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Semiautomatic segmentation of glioblastoma for radiotherapy treatment plannin

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Abstract
During the radiation therapy (RT) process, the treatment is planned and simulated with a treatment planning system (TPS). Contouring identifies the Planning Treatment Volume (PTV), that is the physical RT treatment volume. PTV of Glioblastoma (GB) includes, after expansion, Gross Tumor Volume (GTV, the tumor) and Clinical Target Volume (CTV, tumor plus edema). GlioCAD, a Computer-Assisted Detection software for contouring gliomas in MRI/DTI, was used to delineate GTV. The dataset included the images of 21 patients undergoing RT for GB. For each patient, we co-registered CT-planning images and diagnostic MRI (16 T1-gad, 6 T2 Flair, 13 Flair Fat Sat), which were used for GlioCAD training and validation. CAD outlined the tumor with good accuracy, after ruling out in post-processing some false positives. We identified reliable GTVs, suitable for RT requirements. An evolution of GlioCAD will take into account edema for outlining CTV. The method is promising. Together with a further automatic system for the delineation of organs at risk (OAR) in the brain, the procedure may be helpful for standardization of RT-treatment planning.

Keywords: glioma, glioblastoma, radiotherapy, GTV, contouring, segmentation

1. Introduction

Malignant gliomas are aggressive tumors of the Central Nervous System. The gold standard treatment provides for an initial surgical time followed by radiotherapy and chemotherapy with temozolomide in concomitant and adjuvant setting (Stupp et al. 2005). The prognosis of glioblastoma (GB) multiforme has not improved much over the past ten years since a beneficial in survival with this integrated schedule has been shown. Radiotherapy inevitably induces neurotoxicity and it is normal to consider that limited treatment volumes may consequently reduce it.
However the definition of the optimal radiotherapy treatment volumes in GB remains controversial and may be important to obtain systems that can make the practice of contouring this kind of tumors as homogeneous as possible. Contouring in radiotherapy mainly consists in the identification of two volumes to be treated, when possible, with different doses: the macroscopically visible tumor (GTV, Gross Tumor Volume) and a region (edema) of likely infiltration (CTV, Clinical Target Volume), Fig. 1.
A further margin is added to CTV to create the PTV (Planning Target Volume), which takes into account the uncertainty that may result from positioning errors in the treatment phase.

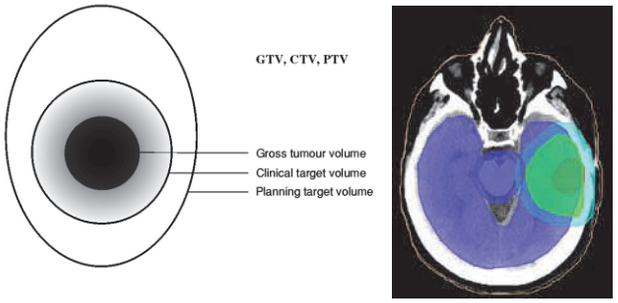

Figure 1. Left: Diagram of the main irradiation volumes (from ICRU 50). Right: an example of manual assessment of GTV, CTV, and PTV (the GBM is in the left brain hemisphere, and the three irradiation volumes are roughly concentric, respectively from the smallest to the largest one).

To improve contouring reliability the radiation oncologist uses centering CT images and diagnostic MR scans.

The treatment volumes in glioblastoma, over the years, have varied in the various cooperative group trials especially differing in margin from the GTV and inclusion of peritumoral edema. For example, the RTOG (The Radiation Therapy Oncology Group) recommends that the initial clinical CTV covers the whole T2 high-intensity areas defined in post-operative MR imaging plus a 2-cm margin, followed by a boost with a field defined by the areas of T1-enhancement (macroscopical residual tumor) and/or the surgical cavity with 2.5-cm margin (Gilbert et al. 2013, 2014). The rationale for peritumoral edema inclusion is the histologically confirmed presence of tumor cells in this area. On the other hand, the EORTC (Organization for Research and Treatment of Cancer) recommends that CTV should include the T1 enhancement area and/or the surgical cavity plus 2-3 cm without the intentional inclusion of T2 areas of edema (Stupp et al. 2005). To support the EORTC protocols there are data that show that the majority of recurrences were within 2 cm away from the primary tumor. Therefore today there is no consensus about the definition of treatment in GB volumes.

