injection for ^{18}F-FDG, and 24 ± 7 sec for ^{11}C-MET (corresponding to point 1, Fig. 1). **T/Np** - peak of the first maximum (**PFM**), is the ratio at the moment of local maximum accumulation, that occurs within the first minute, 38 ± 18 sec for ^{18}F-FDG and 37 ± 24 sec for ^{11}C-methionine (point 2, Fig. 1). **SUVp** is the standardized uptake value in the tumor at the PFM, **P/(T/N)** is the ratio of the T/N at the first maximum divided by the ratio at the end of the acquisition, **grad** is the slope of the ^{18}F-FDG T/N curve (min^{-1}).

Comparisons between patient groups were performed using Student's t test and Statistica software (Statsoft,f USA).

Results

The observed uptake patterns within the outlined tumor VOI (Fig. 2) shows obvious differences between methionine and glucose. Note that the final uptake of ^{18}F-FDG in the tumor does not differ from the uptake in the intact tissue, whereas within the first minute the tumor is clearly identified. T/Np is 1.6-2 times higher than the final T/N for FDG. For methionine this is not the case as P/(T/N) is 0.8-1.0 for tumors of any degree of malignancy.

The quantitative values of the parameters and statistical differences between the groups of patients with tumors of various histological types are presented in Tables 1 and 2. All histological diagnoses show a specific pattern, in particular, oligo tumors have higher values for all parameters with both tracers[4], and therefore malignancy groups (II, III and IV) which combine several tumor subtypes do not look optimal. However, for the sake of consistency and for comparison with the results of earlier publications, such results are also presented. These results should be treated with caution as the values of the parameters may vary depending on the proportions of histological types within each group.

Table 1

Values (with standard deviations) of parameters calculated from PET time activity curves. GB - glioblastoma, AOD - anaplastic oligodendroglioma, AA - ana astrocytoma, OD - oligodendroglioma, DA - diffuse astrocytoma. II, III, IV – grades of malignancy. SUVt - standardized uptake value averaged over the last 20 r scanning with ^{18}F-FDG (10 minutes for ^{11}C-MET), SUVp – tumor SUV at the peak of the first maximum (PFM), T/N, T/Nb, T/Np - final uptake index, T/N at the first pass and at the peak of the first maximum respectively, P/(T/N) is the ratio of T/N in the PFM to the final T/N, grad (for FDG) is the increase in T/N per

	FDG							MET				
Diagnosis	SUVt	T/N	T/Nb	T/Np	SUVp	P/(T/N)	grad	SUVt	T/N	T/Nb	T/Np	SUVp
GB	6.6(3.8)	1.1(0.5)	2.1(1.0)	1.9(1.0)	3.2(1.2)	2.0(1.3)	0.0016(0.009)	4.0(1.5)	3.6(0.9)	2.5(1.1)	3.1(0.8)	3.7(1.3)
III	4.3(1.1)	0.7(0.2)	1.3(0.7)	1.2(0.2)	2.5(0.9)	1.9(0.5)	-0.0050(0.0048)	3.1(1.5)	2.1(0.8)	1.4(0.4)	1.7(0.6)	2.5(1.0)
AOD	4.7(1.2)	0.6(0.06)	1.2(0.2)	1.2(0.2)	3.0(1.0)	2.1(0.3)	-0.0051(0.0017)	4.3(1.5)	2.8(0.8)	1.4(0.3)	2.2(0.3)	3.2(1.1)
AA	4.1(1.0)	0.7(0.3)	1.4(0.8)	1.2(0.3)	2.1(0.6)	1.8(0.5)	-0.0049(0.0062)	2.3(0.8)	1.7(0.6)	1.4(0.4)	1.5(0.5)	2.1(0.6)
III + IV	5.5(3.0)	0.9(0.4)	1.8(1.0)	1.6(0.8)	2.9(1.1)	2.0(1.0)	-0.0015(0.0082)	3.6(1.5)	2.9(1.1)	2.0(1.0)	2.5(1.0)	3.1(1.3)
II	4.4(1.6)	0.7(0.2)	1.2(0.3)	1.1(0.3)	1.8(0.5)	1.6(0.2)	-0.0038(0.0052)	2.0(0.8)	1.8(0.7)	1.3(0.5)	1.4(0.5)	1.9(0.7)
OD	4.8(2.2)	0.7(0.2)	1.2(0.3)	1.2(0.3)	1.8(0.6)	1.6(0.2)	-0.0050(0.0045)	2.3(0.9)	2.0(0.7)	1.3(0.6)	1.8(0.5)	2.2(0.8)
DA	4.1(1.2)	0.7(0.2)	1.1(0.3)	1.0(0.4)	1.7(0.5)	1.6(0.3)	-0.0015(0.0082)	1.8(0.6)	1.7(0.7)	1.2(0.4)	1.2(0.4)	1.7(0.6)

