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Conflict of interest disclosure statement
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Abstract

Purpose The aim of this study was to prospectively investigate tumor volume delineation by amino acid PET and multiparametric perfusion magnetic resonance imaging (MRI) in patients with newly diagnosed, untreated high grade glioma (HGG).

Materials and Methods Thirty patients with histologically confirmed HGG underwent *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine (^{18}F-FET) positron emission tomography (PET), conventional Magnetic Resonance Imaging (MRI) as contrast-enhanced (CE) and fluid-attenuated inversion recovery (FLAIR) and multiparametric MRI as relative cerebral blood volume (rCBV) and permeability estimation map (K2). Areas of MRI volumes were semi-automatically segmented. The percentage overlap volumes, Dice and Jaccard spatial similarity coefficients (OV, DSC, JSC) were calculated.

Results The ^{18}F-FET tumor volume was significantly larger than the CE volume (median 43.5 mL (2.5 – 124.9) vs. 23.8 mL (1.4 – 80.3), $p=0.005$). The OV between ^{18}F-FET uptake and CE volume was low (median OV 0.59 (0.10 - 1)), as well as spatial similarity (median DSC 0.52 (0.07 – 0.78); median JSC 0.35 (0.03 – 0.64)). Twenty-five patients demonstrated both rCBV and CE on MRI: The median rCBV tumor volume was significantly smaller than the median CE volume ($p<0.001$). The OV was high (median 0.83 (0.54 – 1)), but the spatial similarity was low (median DSC 0.45 (0.04 – 0.83); median JSC 0.29 (0.07 – 0.71)). Twenty-eight patients demonstrated both K2 and CE on MRI. The median K2 tumor volume was not significantly larger than the median CE volume. The OV was high (median OV 0.90 (0.61 – 1)), and the spatial similarity was moderate (median DSC 0.75 (0.01 – 0.83); median JSC 0.60 (0.11 – 0.89)).

Conclusion We demonstrated that multiparametric perfusion MRI volumes (rCBV, K2) were highly correlated with CE T1 gadolinium volumes whereas ^{18}F-FET PET provided complementary information, suggesting that the metabolically active tumor volume in patients with newly diagnosed untreated HGG is critically underestimated by contrast enhanced MRI. ^{18}F-FET PET imaging may help to improve target volume delineation accuracy for radiotherapy planning.

Keywords

High grade glioma; tumor volume; ^{18}F-FET PET; multiparametric perfusion MRI; Radiotherapy target volume; GTV

Background

Despite significant advances in diagnostic and therapeutic approaches over the last few decades, the prognosis for patients with high grade glioma (HGG), especially glioblastoma (GBM) remains limited with a median survival of only 15–20 months. Currently, the standard first-line therapy is a maximally safe resection followed by chemoradiotherapy [1]. According to published guidelines, radiotherapy target volumes are based on contrast-enhanced (CE) T1 weighted magnetic resonance imaging (MRI) [2]. The majority of tumor recurrences after radiotherapy occur within the high dose treated volume [3], indicating that the delivered dose may be insufficient for local tumor control. However, dose escalation to the entire planning volume would result in higher radiation exposure to surrounding tissues and associated increased risk of symptomatic radiation-induced radionecrosis [4, 5]. In this respect, the ability to more precisely define areas at high risk of recurrence could be useful to guide a dose escalation protocol. Imaging the biological and molecular characteristics of tumor tissue by positron emission tomography (PET) is an interesting approach to improve treatment planning for high precision radiotherapy. Indeed, molecular imaging with *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine (^{18}F-FET) positron emission tomography-computed tomography (PET/CT) appears more specific and equally sensitive for tumor staging than MRI [6]. Conventional MRI with T1 and T2 weighted imaging depicts brain signal anomalies, but is not specific for brain tumor invasion. HGG are also characterized by extensive microvascular proliferation and a higher degree of vascularity than low-grade gliomas and are known to present with some foci (hotspots) of neoangiogenesis and/or elevated permeability in their center or in surrounding tissue [7]. Dynamic susceptibility contrast (dsc) brain MRI perfusion with contrast leakage correction evaluates several aspects of brain vasculature by assessing different parameters such as relative cerebral blood volume and permeability and could, therefore, provide additional information compared to conventional MRI [8]. Currently, 18F-FET PET and perfusion sequences are not routinely used for target volume definition during radiotherapy planning. The aim of this study was to confirm whether ^{18}F-FET PET and multiparametric MRI provided additional information on localization, such as hotspot neoangiogenesis and/or tumor extent that could guide radiotherapy planning. In addition, we evaluated the differences between the routinely used Gross Tumor Volume (GTV) based on CE MRI (GTV-MRIc) and the tumor volumes estimated from multiparametric imaging MRI and ^{18}F-FET PET.

