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Original article

Automated delineation of brain structures in patients undergoing radiotherapy for primary brain tumors: From atlas to dose–volume histograms

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ABSTRACT

Purpose: To implement and evaluate a magnetic resonance imaging atlas-based automated segmentation (MRI-ABAS) procedure for cortical and sub-cortical grey matter areas definition, suitable for dose-distribution analyses in brain tumor patients undergoing radiotherapy (RT).

Patients and methods: 3T-MRI scans performed before RT in ten brain tumor patients were used. The MRI-ABAS procedure consists of grey matter classification and atlas-based regions of interest definition. The Simultaneous Truth and Performance Level Estimation (STAPLE) algorithm was applied to structures manually delineated by four experts to generate the standard reference. Performance was assessed comparing multiple geometrical metrics (including Dice Similarity Coefficient – DSC). Dosimetric parameters from dose–volume-histograms were also generated and compared.

Results: Compared with manual delineation, MRI-ABAS showed excellent reproducibility [median DSC_{ABAS} = 1 (95% CI, 0.97–1.0) vs. DSC_{MANUAL} = 0.90 (0.73–0.98)], acceptable accuracy [DSC_{ABAS} = 0.81 (0.68–0.94) vs. DSC_{MANUAL} = 0.90 (0.76–0.98)], and an overall 90% reduction in delineation time. Dosimetric parameters obtained using MRI-ABAS were comparable with those obtained by manual contouring.

Conclusions: The speed, reproducibility, and robustness of the process make MRI-ABAS a valuable tool for investigating radiation dose–volume effects in non-target brain structures providing additional standardized data without additional time-consuming procedures.

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Late effects, such as cognitive dysfunction (CD), have an important impact on the quality of life [1] of patients bearing brain neoplasms. The correlation between brain irradiation and CD is well recognized. Few data are reported on dose–volume relationships between CD and specific brain substructures [2–4] partly due to the complexity of a reliable delineation of different brain regions for the absence of clear limits among the anatomo-functional areas. The manual brain definition is a time-consuming, prone to error, operator dependent and poorly reproducible process. A magnetic resonance imaging atlas-based automated segmentation (MRI-ABAS) procedure may overcome the drawbacks inherent to manual operation, but the automated process of adapting normal brain atlases may be affected by brain anatomy alterations due to the presence of pathological and/or iatrogenic deformation. Different approaches to segmenting brain with gross abnormalities in an atlas-based framework have been proposed, although in clinical practice their use is still limited [5]. In the radiotherapy (RT) context, MRI-ABAS procedures, taking into account tumor deformation effects, have been suggested and validated by comparing manual and automated delineation of the brain structures. However, these procedures were mainly focused on intracranial structures conventionally considered as organs at risk in brain RT treatment planning, such as brain stem, cerebellum, and optic chiasm [6–8].

The purpose of this work was to validate an MRI-ABAS procedure for cortical and sub-cortical grey matter areas definition, suitable for dose-distribution analyses in studies of RT-related CD. The key elements of the procedure are a preliminary definition of MRI-based grey matter maps and an atlas-based grey matter ROI definition. Our approach is validated by comparing the segmentation results with those obtained through four manual experts' delineations on a dataset of ten patients undergoing 3D conformal radiotherapy for primary brain tumors. The MRI-ABAS procedure performance was assessed by comparing multiple geometrical metrics, along with the dosimetric evaluations obtained by dose–volume-histogram (DVHs) calculations.

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Patients and methods

Patients database

We considered ten consecutive patients affected by high grade glioma (who were either biopsied or partially or "completely" resected) treated at our institution. Three-dimensional conformal plans were generated using a commercial treatment planning system (XiO, Elekta CMS). RT was administered using two or more non-coplanar 6 MV photon beams from a linear accelerator with a total dose of 60 Gy in 30 daily fractions of 2 Gy. Before RT, all patients underwent brain MRI (3 Tesla MR scanner Trio, Siemens Medical Systems, Erlangen, Germany). MRI studies included three-dimensional, T1-weighted gradient-echo sequences (MPRAGE, T1 W 1 mm^3 voxel) before and after i.v. injection of contrast medium, diffusion-weighted, FLAIR and TSE-T2 W images in the axial plane. The MPRAGE sequences with contrast medium were used to manually contour the structural parenchyma distortion (deformed area, DA). For each patient, the DA was blindly contoured by four different operators: an expert neuro-radiologist (M.Q.) and three radiation oncologists (M.C., M.S. and R.P.). Treatment details and DA information are reported in Supplementary Table S1.