Table 2

Statistical significance for group's differentiation using the parameters of dynamic PET series. Student's t-test was applied. See Table 1 caption for abbreviations.

	FDG							MET					
diagnosis	SUVt	T/N	T/Nb	T/Np	SUVp	P/(T/N)	grad	SUVt	T/N	T/Nb	T/Np	SUVp	P/(T/N)
II vs III + IV	-	-	0.038	0.043	0.003	-	-	0.002	0.005	0.027	0.002	0.003	-
DA vs AA + GB	-	-	0.068	0.073	0.024	-	-	0.014	0.022	0.047	0.005	0.010	-
III vs IV	0.047	0.005	0.026	0.016	0.078	-	0.032	-	0.0002	0.002	0.00005	0.010	-
GB vs AOD	-	0.032	0.065	-	-	-	-	-	-	0.049	0.033	-	-
GB vs AA	0.080	0.044	-	0.053	0.025	-	0.096	0.007	0.00004	0.013	0.0001	0.002	-
GB vs OD	-	-	0.058	-	0.029	-	-	0.028	0.002	0.039	0.003	0.021	-
AA vs AOD	-	-	-	-	0.052	-	-	0.009	0.017	-	0.013	0.040	-
AA vs DA	-	-	-	-	-	-	-	-	-	-	-	-	-
AA vs OD	-	-	-	-	-	-	-	-	-	-	-	-	-
DA vs OD	-	-	-	-	-	-	-	-	-	-	0.043	-	-

T/N parameter averaged over the first 60 seconds post injection was also considered. The results were similar but still inferior to SUVp, therefore T/N60 data were not included in the results.

The mean dynamic SUV and T / N curves shown in Figs. 3 and 4 also demonstrate differences between histological tumor subtypes.

From Table 2, it is clear also that the use of ^{11}C-MET provided significant differences between the different histologic subgroups with a higher number of parameters than did the use of ^{18} F-FDG.

Discussion

In neuro-oncology, a major issue is to differentiate between malignant and fast growing tumors, on the one hand, and less aggressive ones, on the other hand. The gold standard for such grading remains histological analysis, with its molecular biology and genetics components, the accuracy of which have considerably improved over the last 2 decades. However, morphology analysis cannot be easily repeated along the course of the disease. Sometimes it can be difficult to target the area of tissue sampling [5]. For these reasons, imaging techniques, which can be repeated as often as necessary, and provide a view of the full volume of the lesion, became more and more important for the management of the disease. MRI is the most accessible to qualitatively investigate many parameters of the tumor, through its large panel of sequences, like contrast enhancement, diffusion coefficient, perfusion and spectroscopy. However, MRI does not propose quantitative data analysis, and both the resolution and the sensitivity of spectroscopy is still far from optimal. This is why PET

approach, which gives access to metabolic aspects of the tumor, with quantitative or semi-quantitative results, had an increasing role since its introduction in the late 70's. ^{18}FDG is the most universally used tracer [1], but ^{11}C-MET has been for long considered as a tracer of choice for the investigation of brain tumors [6–8], this is why we have used both for our study.