Methods

This prospective monocentric study was approved by the institutional review board of the University Hospital of Brest (N°2016.CE14) and registered in ClinicalTrial.gov registry (NCT03370926). Written informed consent for study participation was obtained from all patients before initiation of any study-specific procedures.

Patient population and imaging protocol

Eligible patients were diagnosed with a histologically-proven high grade glioma tumor, 2016 World Health Organization (WHO) grade 3 or 4 [9], were older than 18 years old, and had a performance status score ≤ 2. Exclusive and/or adjuvant therapy was determined by a multidisciplinary team. Exclusion criteria were: previous encephalic radiotherapy, pregnancy or breast feeding, or contraindication to MRI and/or for ^{18}F-FET PET/CT imaging.

MRI

All patients underwent 3DT2-weighted fluid-attenuated inversion recovery (FLAIR) MRI scan and a 3D-T1-weighted MRI scan after intravenous administration of a standard dose of contrast agent (Gd-DTPA; 0.1 mmol/kg body weight). For perfusion imaging, dynamic susceptibility contrast by gradient-echo echo-planar imaging was achieved. Patients were scanned using a 3 T Achieva dStream MRI scanner (Philips healthcare, Inc.), a 1.5 T Optima MRI scanner (General Electric Medical Systems, Inc.) or a 1.5 T Magnetom Avanto Fit (Siemens healthineers, Inc.).
Perfusion parameters processing was performed using Olea Sphere software (v3.0 Olea Medical, La Ciotat, France) to generate relative cerebral blood volume corrected for contrast leakage (rCBV) and to generate a permeability estimation map (K2). Parameters such as rCBV and K2 that represent neoangiogenesis and vascular permeability respectively can be extracted from DSC MRI. Permeability parameters like K2 derived from DSC are being increasingly implemented in perfusion processing softwares [10, 11].

^{18}F-FET PET/CT

All patients fasted for at least 4 hours before PET/CT, as per the European Association of Nuclear Medicine (EANM) guidelines for brain tumor imaging using labelled amino acid analogues [12].

PET imaging was performed on a Biograph mCT PET/CT system (Siemens, Siemens Healthineers, Knoxville, USA). For attenuation correction, a low dose CT scan was performed without iodine contrast. CT acquisition parameters were 16x1.2 mm pitch 0.55 with automatic kVp and mAs modulation. CT reconstruction parameters were slice thickness 3/3mm, convolution kernel H31s, field of view 500mm for attenuation correction, and slice thickness 2/1.2mm, convolution kernel J30s, safire 3, field of view 300mm for reading. After CT examination, the acquisition was centred on the head and consisted of 40 minutes dynamic acquisition after the intravenous injection of 3MBq/kg. PET dynamic reconstructions were performed with 10x4min frames, the reconstruction algorithm was 3DOSEM + TOF+PSF (TrueX) with 200² matrix, zoom2, 2 iterations, 21 subsets, gaussian post filter 2mm. A single static ^{18}F-FET PET frame was obtained by sum 20-40 min.

The study stipulated the time between histological confirmation and radiotherapy CT planning should not exceed one month, and time between MRI and ^{18}F-FET PET/CT should not exceed 14 days.

Target volume delineation and treatment planning

CT imaging for radiotherapy planning was acquired throughout the entire head. Patients were immobilized using a 3-point customized thermoplastic mask.

The ^{18}F-FET PET/CT and MR images were registered to the planning CT using the internal rigid registration module in MiM Maestro® (MiM software Inc Cleveland, OH 44122, United States). The registration results were checked visually and semi-automatically adjusted by two experts in neuro-oncology (GD, BD) according to anatomical landmarks if required.

As no general cut-off for tumor blood volume currently exists, multiparametric MRI-based tumor volumes (GTV-FLAIR, GTV-rCBV and GTV-K2) were segmented in consensus by two experts in neuro-oncology (GD, BD) using semi-automatic delineation based on edges (Co-pilot MIM software) and with visual evaluation, comparing tumor blood volume with blood volume in normal-appearing tissue in adjacent brain and in similar structures in the contralateral hemisphere [13, 14].

The GTV-FET PET was defined by a 3-dimensional automatic segmentation using a tumor-to-brain ratio (TBR) of ≥1.6 within a 30 mm margin around the GTV-MRIc. The normal contralateral uptake (background activity) was defined as previously described [16].

The Clinical Target Volume (CTV) was defined by adding a 20 mm margin around the GTV -MRIc, respecting anatomical boundaries. The Planning Target Volume (PTV) was created by isocentrically expending the CTV by 4 mm.

