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Meriem Abdallah, Marie Blonski, Sophie Wantz-Mézières, Yann Gaudeau, Luc Taillandier, et al.. On the relevance of two manual tumor volume estimation methods for diffuse low-grade gliomas. Healthcare Technology Letters, 2018, 5 (1), pp.13-17. 10.1049/htl.2017.0013 . hal-01654158

HAL Id: hal-01654158

<https://inria.hal.science/hal-01654158v1>

Submitted on 3 Dec 2017

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On the relevance of two manual tumor volume estimation methods for diffuse low-grade gliomas

M. Ben Abdallah, M. Blonski, S. Wantz-Mézières, Y. Gaudeau, L. Taillandier and J.M. Moureaux

Management of Diffuse Low-Grade Glioma (DLGG) relies extensively on tumor volume estimation from MRI datasets. Two methods are currently clinically used to define this volume: the commonly used three-diameters solution and the more rarely used software-based volume reconstruction from the manual segmentations approach. We conducted an initial study of inter-practitioners' variability of software-based manual segmentations on DLGGs MRI datasets. A panel of 13 experts from various specialties and years of experience delineated 12 DLGGs' MRI scans. A statistical analysis on the segmented tumor volumes and pixels indicated that the individual practitioner, the years of experience and the specialty seem to have no significant impact on the segmentation of DLGGs. This is an interesting result as it had not yet been demonstrated and as it encourages cross-disciplinary collaboration. Our second study was with the three-diameters method, investigating its impact and that of the software-based volume reconstruction from manual segmentations method on tumor volume. We relied on the same dataset and on a participant from the first study. We compared the average of tumor volumes acquired by software reconstruction from manual segmentations method with tumor volumes obtained with the three-diameters method. We found that there is no statistically significant difference between the volumes estimated with the two approaches. These results correspond to non-operated and easily delineable DLGGs and are particularly interesting for time-consuming CUBE MRIs. Nonetheless, the three-diameters method has limitations in estimating tumor volumes for resected DLGGs, for which case the software-based manual segmentation method becomes more appropriate.

Introduction: Diffuse Low-Grade Glioma (DLGG) is a rare primitive cerebral tumour of adults. In [2], Emmanuel Mandonnet *et al.* showed that tumor diameter proves to be a good predictor of the evolution of DLGGs. Consequently, nowadays, patients' monitoring in specialized clinical centers relies heavily on a longitudinal supervision of tumors' diameter evolution. This monitoring uses 2 consecutive, at least 3 months-spaced, axial MRI sequences that are either T2-weighted or, more commonly, FLAIR-weighted. DLGG's volume is estimated from these MRI sequences either through a segmentation followed by a software reconstruction or through the three diameters method. Whereas the three diameters method uses a simple formula to compute tumor volume, software solutions [2], make it possible to reconstruct tumor volume from the manual segmentations of the practitioner on the MRI slices where the tumor lesion appears. Moreover, the three-diameters method is fast compared to the software-based volume reconstruction solution. Therefore, an automatic segmentation algorithm could make the segmentation task time-efficient and improve the therapeutic management of DLGG patients.

The medical imaging community has been aware of the importance of segmentation algorithms and has been organizing MICCAI (International Conference on Medical Computing and Computer Assisted Intervention) conference challenges since 2007. These challenges include the BRATS (BRAIn Tumor image Segmentation) challenge [3] [4], which focuses on brain tumors and which has enabled different research teams to evaluate the performance of their automatic segmentation algorithms [5] [6] [7] [8]. Several solutions were proposed for the segmentation of brain tumors, including support vector machines [5], the Level Set method [9], the k-nearest neighbor algorithm [10] and, more recently, deep learning approaches using convolutional neural networks [6] [7] [8]. However, the major automatic segmentation algorithms proposed so far are more generalized for different brain tumors [7] [8] [9] [10], and hence, neglect particular segmentation difficulties that are specific to DLGG (ill-defined boundaries, heterogeneity of the tumor). Moreover, manual segmentation is still the ground truth in automatic segmentation studies of brain tumours and no algorithm has yet been proved capable of replacing human expertise in a clinical routine. Therefore, at present, software-based manual segmentation should be preferred for follow-up in the treatment of DLGG. To allow quick and timely therapeutical decisions, this procedure needs to be performed

by different clinicians. However, for a distribution of segmentation tasks among various independent practitioners, reproducibility and inter-practitioner inconsistency in segmentation is a major challenge. To our knowledge, no studies have been conducted to assess the reproducibility of DLGG's software-based manual segmentation on MRI datasets [11]. A first purpose of this work is to address this topic by conducting a subjective study on the impact of the practitioner factor on segmented tumor volume. We also investigate the influence of the specialty and of the years of experience on the obtained tumor volume.