The **usual quantification of ^{18}FDG** uptake in clinical practice is referred to SUV and T/N ratio. In the literature, the results of this approach were contradictory [9, 10]. ^{18}F-FDG quantification with SUV or T/N has not been very informative. Even in the case of high glucose uptake no plateau is observed (which is not the case with methionine), so the SUV values are highly dependent on the time elapsed after the tracer injection. Moreover, even malignant tumors with necrosis and BBB damage may have no visible accumulation. In our study however, T/N ratio was better than SUV for differentiating grade IV gliomas (GB) from AA and AOD. Glioblastoma demonstrated higher rates of all measured parameters. The other tumor histological subtypes had a T/N < 1. **With ^{11}C-MET**, the obtained T/N ratios in our study were in good agreement with earlier publications [11–13]. And both the T/N ratio and SUV looked adequate for differentiating grade II or III gliomas from grade IV, but not grade II from grade III. Among earlier publications, only in the subgroup of oligodendrogliomas a highly significant difference was shown between grades II and III [11], which does not appear in our shorter series.

The **study of the first minute** after injection of **^{18}FDG** showed that the T/Nb and T/Np ratios exceeded the final T/N ratio by about 1.6-2 times (parameter P/(T/N) in Table 1) for all types of tumors. Thus, it became possible to identify FDG uptake at the first minute post-injection even if there was no clear over uptake registered 20–40 minutes later (Fig. 2). As the early tracer uptake is partly dependent on tissue perfusion, this observation might suggest that angiogenesis and perfusion are increased early, at least in aggressive tumors, a situation shown by many other investigations, including morphology. However, the relationship between this early uptake of ^{18} FDG and perfusion might not be linear or even clearly established, however, since earlier investigations of perfusion with PET [14] using ^{15} O tracers did not indicate any correlation between tissue blood flow and the vascularization of the tumor among different grades. The most successful parameter in our dynamic ^{18}FDG approach was SUVp, the SUV value at the PFM. According to this parameter, groups with a high degree of malignancy (groups III + IV) were clearly separated from benign tumors (groups II, $p < 0.01$, see Table 2). Therefore, the analysis of the first minute of dynamic PET acquisition with ^{18}FDG was more informative than the analysis of the averaged image at 20 or 40 min post injection, as it is commonly used in clinical practice. It should be noted that most glioblastomas accumulate ^{18}FDG faster than healthy tissue (as it was shown by the positive values of the accumulation gradient), while in other histological types the healthy tissue binds the tracer faster than the tumor tissue, which leads to a reduction of T/N over time.

The **observation of ^{11}C-MET** TACs showed, similarly, that SUVp and T/Np were the best parameters for differential diagnosis, as effective as the commonly used T/N ratio (Table 2). For instance, anaplastic oligodendrogliomas and glioblastomas had close T/N ratios but they differed significantly by T/Nb and T/Np. Diffuse astrocytomas differed from oligodendrogliomas by the T/Np parameter, only with ^{11}C-MET investigations. The ratio T/Np over final T/N for methionine was not correlated with the degree of malignancy (lying in the range 0.8-1.0). This result suggests that the effect of BBB disruption on the total accumulation of methionine is insignificant.

In our series, combination of two dynamic scans, with ^{18}F-FDG and ^{11}C-MET, did not significantly improve the accuracy of differential diagnosis, as it has already been reported in other publications [15]. Most experts consider that ^{11}C-MET alone would be the best choice. But, even if ^{18}F-FDG was inferior to ^{11}C-MET regarding the number of correlated parameters, most PET centers have no access to the latter tracer. In this case, using the SUVp parameter in dynamic ^{18}F-FDG acquisition should have a diagnostic value close to the T/N parameter obtained with a static ^{11}C-MET acquisition.

Conclusions

The study of the first minute passage of ^{18}F-FDG and/or ^{11}C-MET through the tumor and healthy tissues in brain gliomas should not only allow to improve the identification of the different glioma grades, but also to shorten the time spent by the patients under the camera. The most informative parameters are SUVp (standardized uptake value at the peak of the first maximum) with ^{18}F-FDG, and T/Np (T/N at the peak of the first maximum) with ^{11}C-MET. In case of using one tracer, methionine still would be the best choice. Otherwise, the use of ^{18}F-FDG and SUVp would provide results likely comparable to methionine T/N index.