It should also be considered that in addition to the heterogeneity in the contouring protocol that can be adopted by each center, there is heterogeneity in contouring due to manual skill, to image interpretation, and to the experience of each radiation oncologist. There are studies assessing the heterogeneity in contouring in which, after surgical resection, some radiation oncologists have surrounded GTV as the entire surgical cavity, which includes both the space of missing tissue filled by fluid and the resection margin, while others have strictly confined the GTV only in the resection margin (see e.g. (Wee et al. 2015)).

In this context, the need for a reproducible and efficient method for delineating the tumor volumes for RT is critical. In particular, it has been demonstrated that MRI is more sensitive than CT in both lesion detection and in the margin delineation of gliomas, see e.g. (TenHaken et al. 1992), which makes MRI modalities the most appropriate for an automatic or semiautomatic GB contouring system and GTV/CTV delineation.

In this preliminary work, GlioCAD (De Nunzio et al. 2011), a CAD (Computer-Assisted Detection) software system for the contouring of cerebral gliomas in MRI/DTI, was used to delineate the GTV treatment volumes in patients with glioblastomas, in order to get quick and operator-independent semi-automatic contouring. The application of GlioCAD was preceded and followed by data processing steps whose purpose was to conform data to the software, and to make the resulting segmentation more appropriate to RT requirements. In this paper, CAD principles and operations are described, the post-processing procedure designed to make the automatically-contoured volumes comply with radiotherapy needs is analyzed, and some segmentation results are shown.

In Section II, the used dataset is described, together with the manual procedure for GTV contouring, which is needed by GlioCAD to initially learn gross tumor delineation, and the software pipeline is illustrated. Section III shows some preliminary results, while the discussion with a small review of the related literature is in Section IV. The conclusions end the paper.

2. Materials and methods.

The dataset consisted of the images of 21 patients treated for GB at the Radiotherapy Unit of Siena (Italy). For each patient we had centering helical CT images and diagnostic MRI, which were coregistered. MR images (16 T1-

gad, 6 T2 Flair, 13 Flair Fat Sat scans) were used to better identify the macroscopic tumor regions (GTV) and the surrounding edema (CTV). The images, comprising manually defined treatment volumes and organs at risk (OAR), were used for the training of GlioCAD, a CAD system for the contouring and volume calculation of cerebral gliomas in conventional MRI and DTI.

The manual contouring procedure had the following steps:

1. We started from the manual segmentations in T1-gad images and used these series to define the macroscopic tumor volume (GTV) corresponding to the area of contrast enhancement; in the case of a post-operative series, the surgical cavity was contoured including any areas with contrast enhancement surrounding the cavity.
2. A margin of 2 cm was added to this volume to obtain the CTV; edema inclusion was verified by exploiting the FLAIR images; in case of imprecise inclusion, we had to apply manual changes to include edema, by comparing the levels of hyperintensity in FLAIR series. If the expansion gave a volume beyond the limits of the cranial theca or beyond natural anatomical barriers (such as bone structures, falx, ventricular system), manual correction was performed.
3. We added a further margin of 0.5 cm to CTV to create the PTV (Planning Target Volume.

When the patients were candidate to receive an additional dose (up to 60-70 Gy), an expansion of about 0.5 cm was given to the initial GTV to create the so-called CTVboost and another 0.5 cm to create a PTVboost; if there are adjacent critical structures these two volumes may coincide (CTVboost = PTVboost).

In conclusion, in each series of images there was a single GTV but possibly more CTV and related PTV (CTV1 with PTV1 and CTV2 with PTV2) which corresponded to the first part of the treatment at lower doses and the subsequent boost – i.e. an additional dose to a limited volume.

The following part describes the application of GlioCAD to automatic GTV contouring, which is depicted in Figs. 2 and 3. The procedure is based on the combined use of T1-gad images and FLAIR images, all of them coregistered with the CT scans.

