

An Advanced Computer-Aided Diagnosis For Brain Glioblastomas Tumor Exploration Using MRI Modality Imaging

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Abstract

Purpose

Manual analysis of glioblastomas brain tumor explored by the Magnetic Resonance Imaging modalities lacks accuracy and could be considered as fastidious and time consuming. This research intended to offer an advanced Computer Aided Diagnosis ‘CAD’ tool capable of remedying several manual analysis practices and perhaps avoiding human errors during brain tumor surveying. Such an advanced process towards a novel CAD system would be convivial and efficient for glioblastomas brain tumor precise extraction, characterization, monitoring and inspecting their treatment response using different MRI exams.

Methods

Each MRI slice was skull-stripped by a proposed preprocessing approach based on thresholding and morphological operations. Tumor region would be extracted using fast distribution matching developed algorithm based on global pixel wise information. The proposed segmentation technique does not require a complex learning from a large training set, as was the case in the existing methods. In this work, regional parameters would be explored to characterize the brain tumor shape while some developed morphological parameters would be used to characterize the brain tumor shape. Such features would be involved to explore tumor evolution through periodical and different MRI exams, specifically in the purpose to evaluate their response to the addressed treatment.

Results

Experiments were carried out on a dataset of Flair-weighted (Flair) and T1-weighted post-contrast (T1C) MRI modalities including twenty eight pathological selected cases characterizing both high grade and low grade glioblastomas. These were attentively collected with around four to eighteen MRI various exams for each case in cooperation with Neuroradiology Department at Pitié Salpetrière Hospital (Pitié Salpetrière, Paris-France).

The preprocessing and region of interest extraction steps were validated using dice metric parameter compared to the manual segmentation provided by radiologists.

Conclusions

As carefully discussed with the clinical partner, experimental results showed that our proposed Computer Aided Diagnosis ‘CAD’ tool for glioblastomas brain tumor exploration achieves a good agreement. Hence, our proposed CAD system would support decision making and would speed up MRI scans’ analysis.

Keywords: Magnetic Resonance Imaging (MRI), Computer Aided Diagnosis ‘CAD’, Brain Glioblastomas tumor, Region Of Interest Extraction, Feature Extraction ,Tumor evolution monitoring, Treatment response

1. Introduction

Glioblastomas tumors could be considered as among serious pathologies threatening people of all ages since it represents about 17% of all primary brain tumors and about 60-75% of all astrocytoma. They increase in frequency with age, and affect more men than women. Only three percent of childhood brain tumors are glioblastomas (<http://www.abta.org/brain-tumor-information/types-of-tumors/glioblastoma.html>).

Referring to the statistics published by the American Brain Tumor Association, the median survival time is about 14.6 months for adults with more aggressive glioblastomas, treated by radiation therapy and with concurrent temozolamide.

Specific attention has to be made in order to explore such pathology to reduce its threat. The Magnetic Resonance Imaging (MRI) could be considered as one of the main modalities used to explore glioblastomas brain tumor for diagnosis, evaluation as well as for inspection of the addressed treatment effect. Glioblastomas brain tumor exploration is known to involve a large dataset in each exam and the diagnostic accuracy provided by radiologists’ medical image analysis is only about 75% (Kopec et al,2003).

During the past few years, Computer Aided Diagnosis (CAD) systems are considered as an emerging field of biomedical research attesting that advanced technologies affect a lot today’s medicine. Among the past few research works in the field of advanced medical imaging analysis, we could notice the scarcity of CAD system dedicated to glioblastomas brain pathologies’ exploration in order to explore and to inspect their addressed treatment response. Several works were interesting but not sufficiently adequate to respond to the clinical needs (Brown et al, 2000; Krupinski et al,2004), because they

cannot afford real clinical aid to survey and to inspect addressed treatment response.

The authors in (Arakeri et al,2013) presented an automatic computer-aided diagnosis (CAD) system to characterize brain tumors on MR images as benign or malignant case. The study in (Ambrosini et al,2010) presented a high level CAD system for brain tumor detection in a reducing time. Jaya et al (Jaya et al, 2011) used a metaheuristic based Parallel Ant Colony Optimization (PACO) approach in order to extract region of interest and developed a Computer Aided Diagnosis (CAD) system for the detection of brain tumor by using parallel implementation of ACO system. These studies did not offer the possibility to survey the brain glioblastomas tumor evolution.

Such an advanced tool would be then highly recommended since it would enable clinicians to be more and more efficient in brain tumor characterization making possible to inspect treatment response and hence to decide correctly adequate actions to conduct and even identify them at an earlier stage (Brown et al, 2000; Krupinski et al,2004).

In this paper, relying on several past debates with our clinicians' staff, a novel advanced CAD system approach has been investigated in order to explore glioblastomas brain tumor through several MRI scans. The main parts of CAD system dedicated to MRI scans' exploration for brain glioblastomas tumor pathologies would be the preprocessing step, the segmentation process that could yield to the features' extraction permitting tumor surveying progression and hence inspecting the treatment response. One software tool could be provided reassembling all these steps and could be exploited efficiently by the clinical staff.

As a preprocessing step, a skull-stripping approach based on thresholding and morphological operations has been proposed in this work in order to extract brain tissues from the whole MRI scans. The second step could be involved in brain tumor segmentation based on a fast distribution-matching data-driven algorithm through a Graph Cut tool. The third step of the proposed CAD would be related to features' extraction in order to characterize the brain tumor. The regional parameters were extracted to describe the texture changes of the suspicious region and morphological parameters in order to characterize the tumor shape. Each mentioned step was carefully investigated and validated with our clinicians.

The remaining of our paper was organized as follow: In Section 2, we present the related works as well as the motivations. Section 3 was devoted to the Methodology for Computer Aided Diagnosis 'CAD' System. The Experimental results and discussion would be presented in section 4. The conclusions of the current study were drawn in the final section of this paper.

1. Related Work and Motivations

Related Work up on CAD succeeding steps

The Preprocessing step was mainly performed to improve the image quality before engaging the segmentation process. The brain skull-stripping techniques could be highly recommended to facilitate and to ameliorate differentiation between essential brain tissues and extra cerebral features and could be

considered as a critical phase for various neuroimaging explorations. It could offer better segmentation results and reduce the computational time.

Numerous fully automatic skull-stripping approaches have been proposed in the literature. (Segonne et al,2004) proposed a Hybrid Watershed (HWA) approach and compared their performances with four existing skull-stripping methods: Free Surfer's original method (Dale et al,1999), BET toolbox (Smith et al,2002), a watershed algorithm (Hahn et al,2000), and BSE methodology (Shattuck et al,2001). HWA method relied on white matter connectivity to build an initial estimate of the brain volume and applied a parametric deformable surface model, integrating geometric constraints and statistical atlas information, to locate the brain boundary. (Prastawa et al ,2005)implemented an Expectation-Maximization approach to segment the major brain tissue classes and correct the intensity homogeneities. The study in (Cobzas et al,2007) used a nonlinear speed function at the hybrid level set based on an active contour neighborhood model to eliminate boundary leakage.

Segmenting the tumor would be considered as the most important task in the conceived CAD system which accounts for the active involvement of a lot of researchers in this field of investigation. A variety of tumor segmentation approaches has been proposed in the literature and could be classified into three distinguished groups: model-based methods, deformation-based methods, and cluster-based methods. The study in (Cobzas et al,2007)used high dimensional features set calculated from MRI data and registered atlases in order to segment brain tumor. A generative probabilistic model of tumor appearance has been proposed by (Menze et al ,2010)in order to segment brain tumor through different modalities. (Corso et al , 2008)used a Bayesian integration model to minimize the cost of a proposed graph approach to segment both brain tumor and edema.

The author in (Reza et al,2013) proposed fully automated multi-class abnormal brain tissues segmentation in multimodality brain MRI. A novel texture features such as piece-wise triangular prism surface area (PTPSA), and textons, along with intensity difference and regular intensity has have been used in order to characterize different brain tissues. A classical Random Forest (RF) classifier has been used for segmentation and classification.

(Tustison et al ,2013) proposed a novel approach for brain glioblastomas tumor segmentation. The proposed approach is based on the generation of a novel feature images and the concatenation of a random forest models in order to improve performances. Several review paper that addresses the brain tumor segmentation problem has been proposed in the literature (Gordillo et al ,2013; Balafar et al,2010; Patel et al,2014).

Features' extraction would be a very important task in order to characterize the brain tumor allowing ;precise surveying of its evolution and inspecting their treatment response through several MRI scans. The morphological parameters would be extracted in order to characterize the shape as well as the regional parameters to describe the texture changes of the tumor suspicious regions. Several past studies investigated in the features extraction step. This information has always been important allowing efficient diagnosis and higher accuracy especially for the next actions to be conducted. (Velthuizen et al,1999) proposed a genetic algorithm (GA) to estimate a feature set from multi-spectral MRI data in

order to provide a better starting point for the measurement and evaluation of the response of a brain tumor conducted treatment. Among the image processing tools, various studies were interested in a Discrete Wavelet Transform as a processing method to extract brain tumor features (Bagci et al,2007). Gray level Co-occurrence matrix has been also used by Haralick (Haralick et al,1973) in order to realize brain features extraction. Other studies used first and second statistical features extracted from a training point to describe brain tumor features (Caban et al,2009).

Monitoring radiographic brain glioblastomas tumor progression through several MRI exams could be considered as a great challenge to the neuroradiology and neuroncology community. Brain glioblastomas could be characterized by an irregular nature, a growth patterns and an inherent heterogeneous enhancement which makes their surveying process very difficult. Different criteria have been used in literature to detect tumor progression.

The Macdonald Criteria is based on the pathological region's area measurement to assess tumor progression (Macdonald et al,1990) and classify the progression into four classes: stable disease, complete response, partial response, progressive disease.

The Response Evaluation Criteria in Solid Tumors (RECIST Criteria) is based on the evaluation of the brain glioblastomas tumor diameters (Chinot et al,2013). This technique classifies patients into four groups: Complete response, Partial response, Stable disease and Progressive disease.