Furthermore, the use of the three-diameters method remains fairly widespread in clinical practice for DLGG volume estimation. Nevertheless, this approach offers an ellipsoidal approximation of the tumor volume [1] [2] [13], which could be assumed to be less precise than the software-based volume reconstruction solution. In fact, the three-diameters method consists in defining the two largest diameters in the axial plane of an MRI exam at a given date and in drawing the largest diameter in the sagittal or in the coronal plane of an MRI exam carried out on the same date as the axial MRI scan. However, its use is complicated and, sometimes, almost impossible following surgery or radiotherapy treatments because it becomes difficult to define the diameters to be selected (whether or not to include the post-treatment residuals and ill-defined tumor boundaries after treatment). It is also complicated to apply in the case of highly infiltrative DLGG. In spite of these limitations, it was important to study this method of volume estimation because of its wide use within the medical community. To our knowledge there has been no formal study comparing the results obtained by the three-diameters method with those acquired with the software-based volume reconstruction solution based on manual segmentations. A second purpose of this work is to address this topic by conducting a subjective study of the impact of the volume estimation method on tumor volume estimate. In the conclusion, we will present a series of recommendations, that are based on our results, regarding the relevance of the two tumor volume estimation methods.

It should be noted that part of this work has been published in the EMBC's international conference proceedings [12].

Subjective manual segmentation reproducibility's study:

Materials and methods

The subjective manual segmentation study of reproducibility was conducted in PROMETEE¹, the healthcare Living Lab in TELECOM Nancy, France. PROMETEE provides a standard environment that complies with the ITU-BT.500-13 recommendations for subjective tests to evaluate the quality of medical images and videos. The 32-bit free version of OsiriX software was adopted for the segmentation, as OsiriX is one of the best medical imaging softwares including segmentation tools and it is widely used among the neuro-oncology community. An expert neuroradiologist, who does not belong to the study panel, selected 12 longitudinal MRI scans in the axial plane from 9 DLGG patients. The MRI images in the study had 512×512 pixels in the axial plane and a number of slices ranging between 29 and 512. All exams were FLAIR-weighted but for one T2-weighted MRI exam. Moreover, there were 3 Cube MRI exams and 9 regular exams. CUBE MRI sequences are recent GE MRI exams that replace the conventional slice by slice, plane by plane, 2D MRI acquisition of a volume, enabling a single 3D volume scan. The CUBE MRI volume is isotropic, allowing a reconstruction with a similar resolution to that of the native plane. Moreover, sub-millimeter and ultra-thin slices help to better visualize the details of the lesions in the images. Raw, unformatted CUBE MRI dataset is longer to process, as in the case of our test dataset, where the number of slices for these sequences ranged between 256 and 512, with tumoral lesions present in around 100 slices sometimes. Nonetheless, it was important to integrate CUBE MRI exams to compare the results on these new sequences with those of conventional MRI sequences.

A panel of 14 experts was selected to perform the reproducibility test. This panel included 6 neurologists², 4 radiologists and 3 radiotherapists. Moreover, 8 participants had less than 10 years of experience whereas 5 participants had more than 10 years of experience. In order to be consistent with daily clinical practice, there was no specification on the radiological windowing and on the slices to be segmented. The only provided instruction was to delineate DLGG for each slice containing

¹ <http://prometee.telecomnancy.eu>

² Neurologists include neuro-oncologists and neurosurgeons

this tumor. The participants started by completing a visual test on a tablet to detect participants with vision problems. Then, they performed a segmentation on a training dataset whose results were excluded from the final study results. They went on delineating half the exams, taking a 5 minutes break and then completing the delineation of the rest of the exams. At the end, they provided information about their specialty and about their years of experience since residency. Afterwards, for each MRI exam, we saved the manual tracings and we reconstructed tumor volumes using OsiriX based on the Delaunay triangulation reconstruction method. An example of the manual segmentation of an MRI's slice during the test is displayed in Figure 1. Each colored curve corresponds to the segmentation performed by each participant.