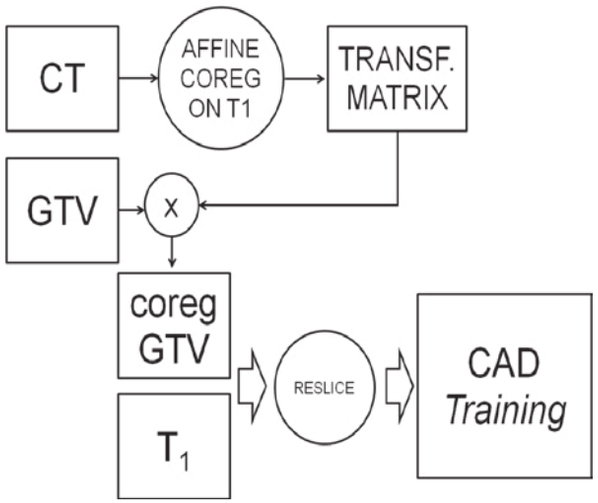

Figure 2. Semiautomatic GTV delineation: preprocessing and CAD training.

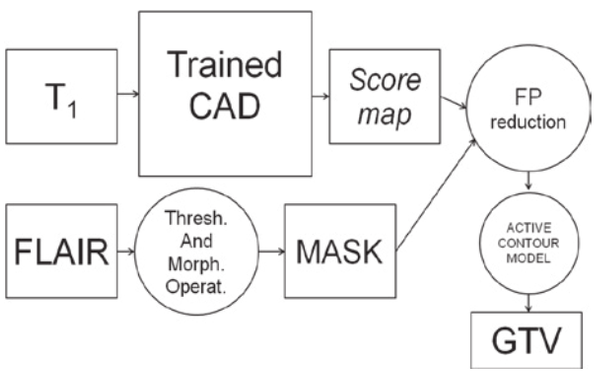

Figure 3. Semiautomatic GTV delineation: Segmentation and post-processing.

GlioCAD is a supervised system, in that it needs an initial set of images where the desired GTV has already been delineated by experts. GlioCAD working scheme (De Nunzio et al. 2011), is based on the calculation of texture features (derived from gray-level histograms, cooccurrence matrices, and run-length matrices) with a sliding-window approach, and on the Fisher Linear Discriminant Analysis as the classification method. After training, the software becomes able to locate and contour by itself the volumes of interest on a different set of images ("validation" set). Accordingly, a preprocessing step followed by a training step is needed. In first place (Fig. 2), the CT images are coregistered (12-parameters affine coregistration) to the corresponding T1-gad,

and the related transformation matrices are used to project the GTV drawn by the radiation oncologist onto the T1-gad images. Coregistrations were performed by *elastix* (http://elastix.isi.uu.nl) (Klein et al. 2010) (Shamonin et al. 2014), which is an open source software tool based on the Insight Segmentation and Registration Toolkit (ITK). *Elastix* consists of a collection of algorithms for (medical) image registration. The modular design of *elastix* allows to quickly configure and compare different registration methods. We used *elastix* command-line interface, which enables automated processing of a large number of images by means of scripting. After coregistration, the T1-gad series with the coregistered GTV was resliced to have homogeneous voxel size in the data set, and was then used to train GlioCAD to recognize and segment the tumor regions in T1-gad.

During segmentation and post-processing (Fig. 3), the trained CAD locates probably cancerous regions in the T1-gad images of the validation set, reducing false positives through a mask obtained from the FLAIR image by thresholding and appropriate morphological operations. An active contour model merges the found regions into a single ROI, smoothing borders and solving inhomogeneity problems. The final identified ROI is used as the (computer calculated) GTV. The quantification of the system accuracy is obtained by the Jaccard coefficient, by comparing the results with the manually defined GTV.

The extension to the CTV will be performed by using again the mask obtained from the FLAIR image, and by considering a 2-cm border added to the GTV by morphological dilation. Finally, to avoid false positives, a descalping mask automatically obtained from the T1-gad images will be applied.

3. Results

Segmentation and accuracy assessment were carried out with Leave One Patient Out (LOPO) Cross Validation: the CAD system was applied in turn to each patient scan (Fig. 3), after training on the remaining images (Fig. 2). In all cases, the CAD outlined the tumor structure with good accuracy. A post-processing step was needed to eliminate some false positives and to make the identified volumes compliant with radiotherapy treatment requirements, with an acceptable hypothesis for the final GTV estimation (Fig. 4). Most of post-processing is automatic, with some manual interventions for verification and refinement. The mean Jaccard coefficient with its standard deviation was $J=0.73\pm0.08$, while the Dice coefficient was 0.83 ± 0.09.