The World Health Organization(WHO) criteria used the sum of the estimated areas of all lesions based on the longest diameter by the greatest perpendicular diameter to classify patients into four classes: Complete response ,Partial response, No change and Stable disease (Suzuki et al,2008).

Motivations

The segmentation accuracy affects a lot the clinical interpretation of MRI scans. Manual segmentation is time consuming and can lacks of efficiency compared to the fully and semi-automatic process. As discussed with our clinical staff, one could notice the importance and the scarcity of CAD system dedicated to brain glioblastomas exploration in order to monitor their evolution and controlling their treatment response. This advanced tool allows the processing of a large dataset in a reduced time and could provide a better surveying in order to obtain more accurate and efficient diagnosis.

Motivated by the above needs, we are interesting to engage the following contributions useful for the development of an advanced CAD system for the detection and characterization of brain glioblastomas tumor in order to monitor their evolution and to control their treatment response through T1-weighted post-contrast (T1C) and Flair-weighted MR scans:

- Brain skull stripping using an automatic approach based on thresholding and morphological parameters.
- Brain glioblastomas tumor extraction through MRI scans using a fast distribution-matching data-driven algorithm. A non-parametric model distribution would be defined to characterize the

normal regions in the current data. Then, the segmentation process would be operated as the optimization of several cost functions of the same form, each containing in fact two terms: (i) A prior distribution matching, which evaluates a global similarity between distributions, and (ii) A prior smoothness to avoid the occurrence of small, isolated regions in the solution.

- Improving the accuracy of the proposed preprocessing approach by comparing obtained results with clinicians' manual segmentation
- Improving the efficiency of the developed brain tumor segmentation by comparing obtained result with clinicians' manual segmentation and through Multimodal Brain Tumor Segmentation (BraTS2012) data set.
- Glioblastomas brain tumor characterization by extracting significant morphological and regional parameters.
- Automatically surveying tumor evolution and inspect their treatment response through several MRI exams.

2. Proposed Methodology for Computer Aided Diagnosis 'CAD' System

[Figure.1](#) illustrates the flowchart of our proposed approach for CAD system dedicated to brain tumor exploring and that involves essential steps for characterization as well as surveying of brain glioblastomas tumors evolution through several MRI exams making possible the control of their treatment response. For one pathological case, and for its MRI exam, this developed methodology includes a preprocessing step, which consists in brain skull stripping process based on thresholding and morphological parameters, a ROI extraction step related to tumor characterization based on a non-parametric fast distribution-matching approach, a feature extraction step useful for characterizing the tumor. An evolution monitoring phase could be hence involved and consists to characterize tumor through several patient's MRI exams so to evaluate its progress and this could yield finally to the clinical decision which concerns the action to be conducted for glioblastomas treatment. The following sections detail and describe each step for the pathological considered case.

3.1. Region of interest 'ROI' extraction: Proposed segmentation methodology

Region of interest extraction could be considered as the most important task in the Computer Aided Diagnosis 'CAD' system since it could affect all following steps. In this section, we present the general formulation of our brain glioblastomas extraction approach. The proposed methodology does not require an intensive external training and present hence the advantage of an optimized execution time (<0.5s per image).

Preprocessing Methodology: the brain skull stripping process

MRI slices preprocessing could be generally used to enhance the image quality and to reduce noise. It could also regroup other processing stages such as skull stripping. However, the brain skull stripping

process from the MRI slices would be an important procedure in neuroimaging data analysis.

The proposed brain skull stripping approach applied on both T1-weighted post-contrast (T1C) and Flair-weighted images could be based on two techniques: Thresholding and morphological operations in order to eliminate extra cerebral tissue not as important as image information such as skull, eyeballs, and skin and to delimit essential brain tissue borders.

Thresholding and morphological operations are used to eliminate extra cerebral tissue. The scalp region is a bright part in flair/T1C brain MRI slices. Initially, from the first MRI slice, an intensity threshold value for the pixels of the input image is calculated using Otsu method (Liao et al,2001) on the flair image due to the white color of the extra cerebral features. We use a dilation operation using the disk structure element to enlarge the obtained zone. The dilation operation adds pixels to the boundaries of the scalp region. The number of pixels added from the scalp region depends on the size and shape of the disk structuring element which is fixed to 7. We multiply then the obtained results with the initial image, then, we get the image (d) as shown in [Figure.2](#)

Brain Glioblastomas Tumor Segmentation Formulation

The glioblastomas tumor region presents different gray level intensities compared to the safety brain tissue. Therefore, we can define two different parts: $\overline{\Omega_I}$ which represents the safety part ([Figure 3](#)) and Ω_I which represents the region which includes the tumor.

As depicted in Figure 3, we estimate a normalized non-parametric model M_I from the safety part of the MRI scans input $\overline{\Omega_I}$.

This model would enclose all the statistical information about the normal region in the MRI brain glioblastomas input image.

According to clinical neurology study, the glioblastomas tumors are generally located on one hemisphere due to their growth on glial cells [43]. In this context, the CAD' operator has just need to select a safety part recovered from both hemispheres in order to define the model M_I that enclose all the statistical information about the normal region in the MRI brain glioblastomas input image. The selection of the safety part could be performed depending on the following clinical cases:

- For clinical cases where the images could be easily divided in two symmetric parts (vertical symmetry) and one of them contains tumor, the operator could select easily the safety part when observing the initial image. If the tumor is located on the left part, the operator needs just to flip the image as described on the following explicative example ([Figure 4_a](#)) and the safety part could be recovered automatically by selecting the first half of the picture, otherwise the left part could be recovered without flipping the image.
- For clinical cases where it is difficult to segment hemispheres with a vertical symmetry, the operator could crop a safety part from the first image as depicted in the following explicative

example ([Figure 4 b](#)). The safety part could be then recuperated from any part from the zone which does not contain the tumor.

The main step of the algorithm consists then on finding within the region which contains the tumor, a region R_I whose intensity distribution most closely matches the estimated model M_I . We extract then the safety part from the pathological one, and therefore tumor glioblastomas region. We state the problem as the optimization of an energy function containing two principle terms: (1) an intensity distribution matching prior that measures a global similarity between non-parametric distributions, and (2) a smoothness prior that avoids the occurrence of small, isolated regions in the solution.

Let $I : \Omega_I \subset D_I \subset R^n (n \in \{2, 3\}) \rightarrow Z_I$ be an image function from a fixed domain Ω_I to the intensity space values Z_I .

D_I represents the whole domain of the input image I . Ω_I would be a subset of the whole image domain containing the tumor. [Figure 3](#) shows a typical T1-Gadolinium weighted. We can notice that the proposed domain can be divided in two different parts: Ω_I corresponds to the right-hand part of the image and represents the part which includes the pathological zone and his complement region,

$\overline{\Omega}_I = D_I \setminus \Omega_I$ which represents the safety part (left -hand part in [figure 3](#))

$M_I(z)$ would be the Kernel Density Estimate for the gray level distribution of $\overline{\Omega}_I$

$$\forall z \in Z_I \quad M_I(z) = \frac{\sum_{p \in \overline{\Omega}_I} K(z)}{A(\overline{\Omega}_I)} \quad (1)$$

Where $A(\overline{\Omega}_I)$ denotes the area (or volume) of $\overline{\Omega}_I$, and $K(z)$ is a kernel function, typically Gaussian:

$$K(z) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{\|z-\mu\|^2}{2\sigma^2}\right) \quad (2)$$

Where μ is the expected value and σ is the kernel width.

The normal distribution approximation has been used in this work in order to estimate the best kernel width σ .

M_I represents a prior model, which includes all the statistical information about $\overline{\Omega}_I$. The main step of the algorithm consists of finding within Ω_I (i.e., the abnormal part) a region R_I whose intensity distribution most closely matches model M_I (Refer to [Figure 3](#) for a typical example). We obtain therefore the safety part which represents the non-tumor region in Ω_I , and consequently the glioblastomas tumor region: $\Omega_I \setminus R_I$.

The problem could be stated as the minimization of a discrete cost function with respect to a binary labeling $L_I : \Omega_I \rightarrow \{0, 1\}$, $R_I = \{p \in \Omega_I \setminus L_I(p) = 1\}$ which defines a variable partition R_I of Ω_I corresponding to the safety part and $\bar{R}_I = \{p \in \Omega_I \setminus L_I(p) = 0\} = \Omega_I \setminus R_I$ which corresponds to the tumor region.

The optimal labeling is acquired by minimizing a global cost function containing a non-linear distribution matching constraint based on the Bhattacharyya measure and a smoothness constraint.

To introduce the cost function, let us first introduce the following notations for any binary labeling $L_I : \Omega_I \rightarrow \{0, 1\}$:

- P_{R_I} is the Kernel Density Estimate (KDE) of the distribution of R_I region.

$$\forall z \in Z_I \quad P_{R_I}(z) = \frac{\sum_{p \in R_I} K(z)}{A(R_I)} \quad (3)$$

Where $A(R_I)$ denotes the area of R_I .

- $B_z(f, g)$ is the Bhattacharyya coefficient, which measures the amount of overlap between two distributions f and g defined over a set of values Z_I :

$$B_z(f, g) = \sum_{z \in Z_I} \sqrt{f(z)g(z)} \quad (4)$$

Our purpose consists of finding an optimal labeling L_I^{opt} that minimizes the following cost function:

$$L_I^{opt} = \min_{L_I : \Omega_I \rightarrow \{0, 1\}} F_I(L_I) \quad (5)$$

With

$$F_I(L_I) = -B_z(P_{R_I}, M_I) + \lambda S(L_I) \quad (6)$$

$-B_z(P_{R_I}, M_I)$ represents the distribution matching term

$\lambda S(L_I)$ represents the smoothness term.