Radiation treatment planning was performed using Pinnacle® TPS (Philips Healthcare, Fitchberg, WI, United States). Volumetric modulated arc therapy (RapidArc, Varian Medical Systems) with 2 coplanar beams was the standard radiation technique. The prescribed dose was 60 Gy in 30 fractions, with the 95% isodose encompassing 95% of the PTV [2].

Calculation of spatial correlation and overlap between MRI-based and ^{18}F-FET PET-based tumor volumes and statistical analysis

As a measure of spatial correlation [17, 18] between MRI-based and PET-based volumes, the Dice Similarity Coefficient (DSC) and the Jaccard Similarity Coefficient (JSC) were calculated [19]. See also Fig 1.

JSC is defined as the ratio of the intersection and the union of the GTV-FET PET and the MRI-based GTVs according to the equation:

$$JSC(V_{PET}.V_{MRI}) = \frac{V_{PET} \cap V_{MRI}}{V_{PET} \cup V_{MRI}} = \frac{DSC}{2 - DSC}$$

DSC was calculated as followed:

$$DSC(V_{PET}.V_{MRI}) = \frac{2\,(V_{PET} \cap V_{MRI})}{V_{PET} + V_{MRI}}$$

The overlap volume (OV) was also calculated. Indeed, using only one metric like the OV could result in misinterpretation [18]. The OV deals with volumetric differences between volumes of interest (VOI) and is defined as the ratio of the intersection to the smallest volume following this equation:

$$OV(V_{PET}.V_{MRI}) = \frac{V_{PET} \cap V_{MRI}}{min(V_{PET}.V_{MRI})}$$

DSC and JSC are similarity coefficients that range between 0 (no similarity) and 1 (perfect agreement). OV is an overlap coefficient, a similarity measure that measures the overlap between two volumes. Descriptive statistics were presented as median and range or mean and standard deviation (SD).The non-parametric Wilcoxon rank-sum test was used for intergroup comparisons. *p* values less than 0.05 were considered significant.

Statistical analysis was performed using the statistical software package Addinsoft, 2018, XLSTAT 2018: Data Analysis and Statistical Solution for Microsoft Excel (Paris, France).

Results

Thirty patients (20 male, 10 female) with newly diagnosed HGG (2016 WHO) and scheduled for concomitant chemoradiotherapy were prospectively included between November 2016 and December 2018. Median (range) age was 63 years (24-77). Patients and tumors characteristics are summarized in Table 1 and supplemental Table 1.

The median delay between MRI and ^{18}F-FET PET/CT was 6 (1 – 40) days. The median delay between surgery/biopsy and radiotherapy planning CT was 22 (13 – 72) days.

Twenty-seven patients were scanned using a 1.5T MR scanner and 3 patients were scanned using a 3T MR scanner.

PET processing failed in one patient due to agent injection issues.

Five patients did not have any rCBV for the following reasons: MR-perfusion sequences failed in 2 patients (due to agent injection issue), generation of rCBV map failed in 1 patient, and 2 patients with complete resection did not have a rCBV.

Of note, 6 of 8 patients with complete resection had a rCBV.

Table 2 presents tumor volumes depending on each imaging modality.

The GTV-FET PET was significantly larger than the GTV-MRIc (median 43.5 mL (2.5 – 124.9) vs. 23.8 mL (1.4 – 80.3), *p=0.005*). Twenty-five patients had ^{18}F-FET PET volume (>5 mL) outside the GTV-MRIc.

In 25 patients with visible rCBV tumor volume, the median rCBV tumor volume was significantly smaller than the median GTV-MRIc (5.3 (0.1 – 91.0) vs. 23.8 (1.4 – 80.3), *p<0.001*). The average K2 tumor volume was not significantly larger than the median GTV-MRIc (29.6 mL (0.9 – 109.9) vs. 23.8 mL (1.4 – 80.3), *p=0.135*).

Twenty-nine patients demonstrated both ^{18}F-FET uptake and CE on MRI. Overlap volume between respective GTVs was low (median OV 0.59 (0.10 – 1)), as well as spatial similarity (median DSC 0.52 (0.07 – 0.78); median JSC 0.35 (0.03 – 0.64)). In subgroup analysis, OV, DSC and JSC remain low but higher in patients who underwent a biopsy only compared to that in patients who had surgery, as presented in supplemental table 2.

Overall, 28 patients demonstrated both K2 and CE on MRI. The OV was high (median OV 0.90 (0.61 – 1)), and the spatial similarity was moderate (median DSC 0.75 (0.01 – 0.83); median JSC 0.60 (0.11 – 0.89)).

Twenty-five patients demonstrated both rCBV and CE on MRI. The OV was high (median 0.83 (0.54 – 1), but the spatial similarity was low (median DSC 0.45 (0.04 – 0.83); median JSC 0.29 (0.07 – 0.71)).

