MRS changes in diffuse intrinsic pontine gliomas correlate with survival

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Introduction: Diffuse intrinsic pontine glioma (DIPG) carry the worst prognosis in pediatric neurooncology, with the majority of patients dying within six to 18 months after diagnosis[1]. With resection impossible and biopsies having failed to show any benefit for patients, researching DIPG biology is challenging due to the lack of tissue samples. Consequently, there has been no significant improvement in outcomes for decades. The goal of this study was to determine whether changes of metabolic profiles in serial MRS correlate with the effectiveness of therapy in subgroups of patients with different survival.

Methods: 52 MRS studies performed in 11 patients with DIPG were reviewed. All 11 patients were enrolled in a clinical trial and received identical treatment. Patients were divided in subgroups of "long survival" (N=4, 26 studies) and "short survival" (N=7, 26 studies). Metabolic profiles at approximately equal time points after radiation therapy were compared. All spectra were acquired on a 1.5T GE clinical scanner using a single-voxel PRESS sequence (TE=35ms, TR=1.5s, 128 averages). The regions of interest (ROI) were documented on at least two orthogonal MRI to ensure that spectra were acquired from consistent locations to the extent possible. Spectra were processed with fully automated LCModel (S. Provencher Inc., Ontario, CA) software. Concentrations of the main metabolites (NAA, Cr, Cho, mI) and metabolite ratios relative to Cho were evaluated.

Results: Average survival was 616±127 days for "long survival" and 326±82 days for "short survival". A representative spectrum of "long survival" shows prominent mI and moderate Cho. In contrast, Cho was more prominent in "short survival" and mI was less prominent at a comparable time after initial diagnosis and treatment (**Fig. 1**). Among all measures evaluated, the best separation of the patient groups was provided by the mI/Cho concentration ratio (**Fig. 2**).

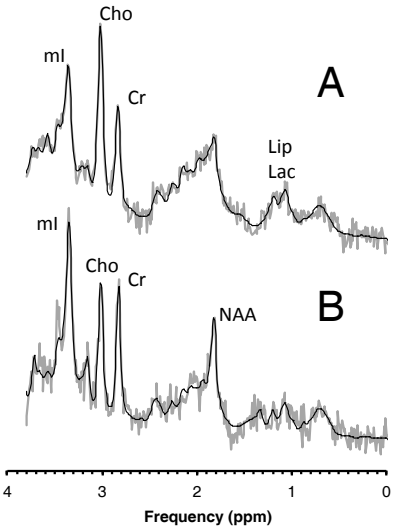

Fig. 1: *Representative spectra of "short survival" (A) and "long survival" acquired at 130 days and 142 days after initial diagnosis. mI = myo-inositol, Cho = choline, Cr = creatine, NAA = N-acetyl-aspartate, Lip = lipids, Lac = lactate.*

Discussion: DIPG patients with different survival show significantly different metabolic profiles ***early*** when clinical relapse has not yet occurred. Albeit this finding needs to be confirmed in a larger cohort of subjects, MRS appears to be a promising tool to evaluate the effectiveness of current and novel therapies in subgroups of patients and possibly individual patients. MRS could be used to optimize/adjust therapy of patients and to accelerate clinical research studies. A caveat is that the observed separation may be specific for the experimental treatment administered to the patients included in this report. However, a preliminary review of a DIPG patient group not enrolled in this study, showed a similar separation of "long survival" versus "short survival" (not reported in detail).

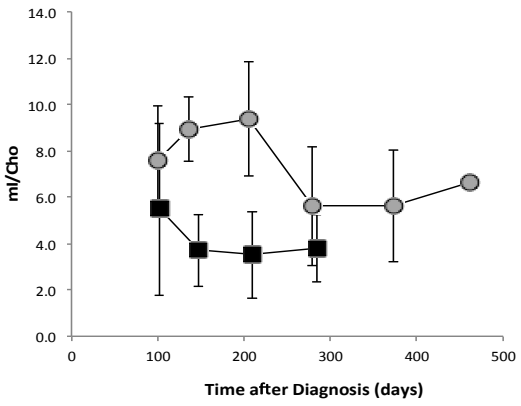

Fig. 2: *Mean mI/Cho concentration ratios (±SD) of "long survival" (grey circles) and "short survival" (black squares) vs. time after initial diagnosis. MR spectra at diagnosis were not obtained. The first time point (≈100 days) is typically after completion of initial radiation therapy before any secondary treatment. mI/Cho were significantly different at the 2nd and 3rd follow-up with "long survival" having higher mI/Cho ratios.*

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References: Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. *Lancet Oncol.* Mar 2006;7(3):241-248