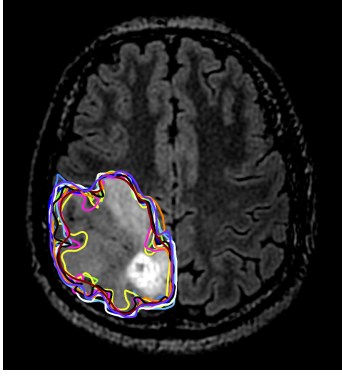


Fig. 1 Example of the manual segmentation of an MRI's slice with OsiriX. Each colored curve corresponds to the segmentation performed by each participant.

The first tests of consistency showed the incoherence of one participant's results. Thus, the following statistical results are based on the segmentations of the 13 consistent participants.

Statistical analysis tools

Let $(x_{i,j})_{i=1\dots 13,j=1\dots 12}$ be the variable corresponding to the 12 tumor volumes for each of the 13 participants. The first aim of this study is to assess the variability introduced by the practitioner factor on tumor volumes. For this purpose, a one-way analysis of variance (ANOVA) is applied on tumor volume $x_{i,j}$. The second aim of this study is to analyze the relationship between the participants' medical specialty as well as their years of experience and tumor volumes. Several objective metrics are applied to achieve this. Among these metrics, the coefficient of variation (COV) [10] quantifies the change in the segmented tumor volumes:

$$COV_j = \frac{\sigma_j}{\bar{x}_j} \quad (1)$$

\bar{x}_j is the mean volume and σ_j is the standard deviation by volume.

We also use the agreement index (AI) [9] which provides, for each volume, the inter-participants agreement, in pairs of participants:

$$AI_{(i,i'),j} = 1 - \frac{2|x_{i,j} - x_{i',j}|}{x_{i,j} + x_{i',j}} \quad (2)$$

for all pair of participants $(i, i'); i \neq i'; i, i' \in \{1, \dots, 13\}$. AI values are upper-bounded by 1 (perfect agreement between participants).

In order to estimate the inter-participant variability on a pixel level, the interoperator variance (IV) [9] is applied. This metric, computed for each commonly segmented slice of each exam, measures the overlap of two segmented regions by each pair of participants. It is defined by:

$$IV = 1 - \frac{A_{M_i} \cap A_{M_{i'}}}{A_{M_i} \cup A_{M_{i'}}} \quad (3)$$

A_{M_i} is the segmented area by participant i and $A_{M_{i'}}$ is the segmented area by participant i' . IV values vary from 0 (perfect matching of pixel values) to 1 (no matching of pixel values).

Finally, the results of the metrics above are confirmed by a Fisher's exact test which is a classical statistical test to use on a small sample of data as in our case [14]. We applied Fisher's exact test on the standard

deviation σ_{y_i} of the standard volume $y_{i,j}$, which is used instead of $x_{i,j}$ to account for the difficulty of segmentation. The standard volume $y_{i,j}$ is computed as follows:

$$y_{i,j} = \left(\frac{x_{i,j} - \bar{x}_j}{\sigma_j} \right) \quad (4)$$

Statistical analysis results

An ANOVA was performed on the segmented tumor volumes and, with a significance level of 5%, we concluded that the practitioner factor has no significant impact on the average values of the volume variable. Regarding the variability introduced by the medical specialization and the years of experience on the tumor volume variable, we computed the mean and standard deviation of the COV, AI and IV metrics for the different categories of medical specialty and of years of experience. The results are detailed in Tables 1 and 2. We can see that the different values are quite close. This was confirmed with a Kolmogorov-Smirnov test which is a classical statistical test to use on a small sample of data as in our case [15]. We applied the Kolmogorov-Smirnov test on the COV metric between pairs of groups (with a significance level of 5%).

It should be noted that tumor volume values are between 1.67 cm^3 and 117.35 cm^3 along the different MRI exams. This large variation in volume size makes COV values more sensitive to small volumes. These results are further confirmed thanks to Fisher's exact test. With a p-value equal to 0.604 for a significance level of 5%, Fisher's exact test could not prove that the medical specialization has a significant impact on the tumor volume estimation. As for the variability generated by the years of experience on the tumor volume variable, Fisher's exact test released a p-value of 0.8961, indicating, clearly, that the number of years of experience could not be shown to have a significant influence on the segmented volume.