Declarations

Ethics approval and consent to participate The study was approved by the institutional review board. All patients provided written informed consent and had agreed on the use of their (anonymized) data for scientific purposes.

Consent for publication The authors declare that they give consent for publication.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Vikhrova Nina, Kalaeva Diana, Konakova Tatiana, Usachev Dmitrij, De Clerck Nora, Pronin Igor designed the study and performed the experiments; Postnov Andrey, Valable Samuel, Toutain Jérôme, Derlon Jean-Michel analysed the results. All authors contributed in the edition of the MS.

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Figures

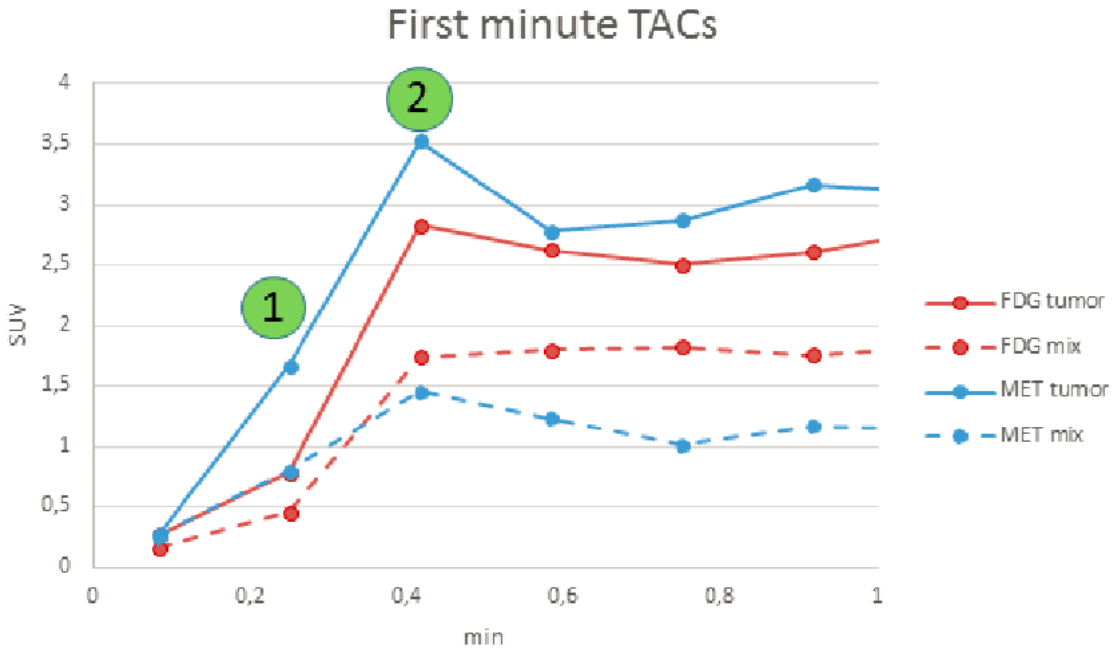

Figure 1

The first minute of 18F-FDG and 11C-methionine (solid lines) passage through the tumor and intact brain tissue (dashed line) in one patient. 1. - peak of the first pass (PFP), 2 - peak of the first maximum (PFM).

