# Spatial Correlation of Metabolic Abnormalities in Non-enhancing Low Grade Gliomas

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**Introduction:**

Grade 2 astrocytoma (AS) and oligodendroglioma (OD) often present as non-enhancing lesions with no distinguishing characteristics on T1-weighted MRI. However, AS and OD behave differently in terms of growth rate [1], patterns of invasion into normal tissue[1], and responsiveness to chemotherapy [2]. The ability to characterize such behavior non-invasively would be advantageous for post-surgical therapeutic planning for patients with subtotally resected tumors, particularly when the residual tumor consists of a mixture of the two tumor types which is often the case. A recent study of the MR spectroscopic features of non-enhancing lesions showed that Grade 3 glioma were more heterogeneous than Grade 2 in terms of their MRS features and that the heterogeneity reflected the underlying growth characteristics [3]. Questions as to whether such differences in heterogeneity exist within the subset of non-enhancing Grade 2 tumors lead to the current study. Herein, we report comparisons of the magnitude or spatial distribution of six MRS metabolites in non-enhancing Grade 2 AS and OD.

**Methods:**

Lactate-edited MR spectroscopy (MRS) (TR=1000ms, TE=144ms, matrix=12x12x8, FOV=120mmx120mmx80mm, NEX=1, nominal voxel size=1cc) was performed on 17 OD patients (age 21-65) and 10 AS patients (age 22-52) with non-enhancing brain lesions prior to their undergoing surgical resection of the tumor. The tumor grades and types were verified histologically from surgical biopsies. Six metabolic markers were analyzed within the two histological subtypes. The markers were voxel-based peak heights of choline (Cho), creatine (Cre), n-acetylaspartate (NAA), lactate (Lac), lipid (Lip) and lactate+lip (LL). Recognizing the intra-subject variability, we first selected control voxels with normal appearing parenchyma and constructed mean and correlation matrix of the markers. Voxels coinciding (>60%) with the lesion on T2-weighted FLAIR images were defined as tumor voxels. Each metabolic marker was normalized by subtracting the mean and dividing by standard deviations of peak heights in the control voxels within the patient. Correlation and logistic regression analyses were performed to differentiate tumor subtypes.

| | OD | AS | Kruskal-Wallis test | Logistic regression |
|---|---|---|---|---|
| | Mean | Mean | P-value | P-value |
| $r_{\text{Cho-Cre}}$ | 0.41 ( 0.26,0.54) | 0.58(0.46, 0.68) | 0.031* | 0.04* |
| $r_{\text{NAA-Lac}}$ | -0.01 (-0.12, 0.06) | -0.21(-0.37, -0.07) | 0.045* | 0.07 |
| $r_{\text{Cho-LL}}$ | 0.15 (-0.015, 0.25) | -0.06 (-0.15,0.08) | 0.008* | - |
| $r_{\text{Cho-Lac}}$ | 0.19 (0.02,0.33) | 0.05 (-0.11, 0.19) | 0.071 | - |

**Table 1 Mean and 90% CI for correlation coefficients**

**Results:**

Cho ($p_{OD}$=0.003, $p_{AS}$=0.05), NAA ($p_{OD}$<0.001, $p_{AS}$ = 0.004) and Lac ($p_{OD}$=0.008, $p_{AS}$=0.03) from non-enhancing tumor tissue showed some difference from control voxels with Wilcoxon signed rank test, but they were not different in OD versus AS ($p_{Cho}$= 0.452, $p_{NAA}$= 0.482, $p_{Lac}$= 0.393). Four of the correlation coefficients ($r$) between these markers showed some difference between the two subtypes (Table 1). The correlation between Cho and Cre ($r_{\text{Cho-Cre}}$) was positively directed in all tumors but the correlation was higher in AS (> 0, p = 0.004) than in OD ( > 0, p <0.001). There was an inverse relationship between NAA and Lac in the AS (< 0, p = 0.04) but no relationship existed in the OD (0, p = 0.74). Table 1 also shows that there were positive correlation between Cho and LL (OD, >0, p=0.02. AS, 0, p=0.5), and Cho and lactate (OD, >0, p=0.016. AS, 0, p=0.73) in OD that were not observed in AS but the difference was significant only for $r_{\text{Cho-LL}}$. We performed a stepwise logistic regression with all 4 correlation coefficients as predictors, but only $r_{\text{Cho-Cre}}$ and $r_{\text{NAA-Lac}}$ was found to have significant regression coefficients. The area under the curve (AUC) of the receiver operating characteristic (ROC) curves were 0.75 for $r_{\text{Cho-Cre}}$ alone, 0.73 for $r_{\text{NAA-Lac}}$ alone, and 0.85 for $r_{\text{Cho-Cre}}$ and $r_{\text{NAA-Lac}}$ .

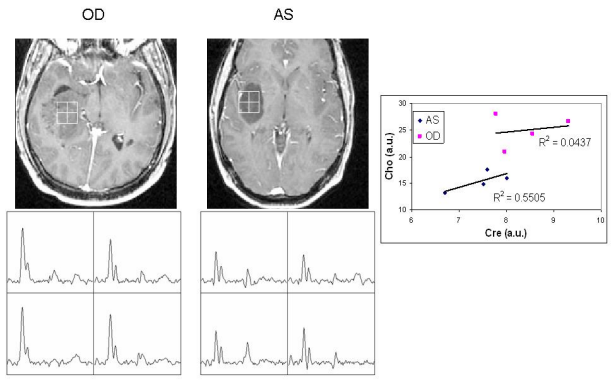


**Figure 1 Correlation between Cho and Cre in AS and OD**

**Discussion:**

Compared with OD, the relative level of Cho and Cre throughout AS lesions was found to be more uniform (Figure 1). AS were further distinguished by a negative correlation between NAA and Lac. Although $r_{\text{NAA-Lac}}$ was small in AS, there was no consistent correlation at all in OD. Further, the addition of $r_{\text{NAA-Lac}}$ to the logistic regression model improved the discrimination between the two tumor types. These associations, though compelling, are not strong enough to be used as classifiers in and of themselves. However, they do provide additional information about the spatial characteristics of metabolism within the two tumor types that may reflect underlying biological processes. MRS-guided biopsy studies are currently being performed to examine the tumor properties that may give rise to the differential patterns that we observed in this study.

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