$S(L_I)$ is a smoothness prior, which regularizes the segmentation boundary (Boykov et al, 2004) :

$$S(L_I) = \sum_{\{p, q\} \in N} r_{p,q} \delta_{L_I(p) \neq L_I(q)} \quad (7)$$

With

$$\delta_{x \neq y} = \begin{cases} 1 & \text{if } x \neq y \\ 0 & \text{if } x = y \end{cases} \quad \text{and} \quad r_{p,q} = \frac{1}{\| p - q \|} \quad (8)$$

N is some neighborhood system containing all pairs $\{p, q\}$ neighboring elements in Ω_I .

The prior smoothness (or regularization) permitted to avoid the occurrence of small, isolated regions in the solution. λ is a positive constant regularization parameter that balances the relative contribution of the distribution matching term and the regularization term. L_I^{opt} will give an optimal boundary-smooth region, $R_I^{opt} = \{p \in \Omega_I \setminus L_I^{opt}(p) = 1\}$, whose intensity distribution most closely matches M_I . This optimal region would be expected to correspond to the non-tumor region or non-edema region in Ω_I . Therefore, the tumor (or edema) region would be finally computed from L_I^{opt} as follows:

$$SR_I = \Omega_I \setminus R_I^{opt} = \{p \in \Omega_I / L_I^{opt}(p) = 0\} \quad (9)$$

The distribution matching term in (6) is a higher-order (non-linear) functional, which is difficult to optimize (Mitiche et al,2010; Mukherjee et al,2011). It has an analytical form that cannot be directly amenable to fast optimizers such as graph cuts (Mikheev et al,2008) or convex-relaxation techniques (Mitiche et al,2010). In the segmentation literature, such non-linear terms are commonly optimized via standard gradient-descent procedures, e.g., active curves and level sets (Mukherjee et al,2011) which result in computationally intensive algorithms (Pham et al,2011).

In this work, we use the recent bound optimization algorithm in (Pham et al,2011). Rather than optimizing directly the initial functional (i.e the Bhattacharyya coefficient in our case), one can solve a sequence of easier sub-problems, each corresponding to a bound of the functional.

$A(u, u^i)$ represents an auxiliary function of a cost function $F_I(u)$ if it satisfies the behind conditions:

$$\begin{aligned} F_I(u) &\leq A(u, u^i) \quad , i > 1 \\ F_I(u) &= A(u, u) \quad \forall u : \Omega \rightarrow \{0,1\} \end{aligned} \quad (10)$$

We optimize iteratively a sequence of instrumental functions, denoted $A(u, u^i), i \geq 1$, in which i denotes the iteration number, and whose optimization is easier than $F_I(u)$. At each iteration i , we can define the following auxiliary function :

$$u^{i+1} = \arg \min_{u \in \{0,1\}} A(u, u^i) \quad , i \geq 1 \quad (11)$$

Using the equality and inequality constraints in (10), one can show that the sequence of solutions in Eq. (11) yields a decreasing sequence of $F_I(u)$:

$$F_I(u^i) = A(u^i, u^i) \geq A(u^{i+1}, u^i) \geq F_I(u^{i+1}) \quad (12)$$

Furthermore, $F_I(u^i)$ is lower bounded and, therefore, converges to a minimum of F_I .

The authors of (Mukherjee et al,2011) derived an auxiliary functional of the Bhattacharyya measure. They further showed that such auxiliary functional is amenable to fast graph-cut optimization using the Boykov-Kolmogorov algorithm (Mukherjee et al,2011). The bound-optimization process in (Mukherjee et al,2011) converges within several iterations (typically less than 5).

In this work, we used the auxiliary functional in (Mukherjee et al,2011) and the Boykov-Kolmogorov algorithm (Boykov et al,2004). Further details on this auxiliary functional and bound optimization can be found in (Mukherjee et al,2011) Also, the graph-cut algorithm of Boykov and Kolmogorov (Boykov et al,2004) is well established in the computer vision literature. Therefore, we omit the details of graph cut optimization here.

Flowchart of the Brain glioblastomas Tumor Segmentation Algorithm

The complete steps of the proposed brain glioblastomas tumor segmentation algorithm are illustrated in [Figure 5](#)

3.2. Brain Glioblastomas Feature Extraction: Morphological parameters and Regional parameters

The manual brain glioblastomas characterization seems to be a tough task for clinicians and could lacks accuracy due to the large data set included in each MRI exam especially in the surveying process. Some essentials parameters were extracted automatically in order to describe brain glioblastomas tumor through several MRI exams to realize the evolution monitoring and inspect their treatment response. Morphological parameters were used to characterize brain glioblastomas tumor shape as well as the

regional parameters were described tumor texture alteration.

Morphological Parameters

As discussed with our clinicians staff, the evaluation of the tumor shape through the morphological parameters computation is one of the discriminating features for brain glioblastomas characterization and also in monitoring evaluation and control their treatment response. In this paper, some morphological parameters such the area, the volume, the perimeter , Elliptic Normalized Circumference (ENC) and solidity were developed. [Table 1](#) provides the morphological parameters used in this study with their mathematical formulation.

NB represents the total number of the pixels constituting the tumor.

SR is the screen resolution.

nb_{per} is the total number of the pixels constituting the tumor perimeter.

The factors 6.4516 and 2.54 come from the conversion of an inch to cm.

The area and volume computation seems to be very important for radiologists since it could provide information about the mass size evolution and therefore considered as a surrogate marker. It could be heavily relied upon to assess response to therapy in recurrent malignant glioblastomas.

Accurate perimeter measurements of glioblastomas shrinkage could offer more information to radiologists about the tumor treatment partial response.

The Elliptic Normalized Circumference (ENC) gives information about tumor shape. To get its value, we draw automatically the closest ellipse to the tumor lesion as seen in [figure 6](#). The ENC could take values in the interval [0 1]. The Higher value indicates that tumor has an elliptical shape and does not contain several speculations.

The Solidity parameter gives information about the lesion shape irregularity. It is calculated as the ratio of the lesion area to the convex hull area as shown in [figure 7](#).

Regional parameters

MR images hold a large amount of texture information that may be relevant for clinical diagnosis. However, treatment process such as chemotherapy and radiation may generate textural change that can be quantified through textural analysis in order to get more information about the lesion. The MRI exams acquisition is related to two principle parameters which are the Repetition time (TR) and the Echo time (TE). The Repetition time (TR) represents the time between successive applications of radiofrequency pulse sequences and the Echo time (TE) represents the delay before the radiofrequency energy radiated by the tissue in question is measured. The same values for these parameters have been used MRI exams for each clinical case, the regional parameters based on the tumor intensity distribution could be used in order to describe the tumor texture during the treatment process. The clinicians suggest evaluating the contrast, the entropy and the homogeneity parameters because they could give information about the homogeneity and the hyper / hypo vascularization of the tumor.

[Table 2](#) gives the detailed mathematical formulation of the above-mentioned regional parameters.

These parameters precisely describe the brain glioblastomas tumor evolution allowing hence for an accurate and an efficient surveying through several MRI exams.

3. Experimental Results: Towards a Monitoring System

The input dataset consists of T1-weighted post-contrast (T1C) and Flair-weighted cerebral MR images of twenty eight pathological cases with various cerebral MRI exams carried out at least twice for each patient (13 females and 15 males) with identified high-grade and low-grade tumors (18 high-grade and 10 low-grade). The patients' ages were in the range of 31–93 years (mean age 62 years). The images were acquired using 3T MRI clinical scanner at Pitie Salpetriere hospital, Paris-France. This clinical heterogeneous database could hence involve in fact enough possible cases for our research, and therefore, it could be considered as realistic testing benchmarks. The MRI input exam images were in Neuroimaging Informatics Technology Initiative (nifty) format with each having a slice thickness of 5 mm. The software SPM8 was used to read this image extension of images files.

T1 Gadolinium -weighted post-contrast and Flair-weighted MR images were used in the experiments as they provide important diagnostic information and appreciable contrast.

The T1 Gadolinium -weighted post-contrast images are characterized by a Repetition time (TR) equal to 820 and an Echo time TE equal to 11 for all MRI exams.

The Flair-weighted MR images are characterized by a Repetition time (TR) equal to 9002 and an Echo time TE equal to 155.5 for all MRI exams.

As mentioned above, our objective in this study consists in detecting, characterizing and surveying tumor evolution according to successive cerebral MRI exams.

Reiterating the preprocessing step and ROI extraction were used to detect the brain tumor for each MRI exams' slices whereas the features extraction was used to characterize and to survey the tumor evolution during the treatment process.

4.1. Segmentation Results

The proposed CAD system involves fully automatic extraction preprocessing algorithm and semi-automatic brain tumor segmentation one on cerebral MR images. The proposed tool was able to perfectly extract the brain tissues in all the cases as well as the tumor region by perfectly distinguish between normal and abnormal tissues and extract the tumor region in all MRI exams of all pathological cases in nearly real time (<0.5s per image simulation time). The extracted part is then used in the characterization process in order to survey the brain tumor evolution during several exams using MRI modality.

Simulation Results

We report these segmentation results of the proposed approaches over the clinical dataset. This section was further supported by several visual illustrations, which depict typical examples of the obtained results using the different types of images in the data set. We apply the brain extraction algorithm on both

flair and T1 Gadolinium modalities.

[Figure 8\(a\)](#) illustrates the initial Flair weighted MR images of the high-grade glioblastomas brain tumor cases from the collected dataset. [Figure 8\(b\)](#) shows the skull stripped image. The brain glioblastomas tumor is delimited by a green line as illustrated in [Figure 8\(c\)](#). [Figure 8\(d\)](#) shows the region of interest which will be used in the feature extraction process in order to characterize brain glioblastomas tumor and then realize surveying process by monitoring the evolution and controlling their treatment response.

Validation

The evaluation of the obtained brain skull stripping results was performed through a quantitative comparison with the results of a manual segmentation provided by our clinician's staff. We evaluate Dice Metric (DM) parameter between the automatic skull stripped results and the manual brain tissue delimitation. DM takes values within the interval [0, 1], where 1 would refer to as a perfect match and 0 represents a complete mismatch. [Figure 9](#) illustrates the Mean Dice Metric (MDM) as function of the case clinical number.