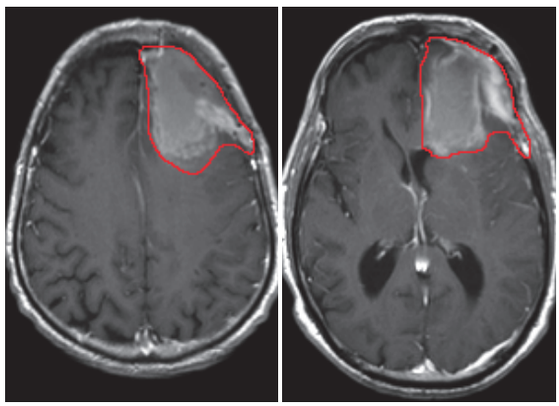

Figure 4. CAD GTV segmentation examples.

4. Discussion

Automatic and semiautomatic segmentation of gliomas (in particular GBs) for volumetric assessment and therapy follow-up have been the subject of an innumerable number of papers (see some recent reviews, such as (Bauer et al. 2013) (Gordillo, Montseny, and Sobrevilla 2013) (Liu et al. 2014) (Simi and Joseph 2015) (Srinivasa Rao and Sreenivasa Reddy 2016)). On the other hand, few works specifically devoted to radiotherapic applications, with a focus on the (semi)automatic contouring of GTV for brain glioma treatment planning, have been published. The subsequent steps, namely automatic expansion to CTV and PTV, have been studied in many papers, some dating back to the nineties, such as (Stroom and Storchi 1997), up to recent works such as (Yan et al. 2014), in which the Authors introduce a method for generating the CTV from GTV using the geodesic distance calculation. These articles will be thoroughly reviewed in a future paper on the expansion to CTV/PTV.

Among the papers concerning (semi)automatic GTV contouring, (Mazzara et al. 2004) compared the effectiveness of knowledge-guided

(KG) and supervised k-Nearest Neighbors (kNN) segmentation for delineating the GTV from MR images of high and low-grade gliomas. The GTV corresponded to the area enclosing several contiguous clusters of enhancing pixels. The average accuracy of the kNN was 56%±6% for 11 cases, whereas that of the KG was 52%±7% for 7 of the 11 cases, compared with the physician's contours. It was observed that kNN and KG are less accurate in contouring GTV in non-enhancing GBs. The study showed severe limitations of the KG-system in handling particular cases such as non-enhancing tumor margins or the presence of non-enhancing cystic necrotic tissues at the center of the tumor. On the other hand, the kNN segmentation method, trained with sample data from MRI slices to segment, lead to more robust segmentation results on all patients.

(Beyer et al. 2006), from the same group, presented a similar and comparative study, extracting GTV with the same two segmentation methods and evaluating the results in terms of predictive dose measurement for therapy planning. It was found that the expert physician reference volume was irradiated within the same level of conformity when using the plans generated from the contours of the segmentation methods. In addition, any uncertainty in the identification of the actual gross tumor volume by the segmentation methods, had small effects when used to generate 3D radiation therapy treatment planning due to the averaging process in the generation of margins used in defining a planning target volume.

(Hori et al. 2010) proposed a method for semi-automated GTV segmentation of GB on brain MR images for radiotherapy planning. Three-dimensional (3D) MR images of 28 GB cases were used. First, a spherical volume of interest (VOI) including the GB was interactively defined. Then, the VOI was transformed to a two-dimensional (2D) image by a spiral-scanning technique. Active contour models were used to delineate an optimal outline of the GB in the transformed 2D image. After inverse transform to the 3D space, a morphological filter was applied to smooth the shape of the 3D segmented region. The computer output was compared with the manually segmented regions by the Jaccard similarity coefficient (JSC) and the True Segmentation Coefficient (TSC), giving on average 74.2±9.8% and 84.1±7.1%, respectively. This paper is written in Japanese.

