Preoperative differentiation between grade II and III gliomas subtypes and genotypes using MR spectroscopy, perfusion and diffusion imaging

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Introduction:

Preoperative differentiation of WHO grade II and grade III oligodendrogliomas (ODII and ODIII) and oligoastrocytomas (OAII and OAIII) is clinically important for establishing an appropriate therapy schema and for patient management. Although histopathology remains the gold standard method for the diagnosis and classification of brain tumors, variations in tissue sampling for these heterogeneous gliomas and restrictions on surgical accessibility make it difficult to be sure that the samples analyzed are really representative of the entire tumor. Conventional magnetic resonance imaging (MRI) is considered, nowadays, to be the reference standard for preoperative diagnosis and for providing helpful information for treatment decision making. However, its ability to differentiate between gliomas subtypes and grades is limited and can result in ambiguous (Figure 1) or misleading results in some cases (1). The first goal of this study was thus to investigate advanced MRI modalities such as proton MR spectroscopy (MRS), diffusion-weighted imaging (DWI) and perfusion weighted-imaging (PWI) in order to help grading and differentiating between gliomas subtypes. Moreover, independently of grade or histological subtype, patients with tumors possessing 1p/19q codeletion and / or isocitrate dehydrogenase 1 (IDH1) gene mutation are more likely to be chemoresponsive and have longer progression free survival and overall survival than those with intact 1p/19q and IDH1 genes (2,3). The second purpose of this work was thus to differentiate between tumors genotypes using MRI parameters.

Materials and Methods:

Forty-four adult patients (21 women, 23 men; mean age 46 ± 15.7 years) with histopathologically proven grade II and grade III gliomas were selected. This population included 23 OA (11 OAII + 12 OAIII) and 21 OD (9 ODII + 12 ODIII). Molecular profile of the tumor was determined by immunohistochemical methods and genes sequencing. The MR exams were performed on a 1.5T scanner (Symphony, Siemens, Germany) using an 8-channel phased-array head coil. Preoperative MRI protocol included anatomical images (T2-weighted, fluid-attenuated inversion recovery (FLAIR) and T1 pre- and post-injection images) as well as EPI-DWI (3 directions, 3 b-values), GE-EPI dynamic susceptibility contrast (DSC) PWI and monovoxel proton MRS (TE = 30 and 135 ms). Morphological parameters such as contrast enhancement (CE), necrosis, hemorrhage, edema, tumor location and limits were coded using a score table. Post-processing of diffusion and perfusion data was performed using Perfscape and Neuroscape softwares (Olea Medical, France). Apparent diffusion coefficient (ADC), corrected relative cerebral blood volume and flow (rCBV and rCBF, respectively) and permeability index (K2) values were calculated in the lesion and normal contralateral area. Post-processing of MRS relative quantification consisted in normalizing each metabolite by the water signal using homemade software developed under IDL software. Uni- and multivariate analyses (JMP 5.1 software) were performed in order to determine which criteria could help differentiating the four gliomas subtypes from each others and tumors genotypes.

Results:

