Combined Proton Magnetic Resonance Spectroscopic Imaging Index Predicts Survival of Children with CNS Tumors Better than Histology

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Introduction

Pediatric brain tumors account for more than 20% of cancers in children under 15 years of age [1]. Pediatric brain tumors differ in histology and outcome from those occurring in adults, and children survive longer than adults [2]. Despite advances in neuroimaging, surgical techniques, radiotherapy, and the availability of newer chemotherapeutic agents used with molecular targeted therapy, the increase in the 5-year survival rate of children with CNS tumors is reportedly 35% [3]. Correct prognosis may lead to more appropriate therapy and improve survival rate in this population. In addition, due to inherent difficulties in performing diagnostic and serial biopsies, there is a clear need for biologically relevant, noninvasive markers if tumors are to be effectively diagnosed and treated. Clinical factors currently used in addition to histopathology to predict outcome and assist in treatment decisions, do not accurately predict outcomes. Molecular biomarkers identified through gene expression have shown independent prognostic significance, and expression microarray data suggest that molecular profiles of biomarkers classify malignant gliomas and predict survival better than does standard histopathology [4]. Identification of gene-expression profiles, however, requires biopsy, impossible in certain cases, due to tumor location. In such cases, a noninvasive *in vivo* adjunct to MRI —proton Magnetic Resonance Spectroscopic Imaging (^{1}H MRSI)— is the only resource. Multivoxel ^{1}H MRSI allows data to be collected simultaneously from within a lesion as well as in adjacent regions, and promises to provide specific, accurate and sensitive biomarkers capable of signaling potential outcomes among pediatric cancer patients [5]. Used on brain tumors, ^{1}H MRSI has shown a reduction or absence of N-acetylasparatate (NAA) and total creatine (tCr) and an increase in choline-containing compounds (Cho), lipids and/or lactate (L). There are few reports on the role of MRSI-derived biomarkers as predictors of survival in patients with brain tumors. We believe ours to be the first study designed to test the hypothesis that, combining information from biologically important metabolites, obtained by MRSI, of CNS tumors in children will increase our ability to predict survival.

Biomarker	Cut-off Value	Sensitivity	Specificity	Accuracy
Cho	≥1.5	67 (12/18)	71 (41/58)	70 (53/76)
Cho/NAA	≥2.0	72 (13/18)	66 (38/58)	67 (51/76)
Cho+0.1L	≥1.8	61 (11/18)	86 (50/58)	80 (61/76)

Table 1: Diagnostic Characteristics of Biomarkers with Cut-off Values Chosen to Provide Maximum Accuracy in Differentiating Patient Survival in Children with CNS Tumors