Our proposed skull stripping approach achieves a good agreement with a mean dice metric value of 0.8496 which attests his performance.

The manual segmentation of brain glioblastomas tumor was carried out by two experienced radiologists denoted R₁ and R₂. [Table 3](#) illustrates the quantitative results obtained by computing DM parameter between obtained CAD 'segmentation (AS)' and manual segmentation provided by the first radiologist M_{R1} as well as the second radiologist M_{R2}.

The obtained results of the semi-automatic segmentation provide a good DM value comparing to the expert radiologists' manual segmentation. The MDM are greater than 0.9 attesting the good performance of the proposed approach for all studied clinical cases. Hence, we could affirm that the proposed methodology offers to clinicians a robust, consistent and accurate region of interest extraction.

The proposed segmentation methodology was also validated using the Multimodal Brain Tumor Segmentation (BraTS2012) dataset (<http://www2.imm.dtu.dk/projects/BraTS2012>).

BraTS 2012 regroups 80 training data and 30 testing data. A publicly available set of training data could be downloaded from Kitware/MIDAS or from the Virtual Skeleton Database. The training data regroups real and simulated data. It consists of multi-contrast MRI scans (T1, T2, FLAIR, and post-Gadolinium T1) of both low-grade and high-grade glioma patients with expert annotations for 'active tumor' and for 'edema'. The simulated images closely follow the conventions used for the real data, except that their file names start with 'SimBraTS'.

All MRI scans and ground truth segmentations are stored using unsigned 16 bit and unsigned 8 bit integers, respectively. All volumes were linearly co-registered to the T1 contrast image, skull stripped, and interpolated to 1mm isotropic resolution. The MRI scans were distributed in the ITK- and VTK-compatible MetaIO file format and stored as signed 16-bit integers, but only positive values could be used. The manual segmentations (file names ending in 'truth.mha') have only three intensity levels: 1 for edema, 2 for active tumor, and 0 for everything else.

The testing data could be similar to the training data, except that the reference segmentation is not

publicly available. Segmentation results should be uploaded directly to the evaluation page to obtain dice metric score.

[Table 4](#) and [Table 5](#) illustrate the quantitative evaluation through both Training dataset and Testing dataset.

The obtained results attest that our algorithm yields a highly competitive performance among existing competing methods with an interesting computing execution time (less than 0.5s per image execution time)

4.2. Feature Extraction and Evolution Monitoring

In this section, we characterize and monitor the evolution of the brain glioblastomas tumor using the morphologic and regional parameters through several MRI exams.

As discussed with our clinicians' staff, the main morphological parameter used to evaluate and monitor tumor evolution is volume. Due to the lack of 3D exams for some clinical cases, they also suggest to compute area and perimeter parameters through several MRI exams. The Elliptic Normalized Circumferences (ENC) as well as the solidity parameters could help radiologists to evaluate the tumor invasion through successive MRI exams since they evaluate the tumor contour development. Their values are between 0 and 1. The lower value could be explained clinically by the presence of several speculation and irregularity due to the invasion and the rapidly growth of the tumoral cells on the nearest safety tissue.

The malignant tumors could be characterized by a heterogeneous texture due to the rapidly growth of the hyper functional tumoral cells. This hyper functionality is due to the vascularization taken from the surrounded safety tissue. Evaluating the homogeneity parameter allows radiologists to evaluate the tumor vascularization evolution.

The necrotic cells appears as black zone in The T1 Gadolinium -weighted post-contrast images and in the Flair-images which may lead to the homogeneity and contrast change of the tumor texture.

The entropy parameter evaluates the disorder in the tumor texture. Brain tumor texture changes could affect a lot the entropy measure. The increase of the value entropy could be explained by the presence of different textures such as the vascularization, the necrosis, the fibrosis...

The first presented clinical case represents a low-grade glioblastomas of a 41 years old patient with fourteen MRI exams. [Figure 10](#) illustrates the morphological parameters evolution during the treatment. As depicted in [figure 10](#), the area value has been increased by 53% indicating a partial response to the treatment (Macdonald et al,1990) . The volume parameter has been decreased by 49% as well as the perimeter value which has been decreased by 51%.

The ENC as well as the solidity parameter values have been decreased during the treatment process which attest that the tumor contour have less irregularity comparing with the first MRI exam due to the non-invasion of the new tumor cells.

[Figure 11](#) illustrates the three selected regional parameters evolution which are entropy, contrast and

homogeneity for a low grade glioblastomas tumor through fourteen MRI exams.

As depicted in [figure 11](#), the entropy value has been decreased, attesting that the brain tumor texture could be considered as more ordered due to the less vascularization of the tumoral cells and the augmentation of the necrotic zone.

Contrast parameter has been decreased through fourteen successive MR scans attesting that the tumor texture becomes darker due to the necrosis zone which appears in black color on T1C and Flair modalities.

We notice that the brain glioblastomas texture homogeneity has been increased during the treatment process. The texture homogeneity value has been increased by 0.04% attesting the partial glioblastomas tumor response to the treatment since there is no new tumoral cells growth.

These obtained results could affirm the partial response to treatment of the low-grade brain glioblastomas and therefore offer to clinicians more information about the tumor nature.

The second presented clinical case represents a high-grade glioblastomas of a 56 years old patient with nine consecutive MRI exams. [Figure 12](#) illustrates the morphological parameters evolution during the treatment. We notice that the proposed morphological parameters change values during the treatment process. The area, the volume have been increased through the four first exams and have been decreased later until the seventh exams. They have been increased later on the eighth and ninth exams. The perimeter value has been doubled between the first and the last MRI exam.

The ENC as well as the solidity parameter values have been increased during the treatment process attesting the brain tumor glioblastomas tumor contour irregularity augmentation due to the rapidly growth of the tumoral cells and their invasion on the surrounded safety tissue which confirms the malignity of such tumor.

The morphological parameters evolution could attest that the brain glioblastomas tumor don't respond adequately to the treatment which affirms the malignity of the proposed pathological case.

[Figure 13](#) illustrates the regional parameters evolution for a high-grade glioblastomas tumor through nine successive MRI exams. The entropy measure has been increased during the MRI exams, which implies a transition from an ordered to less ordered state attesting the non-response to the treatment due to the hyper vascularization of the new tumor cells. The contrast measure has been increased attesting that the tumoral texture is lighter due to the presence of new pathological cells and the reduce number of the necrotic zone which confirms the tumor growth during the MRI exams.

The texture homogeneity value has been also decreased by 0.49% attesting the heterogeneity of the malignant tumor due to the hyper vascularization of such pathology.

The regional parameters evolution attests that the proposed pathological case could be classified as a progressive disease.

4.3 Monitoring Evolution and Action to Conduct

Based on the obtained feature extraction results from the first MRI exam, our proposed CAD system for

Brain tumor exploring allows the radiologists to classify the brain glioblastomas tumor as High Grade or Low Grade tumor. By the time where it is diagnosed, the biggest challenge consists in the accurate disease monitoring to establish whether patients are responding to treatment or not. To address this need, we apply the preprocessing, the Region of interest and the features extraction steps on several MRI exams in order to make surveying process easily for clinicians. The Macdonald Criteria (Macdonald et al,1990) has been used in this work in order to survey brain glioblastomas evolution through the several considered MRI exams. This criterion is based on the area measurement evolution. A complete response to the treatment could be occurred when all enhancing tumor on the MRI consecutive scans at least one month is disappeared and the patient stability is improved. The second class is the partial response which is characterized by a 50% increase of the area lesion. The third class is the progressive disease and it could be characterized by a 25% increase in tumor size. Stable disease occurs in all left behind situations.

Based on the mentioned feature extraction, the radiologists could be able now to more understand the brain glioblastomas tumor progression and therefore prescribe the adequate treatment to the patient. For example, the surgery process, largely used for tumor treatment, and which could be indicated to remove the cancerous region, could be somehow impossible when glioblastomas growth near the parts of the brain that control important functions such as language and coordination.

Other actions to conduct that could be efficiently addressed with the aid of the proposed CAD system could include radiation and chemotherapy. For example, Chemotherapy with controlled temozolomide is generally prescribed to limit the cell glioblastomas tumor growth that could not be removed with surgery. The use of antiseizure and antiepileptic drugs is also recommended in order to reduce glioblastomas brain tumor size.

Radiation therapy uses ionizing radiation to attack malignant cells. It is commonly applied to the cancerous tumor because of its ability to control cell growth. Such serious action could be also controlled and somehow optimized. Some brain glioblastomas tumor requires the combination of the radiation and the chemotherapy treatment that could carefully controlled and optimized.

5. Conclusion

Among the major clinical difficulties met during brain glioblastomas tumor, surveying process in medical image analysis could be due to their unpredictable evolution. MRI scans would be considered as the most useful image modality exam that permits inspection and exploration.

Inspect glioblastomas tumor treatment response is a very important task since it helps radiologists to provide an accurate diagnosis and adequate treatment. Some of the earlier Computer Aided Diagnosis ‘CAD’ dedicated to MRI brain glioblastomas tumor surveying did not rigorously afford clinical aid especially regarding the adequate and/or the optimized treatment and actions to conduct.

An accurate and efficient Computer Aided Diagnosis ‘CAD’ was developed and validated providing a surveying of brain glioblastomas tumor through several MRI exams. The preprocessing step was

carefully conceived and was based on thresholding and morphological operations that achieve a good performance comparing to radiologists' manual segmentation. The segmentation methodology based on Graph Cut tool has been first validated through BraTs 2012 dataset to attest performances comparing to existing ones. Evaluating our segmentation methodology through Brats2013 dataset as well as expected Brats2014 datasets will be a prospect to enhance our CAD system. A comparison with manual segmentation provided by two experimented radiologists has been presented and shows that our proposed segmentation approach achieves a good agreement. Based on distribution matching criteria, the proposed algorithm is semi-automatic and removes the need of an external learning from a large, manually-segmented training set, unlike most of the existing methods. However, the proposed method has few limitations.. In fact, the poor image quality or image artifacts could affect gray level intensity characteristics and may lead to inaccurate segmentation of brain tumor and even its edema. Moreover, for some low grade glioma, the regions of interest appear in low contrast regions and therefore it affects the segmentation results could be affected. There are also some difficulties when segmenting metastasis tumors because such tumors could affect the brain tissues in several zones. Finally, if the tumor is very invasive, recover a safety part could be considered as a heavy task.