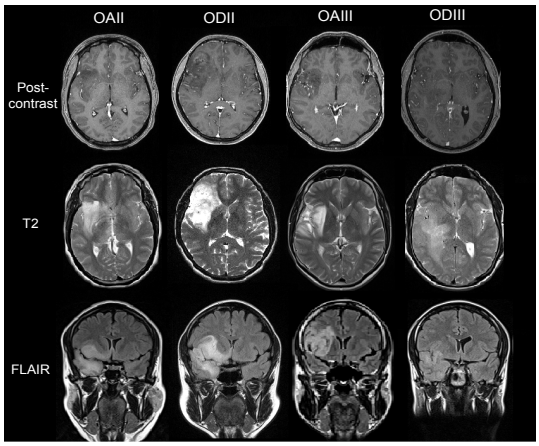

Fig1: *Confounding examples of OAII, ODII, OAIII and ODIII*

ADC was significantly higher in grade II tumors compared to grade III ($p=0.0003$) while rCBV, rCBF and K2 were significantly lower in grade II compared to grade III gliomas ($p<0.0001$, $p<0.0001$ and $p<0.0002$ respectively). Figure 2 shows complete separation between the four glioma subtypes when combining conventional MRI, DWI, PWI and MRS at short and long TE. When considering contrast-enhancing tumors, the same four subgroups could also be separated by combining the same parameters. Tumors presenting IDH1 mutation and 1p/19q codelation (IDH1+/codel) were mostly associated with frontal localization and with the OD type while the wild genotype (IDH1-/nocodel) was correlated with temporal/temporo-insular location and with the OA type ($p=0.048$ and $p=0.0025$ respectively). Combination of conventional, diffusion, perfusion and spectroscopic data helped distinguishing IDH1-/nocodel, IDH1+/nocodel and IDH1+/codel genotypes from each others (Figure 3) and also IDH1+ from IDH1- and the 1p/19q codelated genotype from the no-codelated one.

Discussion: Nowadays, histopathology is still the gold standard method for grading and classifying brain tumors. This study shows that the use of noninvasive MR techniques such as DWI, PWI and MRS could provide valuable information for preoperative differentiation between gliomas according to their subtypes but also according to their molecular status. This could be helpful for designing tailored therapies and for patient management.

References: (1)Dean BL, 1990, Radiology, 411-15; (2)Yan H, 2009, N Engl J Med, 765-73; (3)Walker C, 2006, Neurology, 1661-7

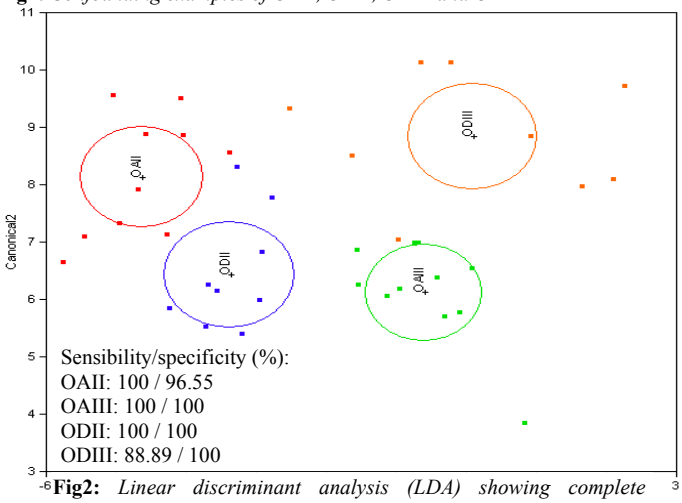

Fig2: *Linear discriminant analysis (LDA) showing complete separation of 4 subgroups.*

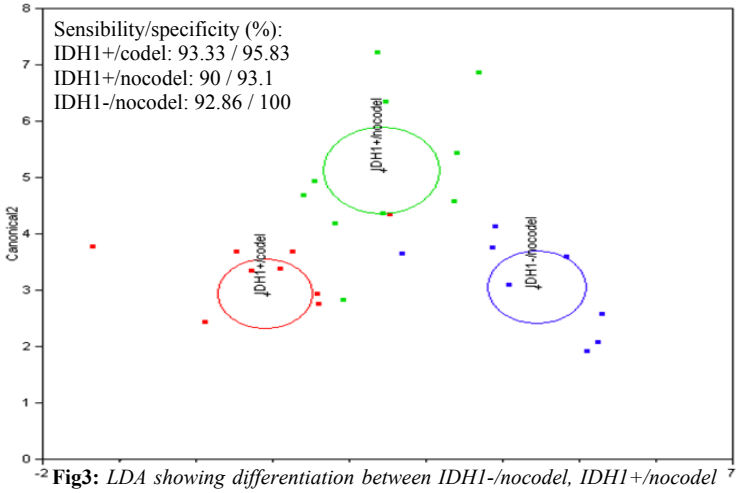

Fig3: *LDA showing differentiation between IDH1-/nocodel, IDH1+/nocodel and IDH1+/codel genotypes.*