Combined Proton MRSI Tumor Biomarkers Improve Accuracy in Differentiating Clinical Grade of Pediatric Brain Tumors

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Introduction

Allthough the majority of childhood brain tumors are low-grade tumors that respond well to therapy, their diagnosis and treatment are complicated by their frequent location adjacent to crucial structures, which restricts diagnostic biopsies. The paucity of biomarkers with prognostic significance is one of the main limiting factors for the development of new treatment strategies. Such biomarkers may be identified by molecular analysis (1) or DNA microarray gene expression (2), but these procedures require diagnostic biopsies which may be limited due to the location of the tumor. Biologically important intracellular molecules or metabolites detected with magnetic resonance spectroscopy (MRS) are promising and may lead to a new era in the management of these tumors, especially due to the non-invasive and non-irradiating nature of MRS. Recently, proton magnetic resonance methods have evolved from single-voxel to multivoxel MRS or magnetic resonance spectroscopic imaging (MRSI) which has an inherent advantage of collecting spectral data simultaneously from multiple regions including the tumor and surroundings, thus assessing the spatial distribution of spectral changes (3). The objective of this study was to test the hypothesis that combining information from biologically important intracellular molecules, obtained by proton MRSI, will increase the diagnostic accuracy in differentiating clinical grading of pediatric CNS tumors.

Materials and Methods

Proton MR spectroscopic imaging exams were performed on 76 children with neuroepithelial brain tumors prior to therapy on a 1.5-T MR system. Proton MR spectroscopic imaging was performed using multi-voxel chemical shift imaging (CSI) with point resolved spectroscopy (PRESS) and volume preselection. Briefly, after selecting a 50-100 cc volume, shimming and water suppression were adjusted. Water suppression was performed using CHESS and volume selection using RF pules with bandwidths of 1100Hz for the 180 degree pulses and 2000 Hz for the 90 degree pulse. Then, a large data set was acquired using phase-encoding gradients in two directions. The following acquisition parameters were used: TR=1s, TE=65msec, 16x16 phase encoding matrix, 160 mm FOV, slice thickness of 10 mm, 1250 Hz spectral width, 2 averages and 512 points. Data sets of 1-1.2 cc nominal resolution were obtained. Data processing was performed on a Sun workstation (Sun Microsystems, Mountain View, Calif.) using analysis software by General Electric (SAGE) and in-house developed software using IDL 5.3.

Results

Normalized Cho (Cho/ntCr) and normalized L (L/ntCr) were higher in high-grade (n=26) than low-grade (n=50) tumors (P<0.001). Multiple stepwise logistic regression analysis confirmed that both Cho/ntCr and L/ntCr were significant independent predictors that correlated positively with tumor grade.

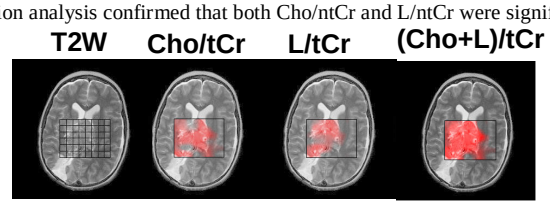

Figure 1: MR and MR Spectroscopic imaging (MRSI) of an 8 year old boy with anaplastic astrocytoma of the right thalamus. T2 weighted (T2W) image also shows hyperintense periventricular signal involving the anterior horns of the lateral ventricles most likely representing subependymal spread of tumor. Choline (Cho/tCr) and lipids (L/tCr) biomarker maps indicate increased choline and lipids throughout the lesion consistent with active tumor. The combined biomarker, (Cho+L)tCr, image suggests a most probable distribution of high-grade tumor. The figure illustrates the relationship of tumor grade and the combined Cho and lipid distribution.

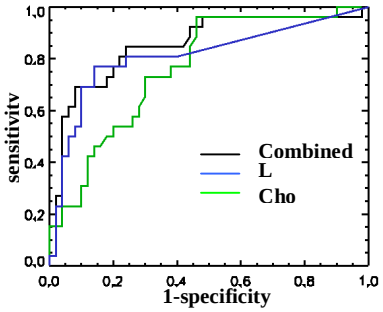

Figure 2: ROC curves for the choline Cho), Lipid/Lactate (L) and combined index. The area under the curve (AUC) is a summary measure of accuracy. Lipids/Lactate (AUC = 0.811) can discriminate high from low-grade tumors better than Cho (AUC = 0.766). The combined index has even better average accuracy (AUC = 0.854)

We combined linearly the two biomarkers using a distribution free approach (4) to optimize accuracy by maximizing the area under the receiver operating characteristic (ROC) curve. The optimum combined index was found to be Cho+0.52L. The table below presents sensitivity, specificity for each biomarker at the cutoff point of maximum accuracy.

Biomarker	% Sensitivity	% Specificity	% Accuracy
Cho	46	86	72
L	77	86	83
Combined	70	92	85

To derive the probability of a high grade tumor, we used cutoff values for choline $\geq$ 1.0 and L $\geq$ 2.0 which created 4 variant combinations of the multivariate predictors:

Cho $\geq$ 1.0	L $\geq$ 2.0	% Probability of High-Grade Tumor
No	No	2.1
No	Yes	22.4
Yes	No	27.5
Yes	Yes	83.6

The ROC curves (Fig.2) show the trade-offs between increasing true positive rate (y axis) and false positive rate (x axis) for various cutoff points. The combined marker has overall greater area under the curve (AUC) which indicates that the combination provides superior diagnostic accuracy compared to each biomarker alone.

Discussion

Proton MR spectroscopic imaging indices may aid in the choice of treatment and influence the decision in adjusting therapy before toxic effects occur (5). Our data suggest that several metabolic indices by proton MR spectroscopic imaging provide information, although only normalized Cho and lipids and/or lactate provide independent prognostic information. Using both proton MRSI-derived measures of Cho and lipids and/or lactate in combination improve overall differentiation of clinical grading of brain tumors in children. Application of such biomarkers as clinical algorithms may help facilitate development of therapies tailored to the biological behavior of the tumor.

References

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