The proposed morphological and regional parameters permitted to better characterize the tumor shape and texture and inspect their treatment response through several MRI exams. The main purpose behind this research was of course to make advances and progress for clinical actions in order to help radiologist in their diagnosis. Clinical decisions and guidelines would be hence so more exact when such Computer Aided Diagnosis 'CAD' could assist clinicians during the treatment process ensuring more accuracy, objectivity and save a lot of time.

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Tables

Table 1. Morphological parameters for brain glioblastomas tumor characterization

Morphological parameters	Formulation	Unit
Area	$\frac{NB * 6.4156}{SR}$	Cm ²
Perimiter	$\frac{nb_{per} * 2.54}{SR}$	Cm
Volume	NOMBRE _{voxel} *VOLUME _{voxel}	Cm ³
Elliptic Normalized Circumferences (ENC)	$\frac{Tumor \ perimiter}{Best \ Ellipse \ perimiter}$	-
Solidity	$\frac{Contour}{Convex \ Hull}$	-

Table 2. Regional parameters for brain glioblastomas tumor characterization

Regional parameters	Formulation
Homogeneity	$\sum_{i,j} \frac{\overline{R_I(i,j)}}{1+ i-j }$
Entropy	$-\sum_i \overline{R_I(i)} \log_2(\overline{R_I(i)})$
Contrast	$\sum_{i,j} i-j ^2 (\overline{R_I(i,j)})$

Table3: Comparison of automatic segmentation and manual segmentation

cases	A_S versus M_{R1}	A_S versus M_{R2}
1	0.89	0.90
2	0.92	0.91
3	0.95	0.94
4	0.92	0.91
5	0.90	0.92
6	0.94	0.93
7	0.88	0.90
8	0.93	0.92
9	0.91	0.93
10	0.87	0.89
11	0.96	0.95
12	0.85	0.87
13	0.91	0.92
14	0.94	0.93
15	0.96	0.95
16	0.97	0.86
17	0.89	0.91
18	0.92	0.89
19	0.94	0.92
20	0.93	0.90
21	0.95	0.94
22	0.88	0.90
23	0.91	0.89
24	0.89	0.92
25	0.93	0.94
26	0.92	0.91
27	0.87	0.88
28	0.92	0.93
MDM	0.9161	0.9093

Table4: Overall DM quantitative Evaluations (Training data)

Dice Mean	Real cases	Simulated Cases
Zikik et al,2011	0.6175	0.7025
Bauer et al,2011	0.5175	0.715
Geremia et al,2011	0.5125	-
Hamamci et al,2011	0.595	0.48
Proposed Method	0.85	0.89

Table5: Overall DM quantitative Evaluations (Testing data)

Dice Mean	Real cases	Simulated Cases
Wei Yang	0.92	0.82
Nagesh Subbana	-	0.75
Liang Zhao	-	0.82
Stephan Bauer	0.87	0.75
Bjoern Menze	0.76	0.78
Darko Žikic	0.91	0.75
Andac Hamamci	-	0.72
Raphael Meier	-	0.65
Tammy Riklin Raviv	-	0.54
Ezequiel Geremia	-	0.62
Hoo-Chang Shin	0.34	0.30
Proposed Method	0.77	0.88

