An exploratory survival analysis of malignant glioma patients using pre-surgery MRI and 3D 1H-MRSI data with recursive partitioning

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In order to characterize the pre-surgery metabolic properties of brain tumors and identify its prognostic importance, MRI and 3D ^{1}H-MRSI (MR spectroscopic imaging) parameters for 43 malignant glioma patients were studied prior to surgery. A Survival tree was generated with a recursive partitioning method. The survival functions for groups of patients with different metabolic activity were compared and significant differences were observed between groups.

INTRODUCTION

Gliomas are the most common primary brain tumor and exhibit relatively poor survival, despite the large number of clinic trials that have been undertaken during the past decade [1]. Characterization of the molecular or metabolic properties of tumors may assist in the identification of prognostic factors and may help to tailor treatment strategy to individual. The goal of this study is to investigate the prognostic significance of the pre-surgery MRI and 3D ^{1}H-MRSI parameters for glioma patients using a survival tree that was generated using recursive partitioning.

MATERIALS AND METHODS

Forty three newly-diagnosed patients with histologically confirmed high grade glioma (22 grade3 and 21 glioblastoma multiforme) were studied prior to surgery. These patients had resection followed by radiation therapy and chemotherapy. MR data were acquired on a 1.5T GE Signa machine. The MRI protocol included axial FLAIR images and post contrast agent T1-weighted volume SPGR images. 3-D MRSI data were obtained using PRESS volume selection (1000/144). Spectral data were quantified automatically using software developed in our laboratory to estimate the levels of choline (Cho), creatine (Cr), N-acetyl aspartate (NAA) and lactate/lipid (LL) [2]. Metabolic indices were calculated within each voxel using an automated regression technique, e.g., CNI (Cho to NAA index), ChCrI and CrNI, that shows the number of standard deviations of difference between the ratio of two metabolites within one voxel and the mean ratio in the control voxels [3]. The metabolic abnormality was defined as the region with index ≥ 2.0. Contour plots of these metabolic abnormalities were created automatically and the abnormal volumes were calculated. Volumes of morphologic abnormalities, i.e., contrast-enhancement, T2-hyperintensity and macroscopic necrosis, were calculated based on manually drawn contours. Maximum and median values of metabolic indices were measured within the morphologic and metabolic abnormalities. The metabolic burden was defined as the integral of the metabolic index within a certain abnormality. Age, MRI and MRSI multivariate parameters were applied to a regression survival tree model using algorithm written in our laboratory based on methods of Segal [4]. Survival times was defined from the time of surgery. The model recursively partitioned the patients into more homogenous groups in terms of prognosis. Log-rank test statistics of the survival function was maximized at each splitting. Kaplan-Meier curves were plotted and compared for each group of patients after partitioning.

RESULTS

Fig 1 shows the survival tree, with proportion of survival longer than 24 months at each leaf node. It suggests age, average ChCrI within ChCrI abnormality, volume of LL abnormality and volume of CrNI abnormality as the prognostic factors affecting survival. We grouped the patients based on similar survival proportion, shown with color in the tree. Fig 2 shows the Kaplan-Meier curves for these three group of patients. The category can be summarized as:
Red: Age > 56 or (Age < 56 and meanChCrI > 3.4 and v. CrNI < 15.0cc);
Blue: (Age < 56 & meanChCrI > 3.4 & v.CrNI > 15.0cc) or (Age < 56 and meanChCrI < 3.4 and v.LL > 18.5cc);
Green: (Age < 56 and meanChCrI < 3.4 and v.LL < 18.5cc).
The P-value of the log-rank test showed significant differences between these three groups. Table 1 shows the number of grade 3 and GBM patients in each group. It was noticed that there was mixture of different grades in each survival group. Fig 3. shows the Kaplan-Meier curve for GBM patients only. The P value of the log-rank statistic shows again significant differences between the three sub-groups. The median survival was also summarized in table 1.

Table 1. number of patients in each group and median survival in months

group	# of G3	# of GBM	median survival	median survival (GBM only)
Green	18	4	NA	NA
Blue	2	10	25.0	23.9
Red	2	7	8.9	10.2

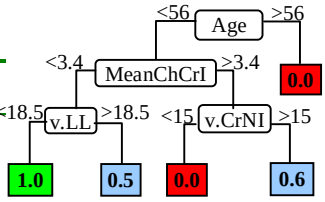

Fig. 1

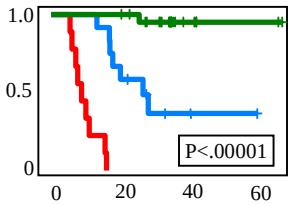

Fig. 2

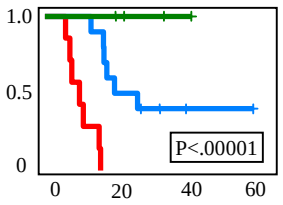

Fig. 3

DISCUSSION

The tree-based model can be considered as a stepwise variable selection procedure that may help draw attention to certain variables and be used to develop hypotheses that can be tested prospectively in a second population of patients. Besides the large size and high dimensionality, what makes a data set more complex is the inhomogeneity, i.e., different relationships hold between variables in different parts of the measurement space. Compared with classical statistic analysis methodology, tree-based model tends to handle with this inhomogeneity more efficiently using recursive partitioning. However, the tree-based model can be data dependent, especially with a small population data. Possibilities for testing the validity of the model include using an independent data set and applying cross-validation. Both of these approaches will be carried out in our on-going study. The exploratory analysis that we have performed indicates that besides older age, patients with higher ChCrI, higher LL and lower CrNI tend to have a higher risk of poor outcome. We hypothesize that the ChCrI describes the malignancy of the tumor while higher LL and lower CrNI is related to poor perfusion within the lesion. Both of these variables are expected to contribute to poor outcome. Note that none of the morphologic parameters were selected by the tree model. The mixture of grade3 and GBM in each survival group suggested that although the WHO grading largely correlates with survival, patients within each grade may have significantly different survival functions. Although the current study is exploratory in nature, we believe that it has given information that will assist in designing future studies. In addition to further analyzing data from patients prior to surgery, we will apply the same methodology to post-surgery MR parameters in order to determine whether they are predictive of survival. Additional clinical parameters will also be included in future studies.

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ACKNOWLEDGEMENT

This research was supported by NIH R01-CA79719.