Semi-Automatic Segmentation Software for Quantitative Clinical Brain Glioblastoma Evaluation

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Rationale and Objectives: Quantitative measurement provides essential information about disease progression and treatment response in patients with glioblastoma multiforme (GBM). The goal of this article is to present and validate a software pipeline for semi-automatic GBM segmentation, called AFINITI (Assisted Follow-up in NeuroImaging of Therapeutic Intervention), using clinical data from GBM patients.

Materials and Methods: Our software adopts the current state-of-the-art tumor segmentation algorithms and combines them into one clinically usable pipeline. Both the advantages of the traditional voxel-based and the deformable shape-based segmentation are embedded into the software pipeline. The former provides an automatic tumor segmentation scheme based on T1- and T2-weighted magnetic resonance (MR) brain data, and the latter refines the segmentation results with minimal manual input.

Results: Twenty-six clinical MR brain images of GBM patients were processed and compared with manual results. The results can be visualized using the embedded graphic user interface.

Conclusion: Validation results using clinical GBM data showed high correlation between the AFINITI results and manual annotation. Compared to the voxel-wise segmentation, AFINITI yielded more accurate results in segmenting the enhanced GBM from multimodality MR imaging data. The proposed pipeline could be used as additional information to interpret MR brain images in neuroradiology.

Key Words: Glioblastoma multiforme; segmentation; clinical validation.

INTRODUCTION

Despite the best available standard therapies, including surgery, radiation, and chemotherapy, the survival in patients diagnosed with glioblastoma multiforme (GBM) remains dismal at 14 months (1). Newer therapeutic strategies aiming at targeting specific molecules are being developed and tested in clinical trials (2). Temozolomide chemoradiation has significantly prolonged survival but produces pseudoprogression that is difficult or impossible to distinguish from recurrence in 30%–50% of patients (1,3). In addition, antiangiogenic therapies have been used in combination with conventional chemotherapy in patients with recurrent GBM, demonstrating radiographic response rates of 35%–50% (4–6). These agents improve significantly patient quality of life but alter the pattern of recurrence by a potent effect on tumor permeability, suppressing enhancement within a solid tumor with a resulting increase in the frequency of infiltrative recurrence (7).

These therapy-induced alterations in the natural history and imaging appearance of treated GBM have made imaging follow-up by conventional magnetic resonance imaging (MRI) difficult, which motivates widespread ongoing research to discover additional imaging biomarkers and has led to a revision in response criteria. Although the most commonly used imaging criteria for evaluating treatment response are still based on measurement of enhancing tumor (the Macdonald Criteria) (8), the increase in infiltrative recurrence and the difficulty in distinguishing recurrence from progression has led to proposal of a new criteria for tumor response that includes abnormality on T2-weighted or fluid-attenuated inversion recovery images as additional markers for progression (the RANO criteria) (9). The RANO criteria also recommends the use of volumetric measurements of enhancing tumor because reliance on cross product diameters is problematic and highly operator dependent in cases of irregularly shaped tumor, multifocal tumor, or tumor with cystic or necrotic components. Recently, volumetric measures were found comparable (10) or superior (11,12) to linear diameter measures as indicators of tumor evaluation.

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Volumetric methods have the advantage of more reproducibly and precisely measuring the size of tumor and are being increasingly used in clinical settings. For example, volumetric measurements of both the enhancing and nonenhancing tumor have been correlated to progression-free survival (PFS) and overall survival (OS) (7,13). To date, the major barrier to widespread adoption of these methods in clinical neuro-oncology has been that manual and assisted manual segmentation methods are quite time consuming for the operator. Because of the presence of heterogeneous signal intensity in necrotic or cystic tumor and at the margin of infiltrative tumors, it is difficult to segment a tumor by hand, and the development of automatic or semi-automatic software tools that can provide efficient volumetric measurement and assist longitudinal shape analysis for follow-up studies could provide significant benefit.