Table 1: Mean and standard deviation of the COV, AI and IV by medical specialty.

Medical specialty	Neurology	Radiology	Radiotherapy
COV (mean±S.D.)	17.99 ±12.44	16.56 ±10.11	14.48 ±12.32
AI (mean±S.D.)	0.74 ±0.28	0.73 ±0.27	0.74 ±0.27
IV (mean±S.D.)	0.27 ±0.07	0.3 ±0.08	0.29 ±0.09

Table 2: Mean and standard deviation of the COV, AI and IV by years of experience.

Years of experience]0; 10]]10; +∞[
COV (mean±S.D.)	16.58 ±11.09	14.86 ±11.88
AI (mean±S.D.)	0.75 ±0.28	0.73 ±0.27
IV (mean±S.D.)	0.25 ±0.05	0.3 ±0.09

Comparison between the software-based manual segmentation method and the three-diameters method:

Materials and methods

We conducted a test in the Living Lab PROMETEE to compare the software-based manual segmentation method and the three-diameters method. For this study, we used the 12 MRI scans that we described in the previous section. In order to compute tumor volume with the three-diameters method, we also included for each MRI exam in the axial plane, the MRI scan in the coronal or in the sagittal plane. There were 11 exams in the sagittal plane and one exam in the coronal plane. For this test, we selected a participant from our previous study on the reproducibility of the manual segmentation of DLGG. This participant had tumor volume results in the previous study which were close to the average of the tumor volumes segmented by all the participants. This allows us to fairly compare tumor volumes obtained through manual segmentation and through the three-diameter method for DLGG dataset. The instruction given to the participant consisted in drawing, for each MRI dataset, the three largest diameters in the axial and in the sagittal/coronal planes. Similarly to our previous study, there was no specification on the radiological windowing and on the slices to be outlined. Figure 2 display an example of an MRI dataset in the study. The Figure shows the three largest diameters as defined in the axial plane and in the sagittal plane respectively.

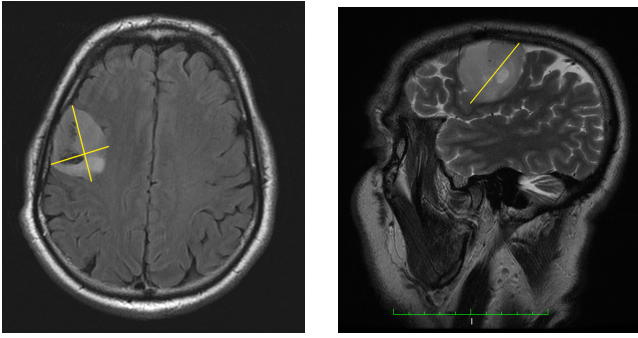


Fig. 2 Example of the two largest diameters as defined on an axial FLAIR-weighted MRI (left) and of the third largest diameter as defined on a sagittal T2-weighted MRI scan (right) in the study with the three-diameters method.

Once the participant had finished drawing the three diameters for all the datasets, we saved the ROIs and then we calculated tumor volume V using the approximative formula:

$$V = D1 \times D2 \times D3/2$$

Where $D1$, $D2$ and $D3$ are the three largest diameters in the 3 spatial planes cite1 [2] [13].

Experimental results and discussion

Tumor volume results are detailed in Table 3. This table presents the values of tumor volumes obtained with the three-diameters method ($3d$) as well as the average of the volumes acquired by software reconstruction from manual segmentations (Av) and the volumes obtained from the manual segmentations of this study’s participant (Vp). We can already notice that tumor volumes are very close. Table 3 also reports the max difference between $3d$ and volumes obtained from manual segmentations. This difference does not seem to be affected by the type of sequence as it is least important for exam 4, a CUBE FLAIR MRI, and most important for exam 12, another CUBE FLAIR MRI.

We started by plotting tumor volume variation curves with the two methods of volume estimation for all datasets. For the software-based manual segmentation method, we included the results of our participant in the previously described test in Figure 3 (green) as well as the average of the volumes obtained by all the participants (blue). We can thus see that the results of the participant in this study are very close to those of the average of all the participants. Moreover, as displayed in Figure 3, the values of the volumes with the three diameters method (red) and with the software-based manual segmentation method are close, especially for MRI datasets from 8 to 11.

