Diffusion Tensor Imaging-based Histogram Analysis for detection and quantification of low-grade gliomas structural changes during chemotherapy

Antonella Castellano[1], Marina Donativi[2], Roberta Rudà[3], Marco Riva[4], Giorgio De Nunzio[2], Antonella Iadanza[1], Matteo Rucco[5], Luca Bertero[3], Lorenzo Bello[4], Riccardo Soffietti[3], and Andrea Falini[1]

[1]Neuroradiology Unit and CERMAC, Università Vita-Salute San Raffaele and Ospedale San Raffaele, Milan, Italy, [2]A.D.A.M., Advanced Data Analysis in Medicine, University of Salento, Lecce, Italy, [3]Neuro-oncology, Department of Neuroscience and Oncology, University of Torino, Turin, Italy, [4]Neurosurgery, Department of Neurological Sciences, Università di Milano, Istituto Clinico Humanitas, Milan, Italy, [5]School of Science and Technology, Computer Science Division, University of Camerino, Camerino, MC, Italy

Purpose

In brain gliomas, Diffusion Tensor Imaging allows to reveal tumoral and peritumoral abnormalities not apparent on conventional MR imaging and to detect the presence of tumor microinfiltration beyond the edge of the T2/FLAIR abnormality[1,2]. Moreover, in infiltrating gliomas, changes in water diffusion patterns after chemotherapy may occur before size variations on conventional MRI[3]. A preliminary study on low grade gliomas demonstrated, with a qualitative approach based on Functional Diffusion Maps, that changes in diffusion parameters within tumor tissue are correlated both with neurophysiological data from intraoperative subcortical mapping and histopathological findings from specimens obtained from image-guided tumor biopsies[4]. A more accurate quantification of these changes in diffusion metrics during therapy follow up of gliomas can be achieved by histogram analysis on diffusion maps, that was previously applied during therapy follow-up of high-grade gliomas in order to identify one or more parameters to quantify the structural changes of the whole tumor burden over time[2]. To date, this approach has never been applied to low-grade glioma therapy monitoring, nor on DTI maps. Objecitive of this study is to apply histogram analysis to quantify changes of DTI metrics over time in low-grade gliomas (LGGs) undergoing Temozolomide (TMZ) chemotherapy.

Methods

We analyzed 16 LGG patients who underwent 3T-MR at baseline and after three and six dose-dense TMZ cycles, without any concomitant treatment that can modify diffusion parameters (i.e. steroids). 3T MR-DTI consisted of a single-shot EPI sequence (TR/TE 8986/80 ms) with 32 diffusion gradient directions (b=1000 s/mm^2) and one image set without diffusion-weighting. 3D-FLAIR sequences, T2-weighted FSE and pre and post-gadolinium volumetric T1-weighted FFE conventional images were acquired for morphological characterization of the lesions and volumetric assessment. The evaluation of response was primarily based on conventional FLAIR images, using RANO (Response Assessment in Neuro-Oncology) criteria that categorized response as partial (PR), minor (mR), stable disease (SD) or progressive disease (PD)[6]. Fractional anisotropy (FA), mean diffusivity (MD) and tensor decomposition DTI-derived maps (p and q maps) were obtained, using an in-house software implemented in MATLAB. Automatic segmentation of pathological areas based on 3D Texture Analysis was performed on each map as previously described[7], and tumor boundaries were visually inspected and manually refined by a neuroradiologist. Histogram analysis was performed on coregistered post-chemio and baseline maps. Histogram parameters were calculated (mean, median, 25th and 75th percentiles, interquartile range, skewness and kurtosis) and their time evolution assessed. Changes in diffusion parameters were compared with standard RANO criteria, volumetric response on FLAIR, and clinical response. The parameters that better predicted the final response were identified by multiple regression analysis. Area under the receiver operating characteristic curves (AUC) were calculated for the best histogram parameter on each map.