All except 2 patients demonstrated both 18F-FET uptake and FLAIR on MRI.

The OV was moderate (median OV 0.76 (0.17 – 1)), and the spatial similarity was low (median DSC 0.50 (0.03 – 0.73); median JSC 0.33 (0.02 – 0.57).

The GTV-FET PET was smaller than the GTV-FLAIR in 18 patients (64.3%). In 23 of 28 patients (82.1%), more than 5 mL of the GTV-FET PET was located out of the GTV-FLAIR.

The OV between GTV-PET FET and CTV was high (median OV 0.95 (0.59 – 1)), but the spatial similarity was low (median DSC 0.31 (0.04 – 0.65); median JSC 0.18 (0.02 – 0.48)).

The CTV volumes were always larger than GTV-FET PET volumes. In 5 of 30 patients (16.7%), more than 5 mL ^{18}F-FET PET tumor volume was out of CTV. Furthermore, there appeared to be a high discrepancy in spatial similarity of theses volumes.

Overlap and spatial similarity are summarized in Table 3, Fig 1 and supplemental figures (2-5).

Discussion

Overall, 80-90% and 95% of HGG relapses occur within a 2 cm and 3 cm margin from the initial CE lesion on CT- or MRI imaging, respectively [5]. ^{18}F-FET PET uptake and MR perfusion imaging could be beneficial in personalizing radiotherapy planning volumes. Previous studies have already assessed the spatial differences between conventional MRI, neoangiogenesis parameter (rCBV) and ^{18}F-FET PET [18, 20, 21]. However, to the best of our knowledge, this presented work is the first prospective study comparing spatial differences between multiparametric perfusion MRI (particularly permeability parameter like K2) and ^{18}F-FET PET.

In line with current recommendations, the GTV is defined by the CE-T1 tumor and/or resection cavity and residual CE tumor, whereas the CTV is defined by an isotropic 20 mm margin around the GTV [2]. However, recent published data suggest that CTV margins could be reduced through ^{18}F-FET PET imaging prior to primary radiotherapy for glioblastoma. Indeed, the pattern of recurrence of ^{18}F-FET PET and MRI-based GTVs with 15 mm CTV margins was comparable to MRI-based GTVs with 20 mm CTV margins [24].

In our current study, the GTV-FET PET was defined by a 3-dimensional automatic segmentation using a tumor-to-brain ratio (TBR) of ≥1.6 within a 30 mm margin around the GTV-MRIc. This threshold is based on a biopsy-controlled study in cerebral gliomas which reported that a lesion-to-brain ratio of 1.6 best separates tumoral from peritumoral tissue [15]. Our results are consistent with the current literature. Indeed, Harat *et al*. analyzed the GBM recurrence patterns in 34 patients with pre-treatment conventional MRI and dual time-point (ie. 10 and 60 min) FET PET [26]. They reported tumor volumes in line with ours with a mean GTV-FET PET of 39 mL (1 – 106) and a GTV-MRI of 29 mL (4 – 78), compared to 43.6 mL (2.5 – 124.9) and 31.3 mL (1.4 – 80.3) in our study. They also suggested that ^{18}F-FET PET better defined failure site than conventional MRI alone, with 26.5% of GTV-FET PET extended beyond the 20 mm margin from the GTV-MRIc. These data are in line with our results: 17% of GTV-FET PET extended beyond the 20 mm margin from the GTV-MRI. Other studies suggested that tumor volumes assessed by ^{18}F-FET PET imaging are significantly larger than those provided by T1 gadolinium weighted imaging [20, 22, 23].

Moreover, spatial correlation analysis demonstrated that both volumes differ notably in their locations: overlap and similarity indices showed low agreements between the different GTVs. ^{18}F-FET PET hypermetabolism was located outside the corresponding CTV in 5 of 30 patients (17%) despite a 20 mm peripheral margin around GTV-MRIc, suggesting areas of tumor activity outside the CTV.
Henriksen *et al.* reported on the DSC between ^{18}F-FET PET and contrast-enhanced MRI tumor volumes in 17 of 32 patients with pretreated low-grade and high-grade gliomas [27]. The estimated spatial similarity was lower than that reported in our study (mean DSC 0.19 versus 0.40). This may be explained by the heterogeneity of the population included in their study. On the contrary, our results are in line with other retrospectives studies on 50 and 20 patients which reported mean DSC of 0.39 and 0.40, respectively [14, 18].