In addition, results for CUBE FLAIR-weighted MRI scans (4, 9 and 12) do not appear to be affected by the choice of the volume estimation method. Indeed, two out of three CUBE FLAIR-weighted MRI datasets show very close results with both methods.

In order to objectively assess the results, we applied the Wilcoxon signed-rank test on all tumor volumes obtained by the two volume estimation methods ($3d$ and Av) with a significance level of 5 %. This test released a p-value equal to 0.9097. Consequently, we do not reject the null hypothesis considering that the volume distributions obtained by the two methods are the same.

Consequently, DLGG tumor volumes estimated with the three-diameters method are quite similar to those determined with a software-based manual segmentation approach. It should be noted that the MRI datasets represent relatively simple DLGG cases, with easily delineable tumor contours. Another test which will include more complex cases (post-surgery or post-radiotherapy MRI scans, highly infiltrating DLGG that are difficult to delineate) is in perspective for this work.

Conclusion: We evaluated the reproducibility of DLGG manual segmentation on MRI datasets with regard to practitioners, their years of experience and their specialty. Based on several commonly used criteria in the literature dedicated to inter-variability assessment, we could not prove that the practitioner factor, the medical specialty factor or the years of experience factor had a significant impact on the estimate of tumour volume, regardless of the type of MRI sequence (Cube sequence, vs. classical sequence). As automatic segmentation algorithms do not yet offer a reliable solution for DLGG, our study confirms the inter-observer reproducibility of manual contouring. This is absolutely essential considering that management of this type of tumor is necessarily multidisciplinary (including, among other practitioners, neurosurgeons, neuro-oncologists, radiotherapists and neuro-radiologists) and that, to date, this point had not yet been demonstrated. For the future, we continue this project by working on semi-automatic algorithms which, in case of correlation with the manual techniques, would save time for clinicians. Moreover, they would make patients’ monitoring and, thus, therapeutic evaluations and decisions more reliable.

Furthermore, we conducted a study to compare two tumor volumes’ estimation methods in the case of DLGG, namely the three-diameters method and the software-based manual segmentation method. The initial results presented on 12 DLGG MRI datasets reveal there is no statistically significant difference between the volumes estimated with the two approaches. We can therefore use the three diameters method for non operated patients in the case of Cube FLAIR MRI scans which are time-consuming to segment manually. If we consider the case of the example in Figure 4, which shows a FLAIR-weighted MRI slice in the axial plane of a diffuse low-grade glioma after a surgery, we can already see the limits of the three-diameters method. Indeed, in order to estimate the tumor volume using the three-diameters method, we need to draw the largest diameter in each of the three planes in space. If we limit ourselves to the two drawings on the axial plane in Figure 4, we quickly realize that we are facing difficult choices: Shall the postoperative cavity be included in the drawing or not? Which tumor residual should be included in the tracing knowing that it is impossible to join all the residuals together with a segment?

This example showcases the limitations of the three-diameters method in estimating tumors’ volumes after surgery. Since most patients diagnosed with DLGG are operated on some point during their follow-up, this method can not answer the problem of calculating the volume for similar cases. The technique based on manual contouring becomes, therefore, more appropriate. As DLGG in this study represent simple cases that are easy to delimit, another study with more complex examples is in perspective, particularly for post-surgery cases. Our ultimate aim is to assist clinicians in defining DLGG volumes as accurately as possible. Finally, we aim to compare these results to semi-automatic segmentations to propose adaptive medical recommendations. Selecting the most appropriate volume estimation method is key to achieve this, enabling a better follow-up of DLGG patients. This work is the starting point for proposing recommendations on which volume estimation method should be used for volume calculation in the case of DLGG. This Letter details our progress towards this goal.

Acknowledgment: Great recognition and thanks are due to all the clinicians from CHRU Nancy and CHR Metz who participated in this study. Namely, we would like to thank: Pr Serge Bracard, Pr Luc Taillandier, Dr Marie Blonski, Dr Basile Wittwer, Dr Guillaume Vogin, Dr Christian Delgoffe, Dr Claire Griffaton-Taillandier, Dr Marie-Alexia Ottenin, Dr Sophie Planel, Dr Fabien Rech, Dr Valérie Bernier, Camille Dahan, Dr Emanuelle Schmitt, Dr Lavinia Jager Simon and Dr Philippe Quetin.