Figures

Figure1: Proposed CAD system Flowchart

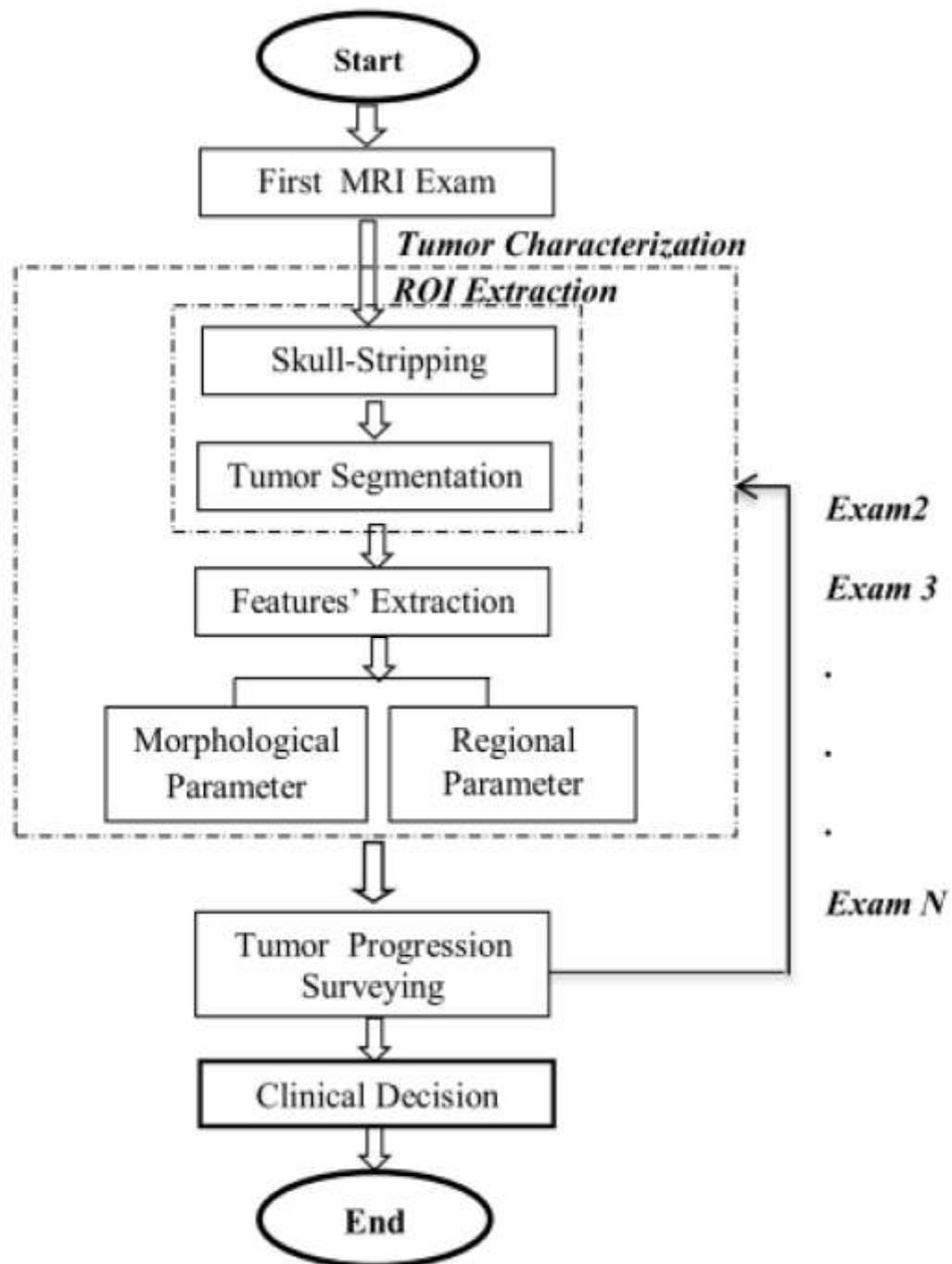


Figure2: Preprocessing steps for the CAD system

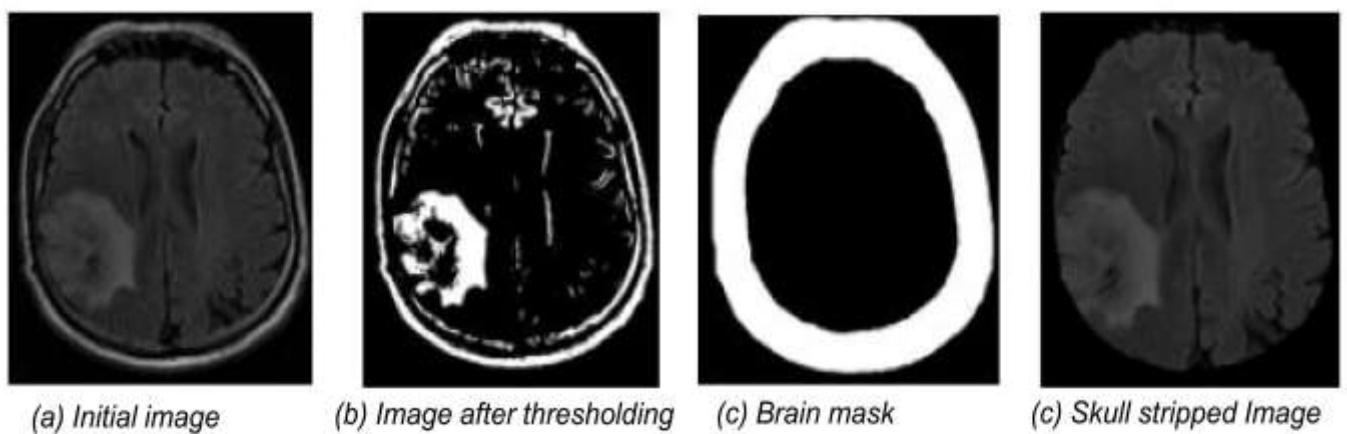


Figure 3. Illustration example for brain Glioblastomas segmentation

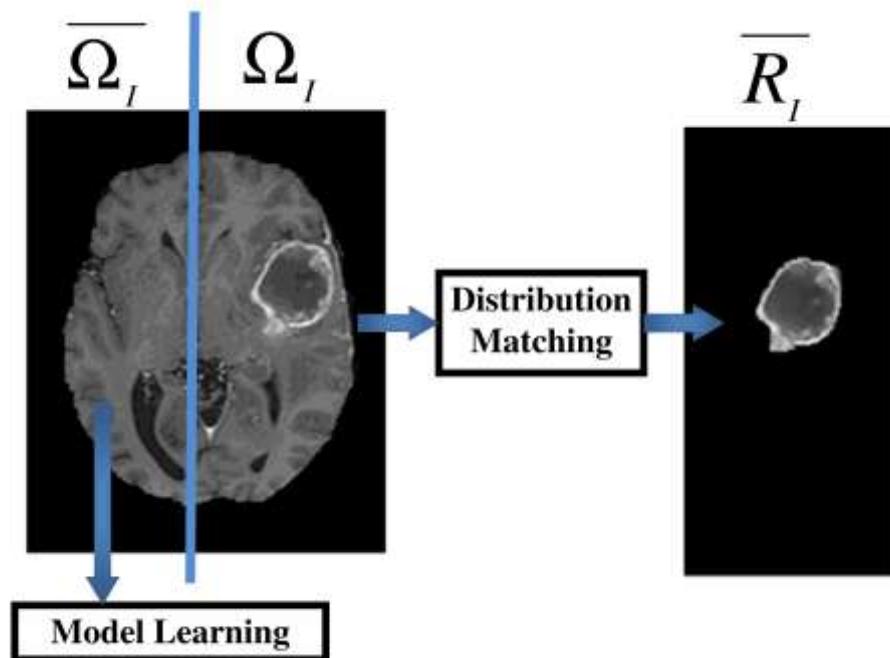


Figure 4. Illustration examples for the model M_I learning: (a) for Symmetric cases (b) Other cases