Results

Tumor volume on p and MD maps was greater than on FLAIR images (P<.001). After three cycles of TMZ, conventional RANO criteria classified all the patient as stable disease (SD) except one with progressive disease (PD); volumetric criteria identified two patients with a minimal tumor response (mR), with the majority of patients classified as SD and one with PD. In all patients, significant changes in DTI metrics (p, MD, FA) were observed after 3 cycles (Wilcoxon test, $p \leq .013$). After 6 cycles, these changes became more significant ($p \leq .006$). 75% of patients had an early clinical response with a significant improvement of DTI metrics even in cases with SD at volumetry. There was a significant direct correlation between percentage changes in 25th percentile on p and MD maps as well as inverse correlation between percentage changes in 75th percentile and interquartile range on FA maps after 3 cycles and final percentage changes of tumor volume (Spearman's test, $p<0.001$). Linear regression analysis established that the percentage change of 25th percentiles on p and MD map significantly predicted final volume change (R^2=.718 and .659, respectively; $p<.0005$). ROC curve analysis demonstrated that percentage change of the 25th percentile on p maps after three cycles was the best predictor of final volumetric response (AUC=0.89). Visual inspection of DTI maps reveals that 25th percentile values of p were located along the edge of the tumor (Fig. 1), supporting the hypotesis that early changes after chemotherapy occur mainly in peripheral tumor areas representing the regions of infiltration on isotropic maps, as previously confirmed by intraoperative findings[4]. Changes in FA maps were more evident after 6 cycles of TMZ and occurrred in the whole tumor burden.

Discussion and Conclusions

In LGG patients, DTI changes may be an early signature for TMZ response, correlating with clinical response better than conventional MRI criteria: structural changes quantified by DTI-based histogram analysis support the hypothesis of a tumor "shrinkage" in response to chemotherapy, especially at the level of margins of infiltration. Quantitative measures derived from this technique can be potentially used to detect structural changes after chemotherapy, thus improving the monitoring of treatment response.

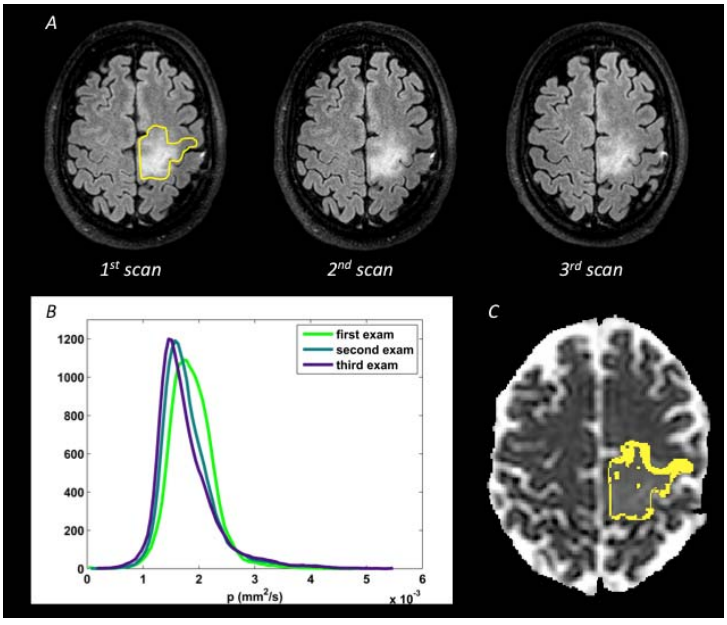

Fig.1▶ *A case of low grade oligoastrocytoma (WHOII). (A) Pretreatment axial FLAIR image shows a left precentral hyperintense lesion, with superimposed yellow ROI generated with computer-assisted segmentation on the correspondent MR-DTI pure isotropic p map (C) at baseline; note that the area of p abnormality is larger than the region of hyperintensity on FLAIR. After 3 cycles of TMZ (2nd scan), axial FLAIR image shows a SD (11% volume reduction), but patient had a significant clinical improvement (>50% reduction of frequency of seizures). After 6 cycles of TMZ (3rd scan), axial FLAIR image shows a mR (30% volume reduction). (B) Histograms derived from DTI isotropic p maps before treatment and after 3 and 6 cycles reveal a continuing shift of the histogram to the left, towards lower values of isotropy, and an increase in skewness. The parameter with the highest percentage change after the first 3 cycles was the 25th percentile (6.7% reduction). (C) On p map at baseline, 25th percentile values are located along the infiltrative borders of the tumor (yellow).*

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