K2 parameter is a tool to assess tumor vascular permeability, and also provides information about tissue vasculature. This parameter is being increasingly implemented in routine clinical practice [7]. In our study, K2 was highly correlated with GTV-MRIc, with a high overlap (median OV 90%). In addition, K2 parameters provided by perfusion weighted imaging were included in their respective CTVs and in hypersignal FLAIR areas

in all except one patient. In this respect, permeability maps do not seem to provide additional information to T1 gadolinium-weighted imaging.

Neoangiogenesis parameter like rCBV also showed high overlap with GTV-MRIc (median 0.83 (0.54 – 1)), but with a low similarity index (median DSC 0.45 (0.04 – 0.83); median JSC 0.29 (0.07 – 0.71)). Each hot spot shown on perfusion imaging was included in its respective CTV and hypersignal FLAIR area. Of note, unlike previous studies on this topic, regional cerebral blood volume maps were corrected for contrast leakage in our study, as this is known to better assess cerebral brain tumor [10]. Although the use of rCBV would not result in radiotherapy target volume modifications, depicting hot spots on cerebral blood volume maps is reliable, easy to perform and could be used to identify subvolume with increased neoangiogenesis that may benefit from dose painting [13].This is still an active field of research, exploring perfusion MRI along with MR spectroscopy and diffusion MR [28].

Our results suggest that the combined use of multiparametric perfusion (rCBV) MRI and ^{18}F-FET PET is superior to conventional MRI alone for the distinction between tumor tissue and peritumoral brain tissue in patients with HGG. Indeed, ^{18}F-FET PET appears to be more helpful for delineation than multiparametric perfusion MRI by adding complementary information outside and inside the radiotherapy target volume, whereas rCBV provides complementary information inside the radiotherapy target volume. Conversely, K2 does not appear to provide additional information. Therefore, ^{18}F-FET PET may result in change in radiotherapy target volume, whereas rCBV could be useful to guide a dose escalation boost inside the initial target volume.

Previous studies have shown that tumor volumes determined by amino acid (L-[methyl-11C] methionine (MET) PET and blood volume imaging are closely correlated [29, 30]. Sadeghi *et al.* found a high correlation between rCBV values and MET uptake values in a group of 18 patients diagnosed with glial tumors [30], indicating that the degree of vascularity is a major factor in the transfer of MET within gliomas. Conversely, our work revealed considerable difference between ^{18}F-FET PET volume and rCBV.
It is important to note that rCBV maps suffer from limitations already underlined in the literature [21, 31]. Perfusion-weighted imaging can easily fail in regions close to a brain-bone-air interface such as the base of skull. It may also be operator-dependant because a clear differentiation from blood vessels can be challenging.

An obvious strength of our study is the prospective design combining ^{18}F-FET PET imaging and multiparametric MRI within a short delay. Our cohort is homogeneous and imaging studies were obtained before any treatment initiation. In addition, three different quantitative measurements were used to describe volumetric and spatial differences between the ^{18}F-FET PET and multiparametric MRI volume (Figs 2-3). Moreover, while GTV-MRIc is routinely outlined manually from contrast uptake areas on MR T1-weighted imaging, we used a semi-automatic delineation based on edges in order to limit interobserver variability which requires further study and analysis.

Our study has some limitations. First, the patient cohort is small but, as stated earlier; this is the first prospective study on this topic. Second, although the median delay between MRI and PET was only 6 days, this could have influenced our results, particularly the values obtained for the similarity indices. However, this delay reflects routine clinical practice, as obtaining both imaging studies in a short period of time is not always achievable. Third, MRI examination was performed on different MRI scanners, with 27/30 patients on a 1.5T. This may limit the generalisability of the results for 3T MRI [32], although this also reflects the real-life practice.

Of note, combined multiparametric imaging (e.g PET and MRI) should also be supported by a reliable image registration method. Ideally, MRI and PET should be performed during the same procedure with the use of a PET/MR scan, with the patient in the same thermoplastic mask.

Finally, the contribution of these imaging modalities for delineation on clinical outcomes should also be assessed prospectively. Munck af Rosenschold *et al.* retrospectively studied the influence of hippocampal-sparing using image-guided volumetric modulated arc therapy technology in combination with ^{18}F-FET PET [25]. The use of ^{18}F-FET PET in target delineation for radiotherapy planning should, at least in theory, improve the radiation dose coverage of infiltrative disease. In their study, no change in either progression-free survival or overall survival by adding GTV-FET PET to the conventional GTV-MRI volume was observed.

In summary, in this monocentric prospective study, multiparametric MRI (rCBV, K2), particularly on 1.5T, are highly correlated with CE T1 gadolinium whereas ^{18}F-FET PET provides complementary information, suggesting that the metabolically active tumor volume in patients with newly diagnosed untreated HGG, especially GBM, is critically underestimated by contrast enhanced MRI. ^{18}F-FET PET imaging may help to improve target volume delineation accuracy for radiotherapy planning. Future studies should address the added

value of these new imaging modalities in depicting anaplastic foci. These multiparametric imaging techniques could also be helpful for surgical biopsy planning.