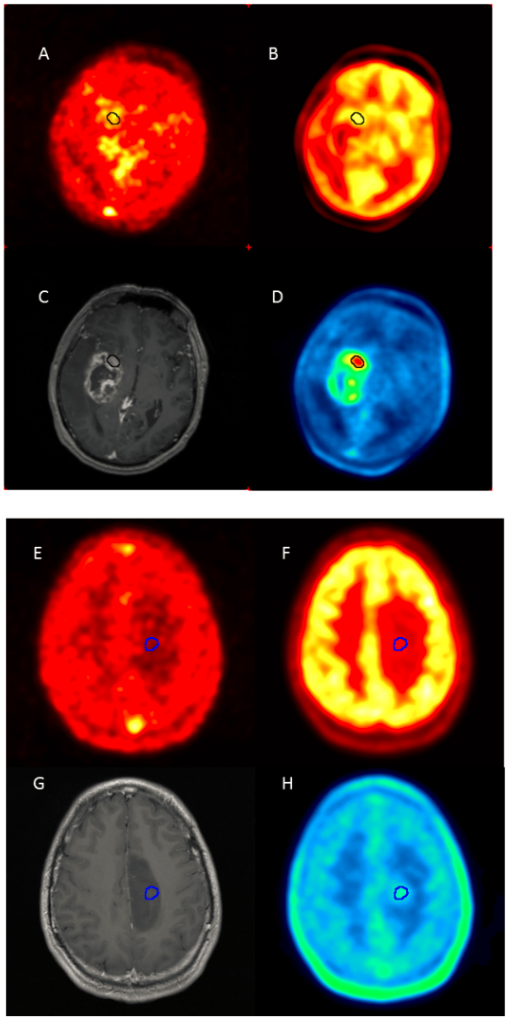

Figure 2

PET and MRI images in Glioblastoma (left) and Diffuse Astrocytoma (right). A,E) 18F-FDG, 0-60 seconds p.i., B,F) 18F-FDG, 35-40 minutes p.i. C, G) T1w MRI with Gd contrast, D,H) 11C-methionine, 15-20 minutes;

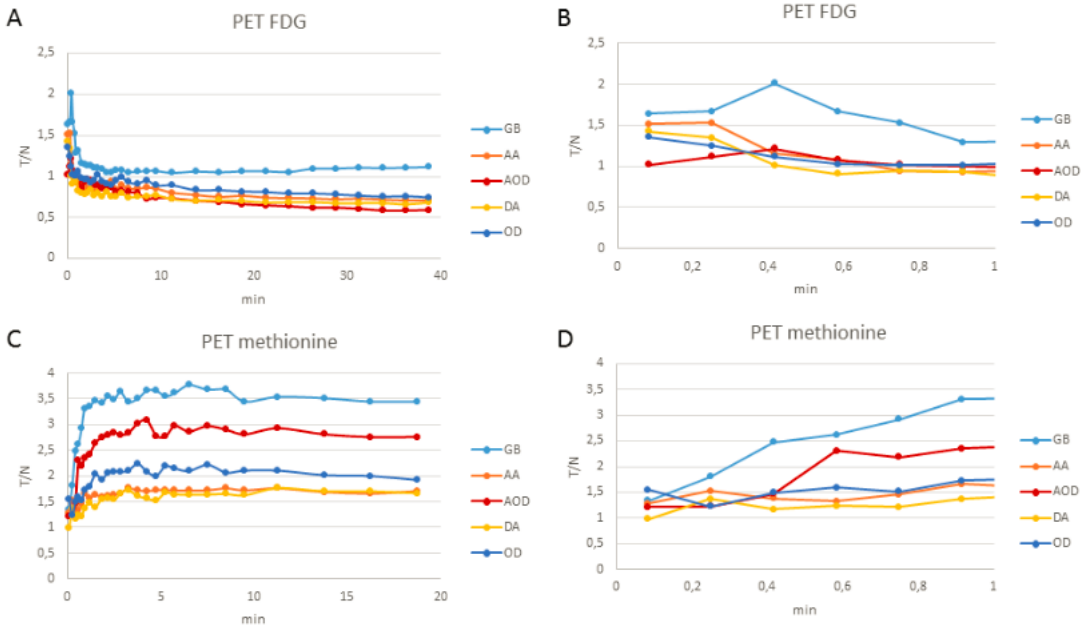

Figure 4

T/N for FDG (A, B - first minute) and methionine (C, D - first minute) for tumors of various histological types. Curves represent average over groups.