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Table 3: Volumes obtained with the three-diameters method $3d$ and with volume reconstruction from manual segmentations Vp and Av and max difference between $3d$ and volumes from manual segmentations.

Exam number	1	2	3	4	5	6	7	8	9	10	11	12
3d (cm^3)	69.31	34.03	20.94	2.60	41.24	14.34	33.13	12.43	8.95	32.22	45.39	111.43
Vp (cm^3)	77.59	36.22	24.42	2.15	32.62	19.58	29.23	11.48	9.18	31.40	44.35	105.08
Av (cm^3)	77.02	39.51	28.04	2.64	32.48	17.91	30.07	11.85	9.36	29.95	44.74	99.19
Max differences (cm^3)	25.70	29.15	24.76	3.05	12.80	7.80	5.34	3.74	3.32	6.44	11.99	41.67

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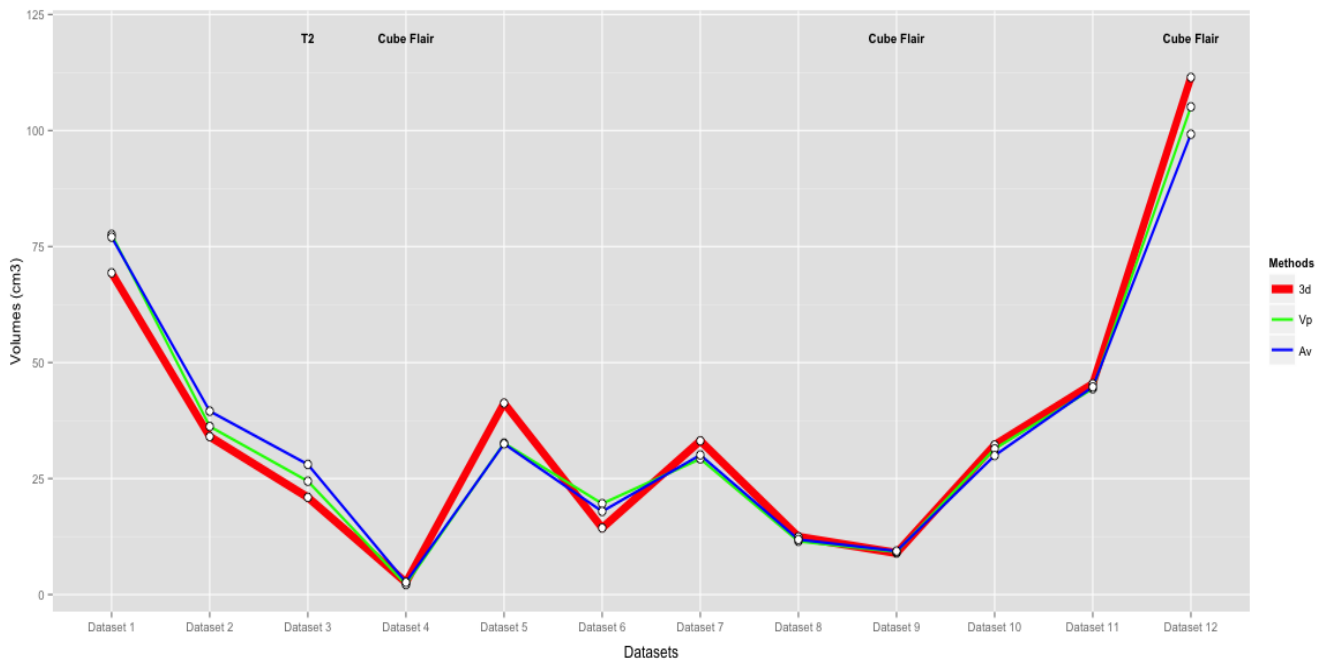


Fig. 3 Change in tumor volume based on MRI datasets with the three-diameters method (red) and with a software-based manual segmentation method for the average of the volumes obtained by all the participants (blue) and for the results of our participant in the previously described test (green).

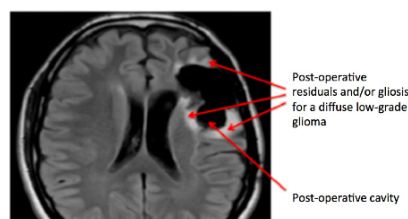


Fig. 4. Example of a FLAIR-weighted MRI slice in the axial plane of a diffuse low-grade glioma after a surgery.