Figures legends

Fig 1: Two examples showing similar Dice (DSC) and Jaccard (JSC) coefficients but different Overlap Volumes (OV), highlighting the fact that they should be analysed simultaneously to avoid misinterpretation. *Modified from Lohmann et al. 2018,* Eur J Nucl Med Mol Imaging.

Fig 2: Example showing differences between T1 gadolinium-weighted and T2 FLAIR-based tumor volume (red) and ^{18}F-FET PET imaging (blue).

Fig 3: Example showing differences between T1 gadolinium-weighted imaging (top left), rCBV (bottom left) and K2 imaging (bottom right). Yellow edge shows neoangiogenesis with high rCBV. Red edge shows T1 gadolinium enhancement and blue edge shows high permeability areas (K2 imaging). All pictures were registrated with the radiotherapy CT planning (top right).

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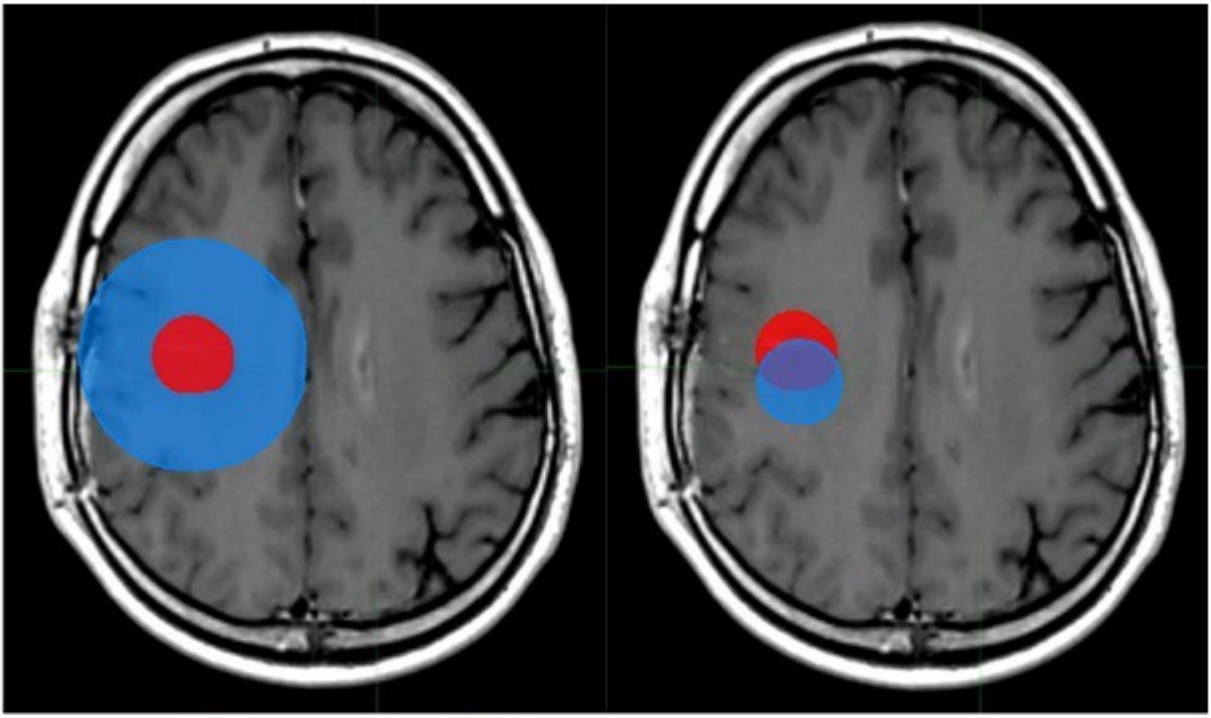
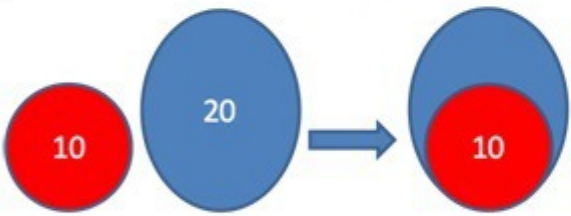
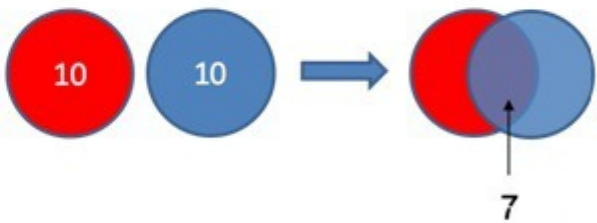