The Expectation Maximization (EM) algorithm, applied on a Gaussian mixture model consisting of pure superpositions of Gaussian distributions, was employed in (Simon et al. 2012) to delineate the Apparent Diffusion Coefficient (ADC) areas of high and low proliferation in heterogeneous gliomas from predefined manual GTVs on 2D DWI slices. The EM was initialized manually from the contoured ROIs. The result was a reproducible quantification in regions of tissue inhomogeneity. Reproducibility of this approach was evaluated in 10 patients with glioma. Moreover, an automatic initialization approach that completely removes user-induced variability was introduced.

In (Unkelbach et al. 2014) brain segmentation (normal tissues vs tumor) was obtained by an algorithm based on EM, which uses a probabilistic normal tissue atlas as spatial prior. For every voxel, it estimates the posterior probability for three normal tissue classes (white matter, gray matter, and CSF), as well as the lesion outlines on T1 post gadolinium and T2-FLAIR. It then uses the Fisher-Kolmogorov glioma growth model to assess lesion infiltrations in normal appearing regions of the brain. In the paper, the need for reliable segmentation of anatomical boundaries such as the *falx cerebri* and the *tentorium cerebella* is put in evidence. The target volume for radiotherapy planning is defined as an isoline of the simulated tumor cell density. Dice metrics are given between manual and model-derived CTV volumes (values range from 0.74 to 0.84).

(Dittmann et al. 2013) considers that conventional imaging modalities reveal only the central part of the tumor with a high cellular density, but fail to detect microscopic tumor cell infiltrations. Mathematical models can be used to integrate known growth characteristics of gliomas into the target delineation process. In the paper, the Authors demonstrate the use of diffusion tensor imaging (DTI) for simulating anisotropic cell migration in a glioma growth model that is based on the Fisher-Kolmogorov (FK) equation. For a clinical application of the model, it is crucial to develop a detailed understanding of its behavior, capabilities, and limitations. For that purpose, the Authors perform a

retrospective analysis of glioblastoma patients. It was found that, depending on the location of the tumor relative to major fiber tracts, DTI can have significant influence on the shape of the radiotherapy target volume.

Finally, the work described in (Stretton et al. 2013) is worth noting and is related to (Dittmann et al. 2013). Tumor growth models based on the FK equation are employed again, but replacing DTI (costly and not always available) with an isotropic diffusion map or an anisotropic high-resolution DTI atlas formed by averaging DTIs of multiple patients. Three metrics are used to quantify the impact of replacing the patient DTI: the shape of the simulated glioma, the estimation of the tumor growth parameters, and the prediction performance on clinical cases.

The preceding review shows that the literature does not offer a large quantity of papers devoted to the specific subject of GTV automatic or semiautomatic contouring. Direct comparison of our results is possible only with (Mazzara et al. 2004) and (Hori et al. 2010).

In (Mazzara et al. 2004) the ground truth for accuracy assessment is obtained by multiple contours drawn by three physicians, and the probability that a given pixel is properly classified as part of the tumor (its "weight") is determined by the number of times that this pixel was included in the outlines prepared by the radiation oncologists. Accuracy for the computer segmentation is then defined as the ratio of the total sum of weights contained within the computer segmentation volume to the total weights generated from the volumes produced by the physicians. This measure is a kind of probabilistic true-positive rate (i.e. sensitivity). Observing that by definition the Jaccard coefficient is always lower than or equal to sensitivity, our method clearly outperforms their results. As to (Hori et al. 2010), the absence of an English version of the paper makes a detailed comparison difficult. As to segmentation quality, our results in terms of Jaccard coefficient look similar.

5. Conclusions

The proposed method is promising, although still under development and not fully automatic. In the next future, it will be tested on a larger set of images, and the procedure will be made as automatic as possible. The following step will be CTV/PTV automatic delineation, which is currently work in progress. Together with the use of automatic or semiautomatic systems for OAR delineation, for which the literature already presents various solutions often based on atlas-driven approaches, e.g. (Isambert et al. 2008) (Daisne and Blumhofer 2013) (Consona et al. 2014), the procedure may be of help to optimize radiation-treatment planning in patients with GB, in particular to make the process of contouring as homogeneous as possible without operator-dependent variability and to obtain limited treatment volumes in order to reduce RT-related neurotoxicity.

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