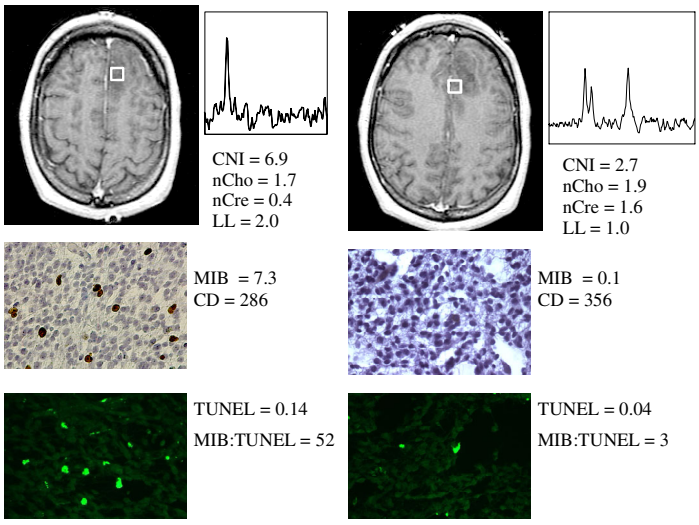
Intratumoral correlation of MR spectroscopic and growth characteristics of Grades II and III glioma

T. R. McKnight[1], T. Love[2], A. Bollen[3], M. Berger[2], S. Nelson[1], S. Chang[2], K. Lamborn[2]

[1]Radiology, University of California, San Francisco, San Francisco, CA, United States, [2]Neurological Surgery, University of California, San Francisco, San Francisco, CA, United States, [3]Pathology, University of California, San Francisco, San Francisco, CA, United States

Introduction: The accurate diagnosis of Grades II and III gliomas is crucial for the effective treatment of patients with such lesions. Both tumors may appear as non-enhancing or minimally-enhancing lesions on T1-weighted MRI, although post-surgical management of Grade III glioma is often aggressive (eg combined chemo- and radiotherapy) while Grade II glioma may not receive further treatment. The extraction of a single biopsy during surgery that shows mitotic activity is sufficient to upgrade a tumor from Grade II to III. Increased cell density is also a histologic feature of Grade III glioma. As both increased cellular proliferation and density contribute to the in vivo MRS Cho peak, we hypothesized that MRS may help identify tumor regions with the most aggressive growth characteristics that would be optimal locations for biopsy retrieval. We investigated the ability to use one or more MRS parameters to predict the MIB-1 proliferative index (MIB-1), the TUNEL cell death index (TUNEL), the cell density (CD), and the ratio of MIB-1:TUNEL activity within different regions of the same tumor.



Methods: Pre-surgical three-dimensional MR spectroscopic imaging (TR/TE=1000/144 ms,16x8x8 or 12x12x8 matrix, 1 NEX, 1 cc nominal voxel) was performed on 21 patients with untreated Grades II (5 AS, 4 OA, 2 OD) and III (7 AS, 1 OA, 2 OD) glioma using a 1.5T GE LX system. Two to four biopsies were collected from each patient during MRI-guided surgical resection of the tumors. In all 51 biopsies were excised, fixed in 10% formalin, paraffin-embedded, and sectioned for subsequent immunohistochemical (IHC) analysis. One set of paraffin sections was stained with the MIB-1 antibody to the Ki-67 cell cycle antigen and counterstained with hematoxylin to obtain both the MIB-1 and CD values. TUNEL assays were performed on sister sections from each biopsy to assess the apoptotic activity in the tissue. The ratio of MIB-1:TUNEL was calculated to determine net rate of tumor growth. The CNI was calculated as described previously [1] and the Cho and Cre peak heights were normalized by the average values in NAWM of each patient. The area of the lactate/lipid (LL) peak was normalized by the standard deviation of the noise at the right end of the spectrum. With the exception of LL, each parameter was ranked within patient in order to identify intratumoral correlations. The LL values were assigned a value of 1 or 0 if the value was greater or less than 6.0, respectively. Multivariate and univariate linear models were used to determine whether the MRS parameters predicted the IHC parameters. All statistical analyses were performed using the SPSS statistical package.

Results: The MIB-1 was positively correlated with the CNI, in both multivariate ($p=0.006$) and univariate ($p=0.013$) analyses. The MIB:TUNEL ratio also increased with the CNI in univariate analyses ($p=0.005$) and with both the CNI and nCho in multivariate analyses ($p<0.001$ and $p=0.008$, respectively). The only correlation with CD was a positive relationship with CNI (univariate $p=0.025$). To confirm that the associations found among all patients were consistent within the histologic subgroups, we performed independent analyses on the Grade II gliomas, the Grade III gliomas, the astrocytic tumors and the tumors with an oligdendroglial component. Of the correlations that were found in the overall data, only the relationship between the CNI and MIB:TUNEL ratio was consistently positive in all subgroups although it did not always reach significance. Both the Grade III and the oligodendroglial tumors also exhibited strong positive relationships between the CNI and CD and between the CNI and MIB-1.

Discussion: We demonstrated that the CNI predicted the MIB-1, MIB:TUNEL ratio, and CD within cohort of Grades II and III gliomas. Further, the CNI consistently predicted the relative MIB:TUNEL ratio within histologic subgroups. These results suggest that the CNI is a robust marker of aggressive tumor activity for these tumors. Previous studies from our group and others have reported a definitive correlation between a Cho index and MIB-1 [2-4], while other report no correlation with MIB-1 but a correlation with CD[5, 6] at all. None of the aforementioned studies, however, looked for correlations within patients. Our findings of intratumoral correlations with aggressive growth activity suggests that the CNI may be useful for directing biopsies of suspected low grade tumors.

Acknowledgements: The authors would like to thank the UCSF Brain Tumor Research Center Tissue Bank and the NIH (NCI K01 CA 90244) for their support of this study.

1. McKnight, T.R., et al., J Mag Reson Im, **13**(2): p. 167-177 2001.
2. Tamiya, T., et al., Neuroradiology, **42**(5): p. 333-8 2000.
3. Barbarella, G., et al., Int J Oncol, **12**(2): p. 461-8 1998.
4. McKnight, T., et al. *ISMRM*. 2002. Honolulu, HI.
5. Gupta, R.K., et al., J Neurooncol, **50**(3): p. 215-26. 2000.
6. Nafe, R., et al., J Neurooncol, **63**(3): p. 233-45 2003.