$$DSCa = \frac{2 \cdot 10\ mL}{20\ mL + 10\ mL} \cong 0.7$$

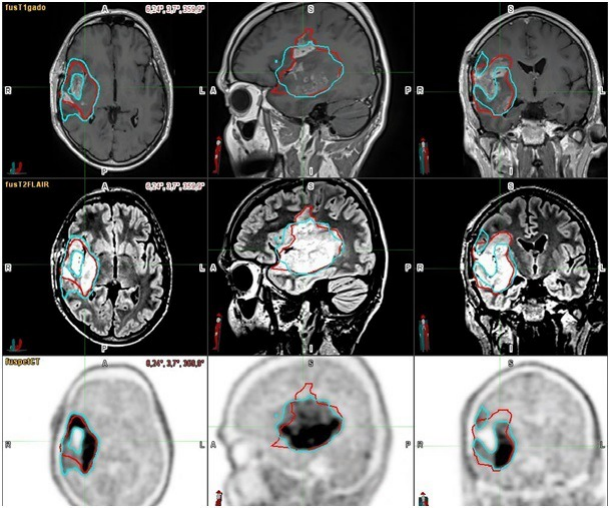
$$DSCb = \frac{2 \cdot 7\ mL}{10\ mL + 10\ mL} = 0.7$$

$$JSCa = \frac{10\ mL}{10\ mL + 10\ mL} = 0.5$$

$$JSCb = \frac{7\ mL}{7\ mL + 3\ mL + 3\ mL} = 0.5$$

$$OVa = \frac{10\ mL}{10\ mL} = 1 = 100\%$$

$$OVb = \frac{7\ mL}{10\ mL} = 70\%$$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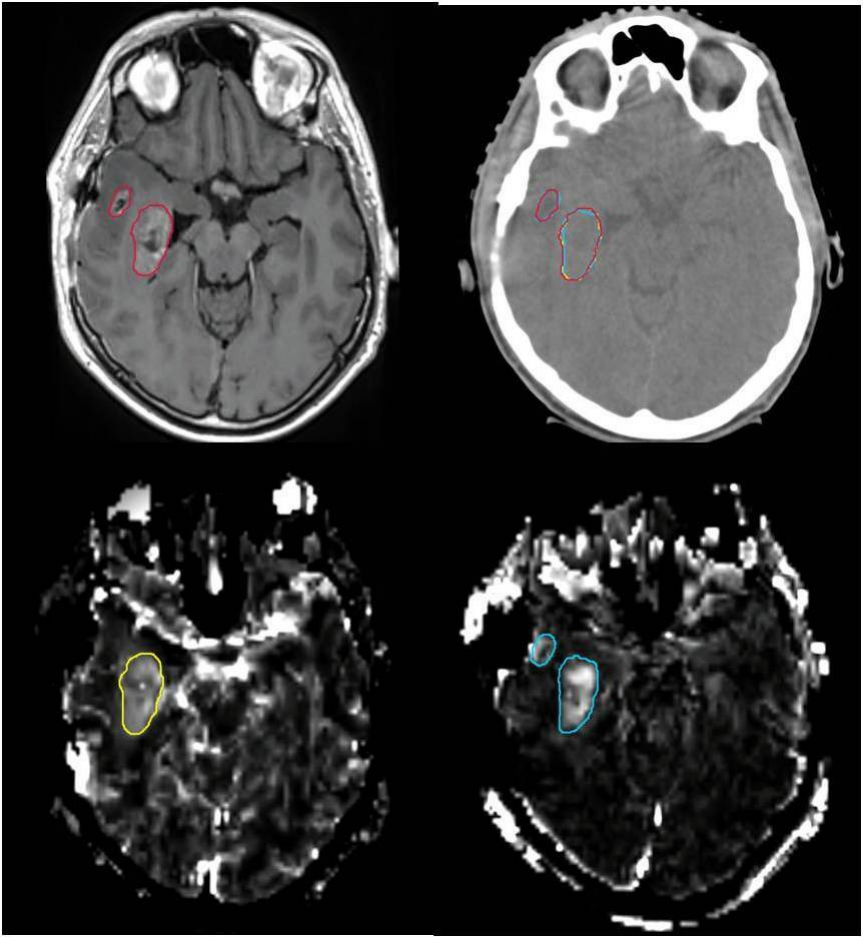

Table 1: Patients characteristics

Characteristics		Median/Nb.	Range/percent
Age		63	24 – 77
	Male	20	66.7
	Female	10	33.3
Histology			
	Grade III	5	16.7
	Grade IV	25	83.3
Multifocal			
	Yes	5	16.7
	No	25	83.3
Extent of resection			
	Biopsy only	14	60
	Partial (>5% remaining)	4	10
	Subtotal (<5%remaining)	4	13.3
	Complete	8	16.7