MRI-ABAS procedure

MRI-ABAS aims at obtaining a set of grey matter regions of interest (ROIs) for each MRI study using a standard atlas of the brain. Accordingly, from the Talairach atlas [9,10] we preliminarily grouped selected brain sub-regions, obtaining the following customized set of 15 brain ROIs: frontal lobes, parietal lobes, occipital lobes, temporal lobes, cingulate gyrus, medial temporal lobes, insular lobes, deep grey matter (i.e. basal ganglia plus thalami) and cerebellum. These ROIs were then superimposed on each patient's MRI using a set of functions included in the Statistical Parametric Mapping software (SPM.8, www.fil.ion.ucl.ac.uk/spm/) as briefly described below.

For each MRI study, a map of the probabilities for each brain voxel belonging to grey matter (GM) was obtained. DAs were used as mask to exclude from the processing the brain voxels with abnormal signal. GM probability map was then converted into a binary map. To transfer the 15 ROIs in the MRI-space an elastic deformation was applied. Finally, the intersection of each ROI in the MRI-space with the GM map provided the automated ROI-set. Further details of the MRI-ABAS procedure are reported in the Supplementary Material Section.

Dosimetric analysis

The ROI-sets were converted in DICOM-RT format using a home-made software (Brain Converter, BRACO) developed in MATLAB (version 7.6.0.324, The Mathworks, Inc., Natick, MA). For each ROI, BRACO extracts the coordinates of the contours and compiles the corresponding RT structure-set file. The MPRAGE sequences without contrast medium were co-registered with the corresponding planning CT-scan using the automated rigid body co-registration method based on the mutual information algorithm embedded in SPM [11]. The RT structure-set files were transferred from the MRI-space into the planning CT-space using the resulting co-registration matrix. Superimposing the dose map from each patient, the dosimetric evaluation was performed using the Computational Environment for Radiotherapy Research (CERR) software [12]. The DVHs were generated for each ROI (automated and manual) and the mean dose (D_{mean}), the dose to 95% of volume (D95), and the dose to 5% of volume (D5) were calculated as representative metrics.

The execution time for each study was recorded for both the automated (including DA delineation and computer time) and manual procedures.

Validation procedure

For each study, four sets of manual GM ROIs were generated. To this end, the brain structures were manually delineated on MRI images by the four aforementioned operators, using the Talairach atlas as guidance, and the intersection of each ROI with the GM map provided the manual ROI-set.

The Simultaneous Truth and Performance Level Estimation (STAPLE) algorithm [13] was used to generate, from the four manual ROI-sets, a probabilistic estimate of the reference manual ROI-set (STAPLE-manual), used as ground-truth for the present validation.

Similarly, using the four DA objects defined by each operator, four different automated ROI-sets have been obtained for each study. To assess the influence of the DA contour variability on the automated results, a probabilistic estimate of the reference automated ROI-set (STAPLE-auto) was also obtained.

To quantify inter-operator and between-method differences, the following eight metrics were used: the relative volume differences in ROIs' volumes (ΔVolume, i.e. volume measurement error) and the Dice Similarity Coefficient (DSC, i.e. degree of volumetric overlap) [14] as volumetric measures; the mean absolute surface distance (MSD) [15] and the mean slice-wise Hausdorff distance (MSHD) [15] as shape error measures; the distance between the centres of mass (ΔCOM, i.e. position error) as distance metrics; the differences in D_{mean}, D5 and D95 (ΔD_{mean}, ΔD5 and ΔD95) as dosimetric measures.

The validation procedure included three evaluations: (a) direct assessment of inter-operator variability and evaluation of MRI-ABAS in this framework, (b) assessment of MRI-ABAS reproducibility with respect to STAPLE-auto, and (c) assessment of MRI-ABAS accuracy with respect to STAPLE-manual.

Inter-operator variability

Pairwise comparisons between each couple of the four operators (identified as R1, R2, R3, R4), and between each operator and STAPLE-auto were performed. This analysis allowed to assess whether STAPLE-auto differed more from the operators than the operators did from each other. Inter-operator analysis was performed by the Mann–Whitney test ($p < 0.05$, two-sided, were considered statistically significant).

Reproducibility

The eight metrics were calculated between automated ROIs and STAPLE-auto (as measure of the robustness of MRI-ABAS in relation to DA contour variability), and compared to the corresponding metrics calculated between manual ROIs and STAPLE-manual. Reproducibility differences between the two methods (MRI-ABAS vs. manual) were assessed by the Wilcoxon's signed-rank test for paired data.

Accuracy

The eight metrics were calculated between automated ROIs and STAPLE-manual. The accuracy of MRI-ABAS was considered as acceptable, when for each metric, the median value fell within the 95% reference interval (e.g. non parametric 95% confidence interval) [16] of the manual method.

All left and right brain structure pairs were combined for both the geometric and the dosimetric analyses.

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