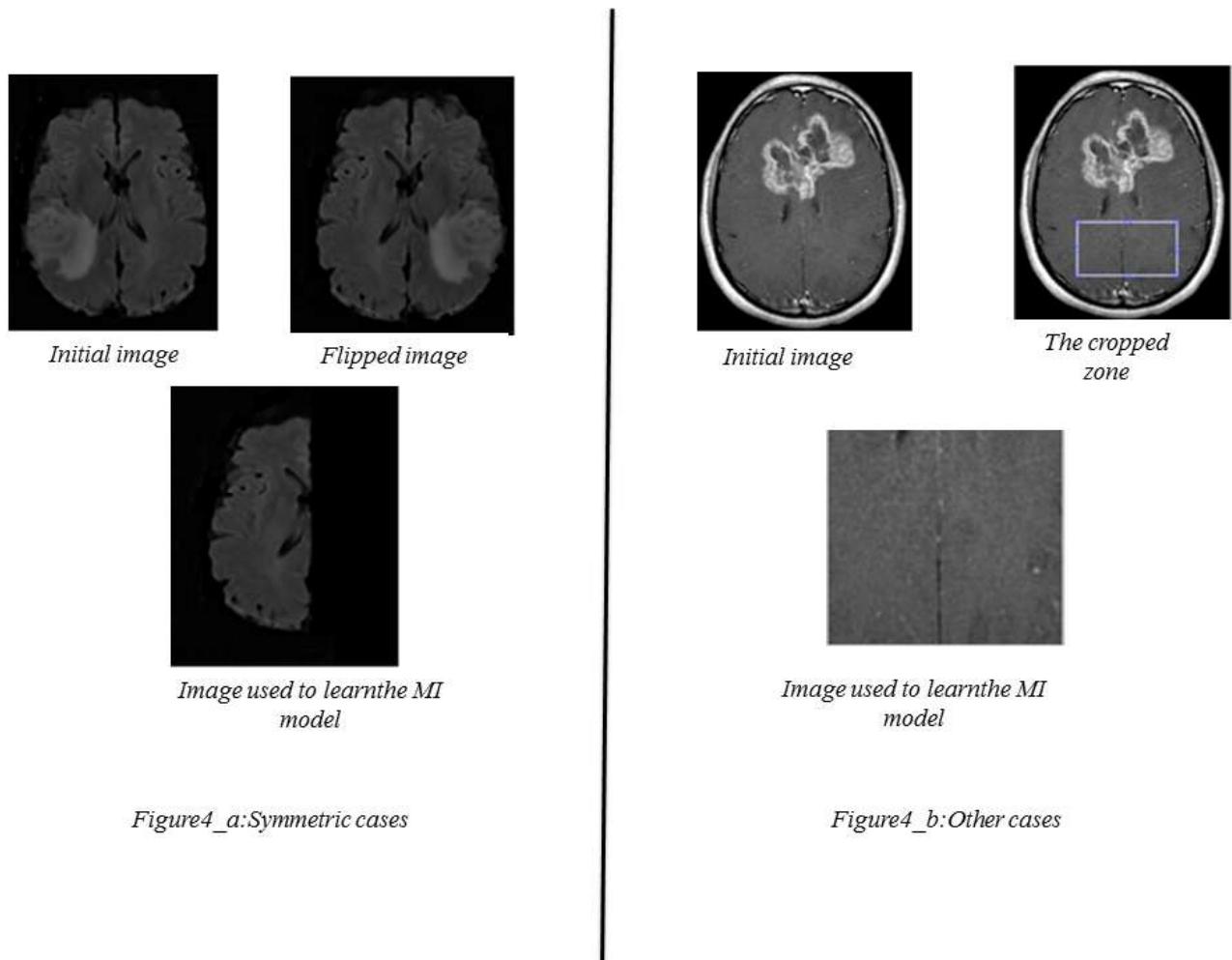


Figure 5: Flowchart of the Brain Glioblastomas Tumor Segmentation Algorithm

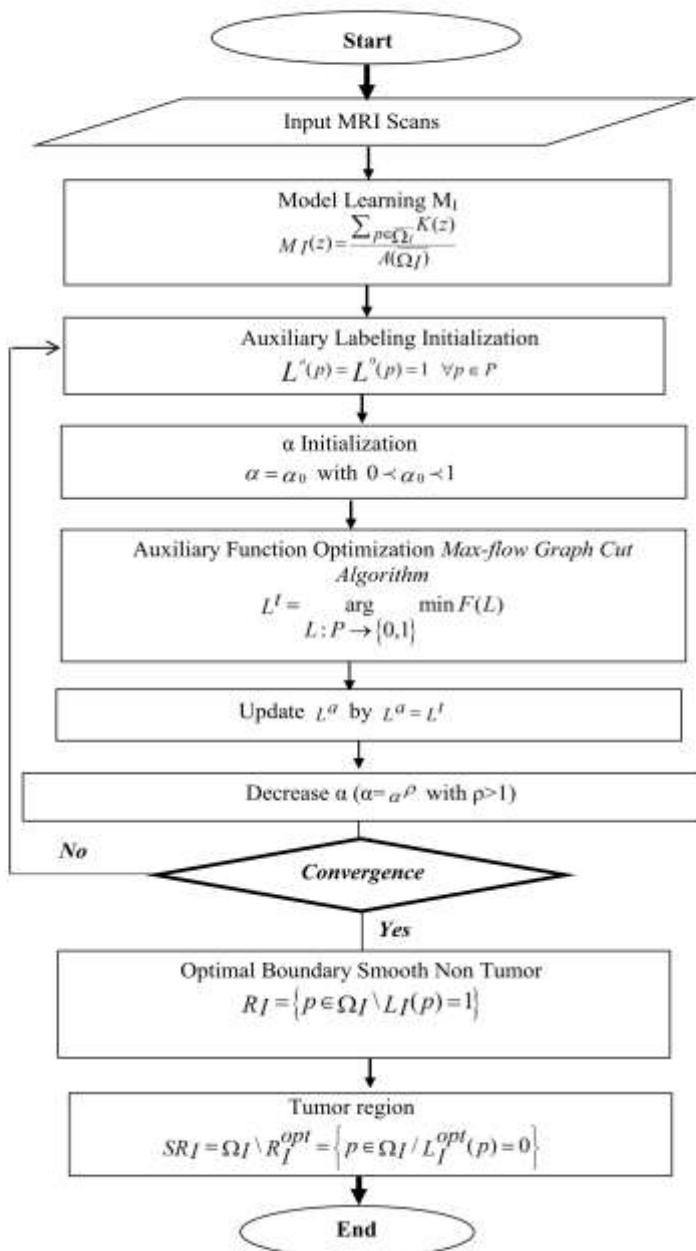


Figure6: Elliptic Normalized Circumferences (ENC) definition

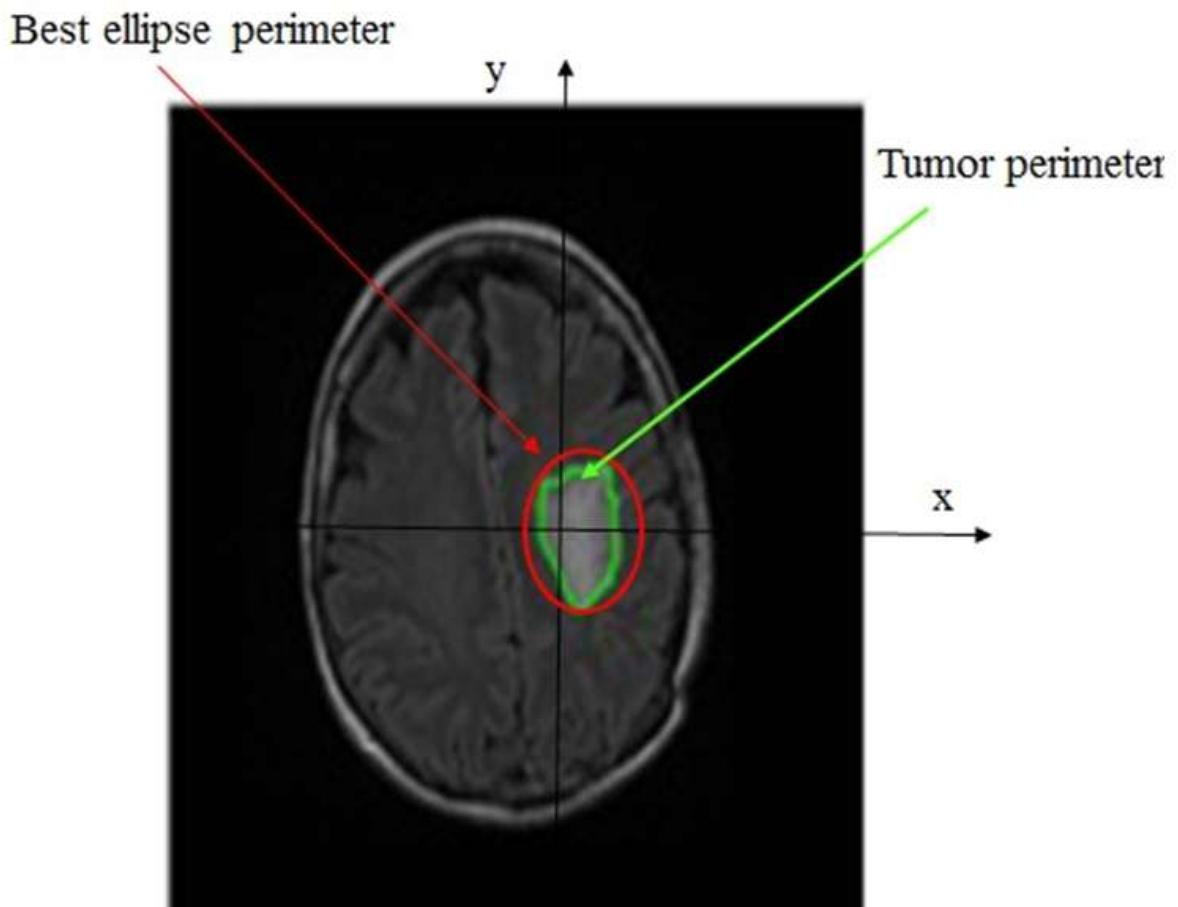


Figure 7: Solidity parameter

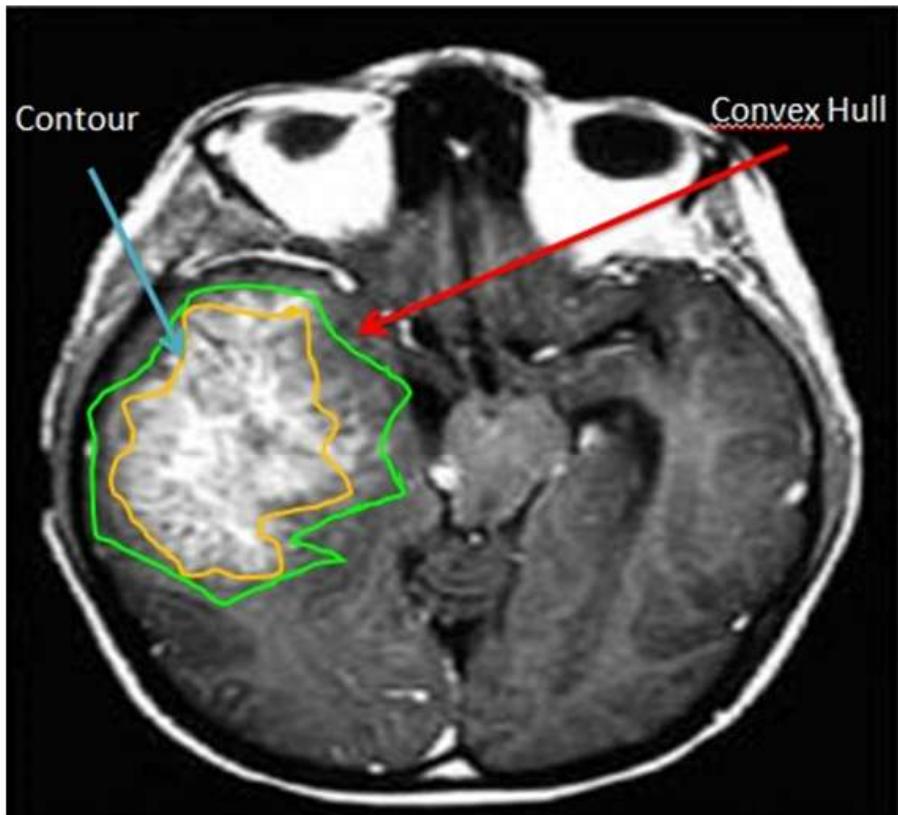


Figure8. Results of brain tumor segmentation on the first exam MRI slices

(a) Initial Flair-weighted brain MR image, (b) brain Skull stripping, (c) Brain tumor segmentation,(d)

Region of interest extraction

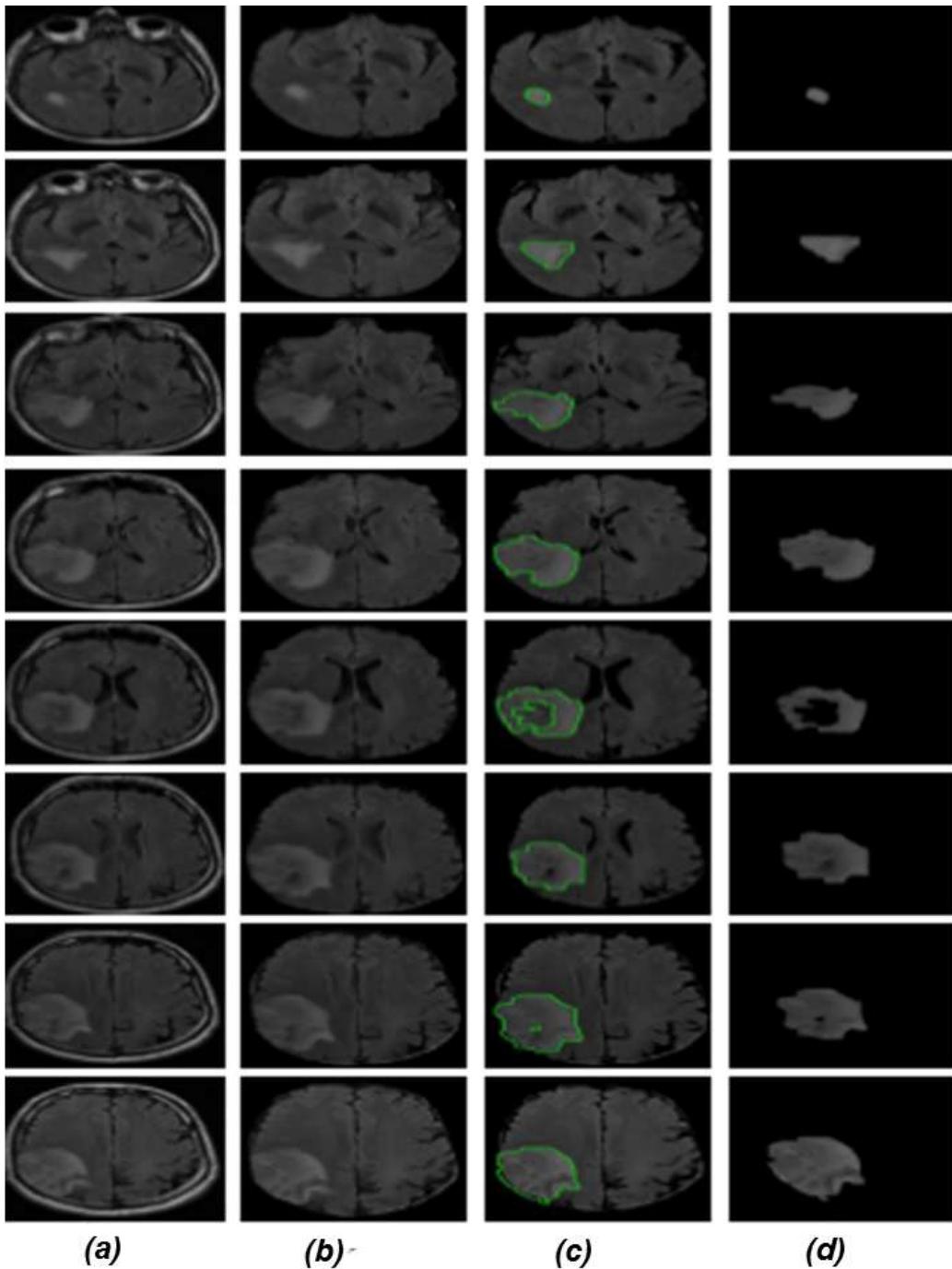


Figure9: Mean Dice Metrics value for brain skull stripping on clinical dataset

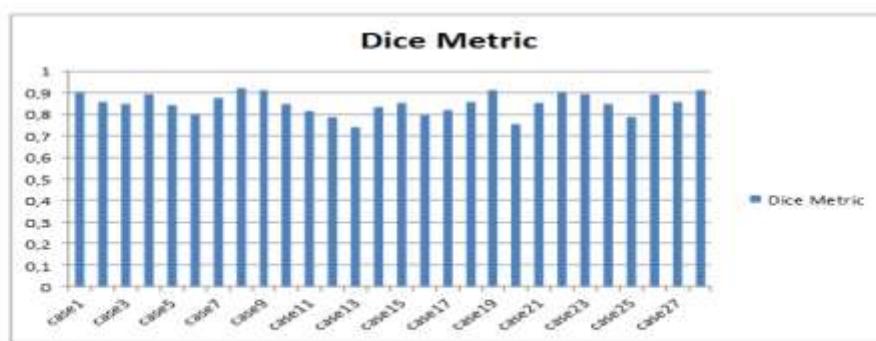


Figure10: Morphological parameters' evolution for a low grade case through fourteen MRI exams:

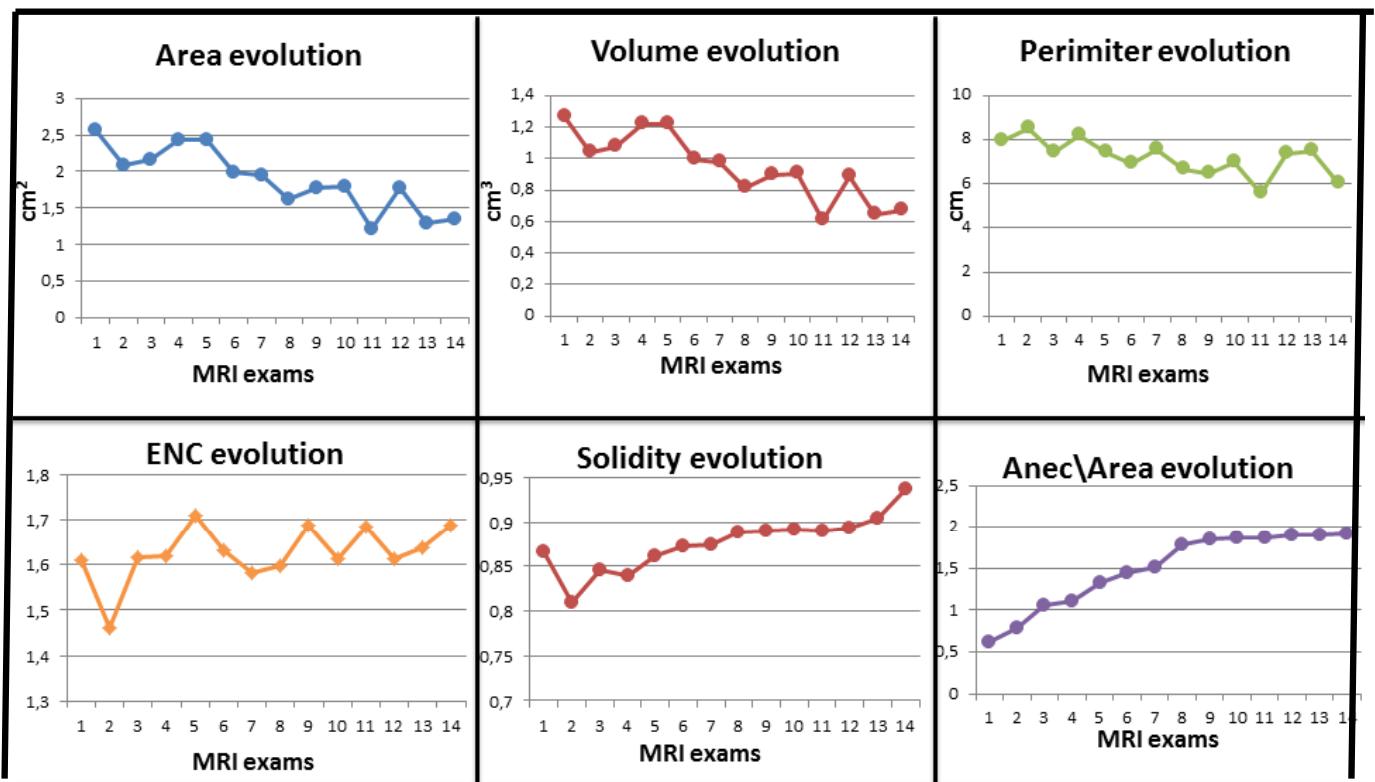


Figure11: Regional parameters' evolution for a low grade case through fourteen MRI exams

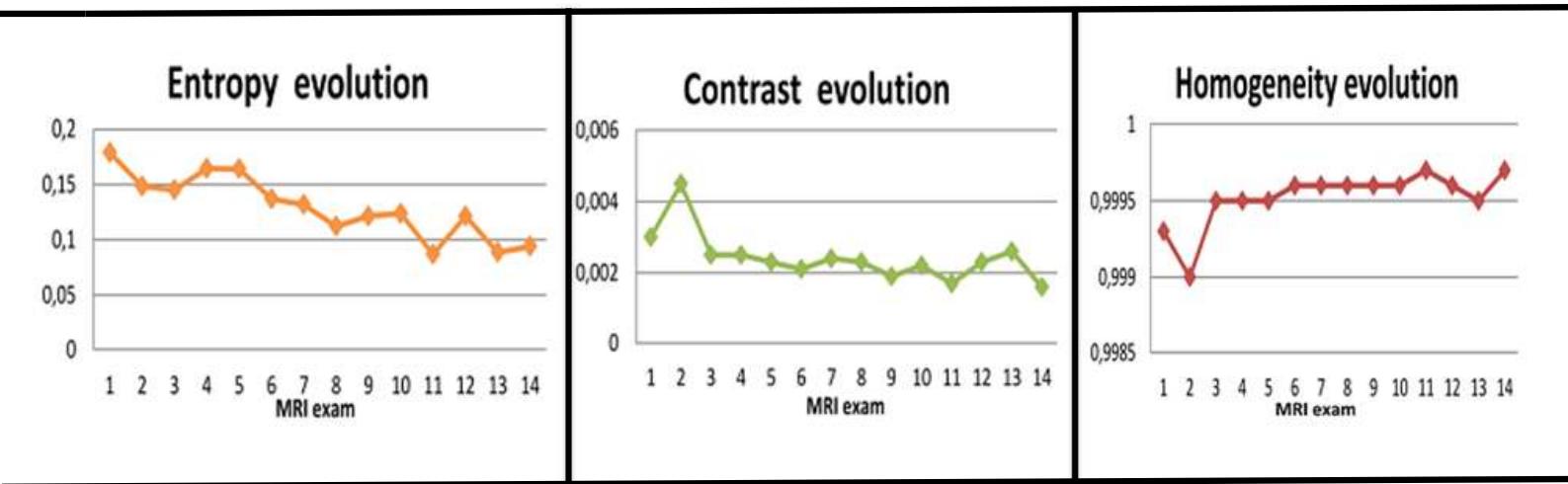


Figure12: Morphological parameters' evolution for a high grade case through nine MRI exams

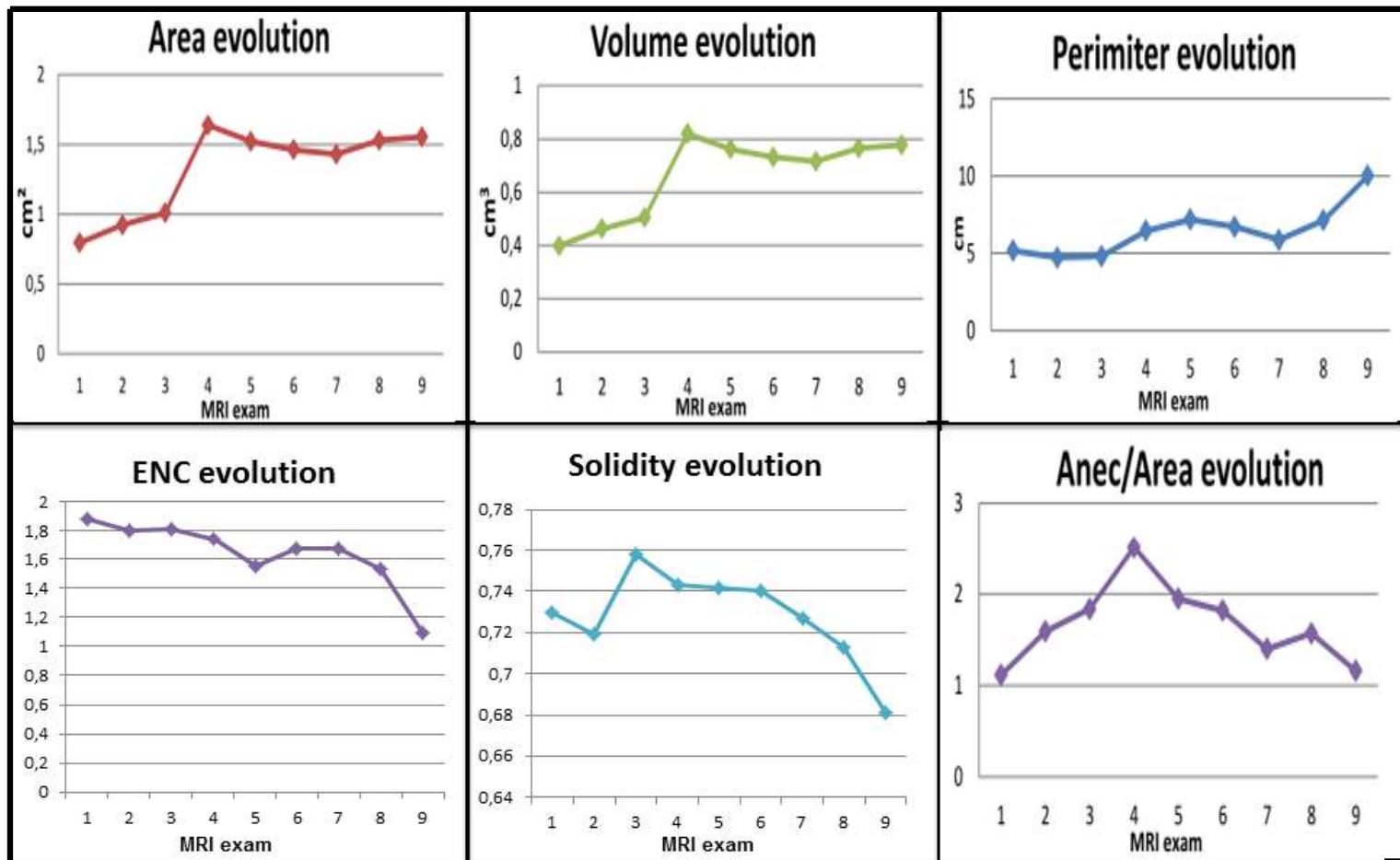


Figure13: Regional parameters' evolution for a high grade case through nine MRI exams