Table 2: Volumes of interest (mL) for each patient

N°	CTV	GTV-MRIc	GTV- FLAIR	GTV-K2	GTV-rCBV	GTV-FET PET
1	150.83	10.95	65.36	10.41	3.68	14.18
2	355.27	41.78	77.08	46.81	6.13	78.54
3	274.94	80.27	187.53	97.99	4.42	71.66
4	313.57	73.68	226.32	109.96	26.18	63.58
5	170.87	28.51	83.14	24.89	NA	18.21
6	93.14	4.88	9.86	5.14	NA	2.54
7	185.34	24.34	66.18	37.38	3.44	26.83
8	238.95	51.02	53.52	52.29	29.91	60.91
9	275.48	43.6	119.63	65.75	24.48	46.47
10	181.46	33.99	111.55	33.29	15.34	49.66
11	131.36	22.52	99.7	34.52	0.74	66.43
12	237.26	38.2	116.73	33.36	35.09	63.92
13	84.02	11.98	NA	6.99	0.77	13.24
14	116.04	14.5	27.15	25.98	21.03	30.61
15	223.16	51.82	85.62	49.5	NA	124.9
16	294.11	79.21	112.18	89.15	37.25	61.4
17	97.7	1.92	21.48	7.64	14.4	36.53
18	226.78	10.61	96.85	25.67	19	100.7
19	169.02	9.38	53.01	9.99	3.46	24.88
20	131.51	5.62	5.65	0.9	0.7	36.72
21	38.91	1.36	0.3	2.4	0.67	13.58
22	284.01	33.23	161.53	36.61	31.4	44.62
23	82.33	8.97	10.18	2.44	1.32	8.33
24	120.5	15.45	15.12	6.72	0.15	5.76
25	106.14	5.58	20.45	5.36	7.86	16.6
26	245.89	20.51	112.99	34.55	26.37	55.29
27	161.04	23.35	30.63	NA	NA	46.85
28	572.91	78.73	129.82	81.51	91	81.93
29	367.82	69.64	132.78	102.35	43.49	NA
30	224.12	43.65	80.28	NA	NA	42.41

NA = Not Applicable.

Table 3: Overlap and spatial similarity

Characteristics		Mean	SD	Median	Range
Tumor volume (mL)					
CTV		205.1	109.9	183.4	38.9 - 572.9
GTV-FET PET		43.6	30.3	43.5	2.5 - 124.9
GTV-MRIc		31.3	25.1	23.8	1.4 - 80.3
GTV-FLAIR		77.1	58.0	78.7	0.3 - 226.3
GTV-rCBV		14.9	19.8	5.3	0.1 - 91.0
GTV-K2		34.6	33.3	29.6	0.9 - 109.9
GTV-MRIc Overlap volume					
GTV-FET PET		0.59	0.26	0.59	0.10 - 1
GTV-rCBV		0.82	0.13	0.83	0.54 - 1
GTV-K2		0.86	0.10	0.90	0.61 - 1
GTV-MRIc Similarity coefficient					
GTV-FET PET	DSC	0.40	0.22	0.52	0.07 – 0.78
	JSC	0.28	0.18	0.35	0.03 – 0.64
GTV-rCBV	DSC	0.42	0.27	0.45	0.04 – 0.83
	JSC	0.31	0.23	0.29	0.07 – 0.71
GTV-K2	DSC	0.67	0.21	0.75	0.01 – 0.83
	JSC	0.54	0.22	0.60	0.11 – 0.89
CTV Overlap volume					
GTV-FET PET		0.91	0.09	0.95	0.59 - 1
GTV-FLAIR		0.95	0.05	0.98	0.59 - 1
GTV-rCBV		0.99	0.01	1	0.91 - 1
GTV-K2		0.99	0.01	1	0.95 - 1
CTV Similarity coefficient					
GTV-FET PET	DSC	0.32	0.13	0.31	0.04 – 0.65
	JSC	0.20	0.10	0.18	0.02 – 0.48
GTV-rCBV	DSC	0.20	0.15	0.19	0.01 – 0.52
	JSC	0.12	0.10	0.11	0.01 – 0.35
GTV-K2	DSC	0.25	0.14	0.24	0.01 – 0.51
	JSC	0.15	0.10	0.13	0.07 – 0.35

SD = Standard deviation; CTV = Clinical Target Volume; GTV = Gross Tumor Volume;
DSC = Dice Similarity Coefficient; JSC = Jaccard Similarity Coefficient