Materials and Methods: ***^{1}H MRSI-*** exams of 76 children (median age at diagnosis: 74 months) with brain tumors were evaluated. MRSI was performed using multivoxel chemical shift imaging with point-resolved spectroscopy (PRESS) and CHESS for water suppression. Typical acquisition parameters were TR=1s, TE= 65 ms (to reduce lactate contributions and to increase lipid sensitivity), 16×16 phase-encoding matrix, 160 mm FOV, slice thickness 10 mm, 1250 Hz spectral width, 2 averages / 512 points, resulting in data sets of 1-1.2 cc nominal resolution. Data were apodized with a 1.0 Hz Lorentzian filter, Fourier-transformed in the time- and spatial domains and phased. The broad components of the baseline were subtracted prior to peak area calculations. Finally, the areas of selected metabolite peaks were estimated using the PIQABLE algorithm [6]. Important biomarkers—choline-containing compounds (Cho), N-acetylaspartate (NAA), total creatine (tCr), lipids and/or lactate (L)—were measured at the "highest Cho region" and normalized to the tCr of surrounding healthy tissue. Neuropathological grading was performed using World Health Organization (WHO) criteria. ***Biostatistics-*** Survivor (n = 58) and non-survivor (n = 18) data were compared to median levels of Cho and L using univariate analysis and the Mann-Whitney *U*-test. Tumors were classified as low-grade (WHO grade I or II) or high grade (WHO grade III or IV). Association between tumor grade and survival was determined by Pearson χ^2. Diagnostic characteristics of sensitivity, specificity and accuracy were calculated for each metabolite and biomarker combination, using best cut-off values and standard formulas. The linear combination Cho+0.1Lipids maximizes the area under the ROC curve [7] to achieve optimal diagnostic accuracy. Area under the ROC curve (AUC), the most widely used index for diagnostic accuracy, was estimated nonparametrically and used as a measure of test accuracy. AUCs were compared using the Z-test. Multiple stepwise logistic regression (backward selection) was applied to determine whether metabolites (i.e., Cho, L, Cho/NAA, Cho+0.1L) and WHO grade were independent predictors of survival outcome (dead vs. alive). The logistic regression equation includes coefficients, standard errors, adjusted odds ratios, 95% confidence intervals (CI), and the likelihood ratio chi-square test for parameters in the final model obtained by maximum likelihood estimation. The probability of a high-grade tumor was estimated for a range of predictor combinations. Patients were categorized on the basis of their Cho (cut-off point ≥ 1.5), L (cutoff ≥ 0.6), Cho/NAA (cutoff ≥ 2.0), Cho + 0.1L (cutoff ≥ 1.8) and tumor grade values, and Kaplan-Meier survival analysis was performed in each category. The log-rank test was used to assess differences between survival curves. Multivariate Cox proportional-hazards regression analysis (backward selection) was performed to determine time-related risk factors as independent predictors of survival. Statistical analysis was performed using SPSS (version 14.0, SPSS Inc., Chicago, IL). Two-tailed values of $P \leq 0.05$ were considered statistically significant.

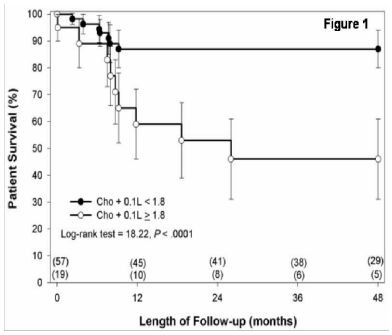

Figure 1: Kaplan-Meier survival curves according to choline (Cho) + 0.1L. Survival was significantly higher in patients with Cho + 0.1L < 1.8. Numbers in parentheses represent patients who were in the follow-up with Cho + 0.1L < 1.8 (top row) and patients who had not died, although continued to be at risk with Cho + 0.1L ≥ 1.8 (lower row).

Results: Fifty-eight of 76 (76%) patients were alive at the end of the study period. The mean survival time for all subjects was 52 months. Univariate analysis demonstrated that Cho, L, Cho/NAA and tumor grade differed significantly between survivors and non-survivors ($P \leq 0.05$). Multiple logistic regression and stepwise multivariate Cox regression indicated that Cho + 0.1L was the only independent predictor of survival (likelihood ratio test = 10.27, $P < .001$; Cox regression, $P = .004$). The combined index Cho + 0.1L was more accurate and more specific predictor than Cho or Cho/NAA (Table 1). Accuracy and specificity for Cho+(0.1L) were 80% and 86%, respectively. Kaplan-Meier analysis revealed highly significant differences in survival times based on Cho+0.1L≥1.8, where patients over the cut-off value had earlier mortality and more events (log-rank test = 18.22, $P < .0001$, Figure 1).

Discussion: MRSI provides important prognostic information in both children and adults. As reported previously Cho/NAA ratio predicts progression in pediatric brain tumors [7]. In this study, Cho/NAA≥2.0 predicted poor survival outcome but the best and only independent predictor of survival was a combined index Cho + 0.1L. We conclude that brain proton MRSI biomarkers predict survival of children with CNS tumors better than does standard histopathology. More accurate prediction using this noninvasive technique represents an important advance and may suggest more appropriate therapy, especially when diagnostic biopsy is not feasible.

References

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