Tumor segmentation algorithms are classified into voxel-based or deformable shape model-based methods. Fuzzy clustering methods (voxel-based) are among the more popular approaches (14–18) and classify each voxel into either one of the normal brain tissues (gray matter, white matter, and cerebrospinal fluid) or tumor tissues. The algorithm developed by Philips et al (18) can differentiate clinically vital boundaries of tumor and edema from hemorrhage in multimodal MRI. The performance of multimodal intensity-based clustering can be limited by overlapping of intensity between tumor and normal tissues (19,20). To account for this, additional features such as multidimensional intensity vectors have been designed for the clustering. Clark et al (21) has integrated knowledge-based techniques and multimodality clustering to segment GBM tumors. Fletcher-Heath et al (17) presented the first tumor segmentation for nonenhancing MRI data, including T1, T2, and proton density–weighted images, to track tumor size over time. Prastawa et al (22,23) designed a knowledge-based tumor segmentation algorithm that learns voxel-intensity distributions from normal brain and detects outlying tumor voxels. Kaus et al developed a spatially varying statistical classification algorithm using a template to moderate the segmentation obtained by statistical classification (24,25).

A second class of algorithms use deformable shape models to segment tumor from normal brain. These methods are derived from the traditional Snake model (26) that uses surfaces to match tumor boundaries. The concept of these techniques is the use of energy function and various shape models: the external energy derived from the matching degree between the shape and the image features is used to distinguish tumor from normal tissues, and the internal energy is used to constrain the tumor shape. To adjust for the change of topology, implicit models such as level sets (27–32) can be used. Intensity distributions within and outside tumor region have been used for level set segmentation (33–35).

Voxel-based segmentation algorithms can better adapt the segmented tumor shape to local image, and deformable model-based segmentation schemes are more robust but generally need proper initialization. To take the advantages of both algorithms, we propose an (Assisted Follow-up in NeuroImaging of Therapeutic Intervention (AFINITI) pipeline for segmenting MRIs by combining them. In the first stage, the voxel-based segmentation using the Oxford Center for Functional MRI of the Brain (FMRIB) Software Library (FSL), and the FMRIB's Automated Segmentation Tool (FAST) (36,37) is performed automatically for initial tumor segmentation from T1-weighted images. The T2-weighted images are also automatically segmented and combined with the T1 segmentation results. Then, a level set–based segmentation is used to refine the segmentation results with minimal manual input by embedding the major functions of ITK-SNAP (38). These tools are integrated into one pipeline with a single graphic user interface (GUI). We validate the AFINITI pipeline by applying the software to 26 clinical GBM cases by comparing the results with those obtained using manual segmentation.

METHODS

Patients and Data

The protocol was approved by the institutional review boards for retrospective retrieval and analysis of patient clinical and imaging data. Serial MRI scans from 26 consecutive patients with diagnosis of GBM at Brigham & Women's Hospital between 2004 and 2009 who had interpretable high resolution MRI scans were retrieved.

All MRI scans were performed on 1.5T or 3T MRI scanners, and the imaging protocol contains at least an axial three-dimensional (3D) Spoiled Gradient Echo (SPGR) T1-weighted series covering the whole brain acquired at a 5- to 10-minute delay after the intravenous administration of 0.1–0.2 mmol/kg gadopentetate dimeglumine contrast agent, and axial two-dimensional T2-weighted MRI sequences. The slice thickness in all cases was between 1.0 and 1.5 mm for 3D SPGR sequences and 6 mm for the two-dimensional Fast Spin Echo (FSE) T2-weighted sequences. The typical 1.5T 3D SPGR parameters were set as: repetition time = 25 ms, echo time = 6 ms, field of view = 200 mm × 240 mm, and matrix = 224 × 224.

Manual segmentation was performed under the supervision of two practicing faculty neuroradiologists (G.S.Y., R.Y.H.) by a research associate trained in neuroanatomy and neuroimaging (K.S.), and the final segmentations were reviewed and corrected jointly by G.S.Y. and R.Y.H. to minimize the bias among raters. Segmentation was performed using ITK-SNAP by manually tracing the boundary between the areas of abnormal enhancement and normal tissue on the 3D SPGR images, excluding nonenhancing, presumably necrotic or cystic portions of tumor but including areas of heterogeneous enhancement felt to represent tumor.

The AFINITI Software Pipeline

The goal of AFINITI is to seamlessly implement the state-of-the-art neuroimaging tools into one package to facilitate