Using quantitative choline measurements to predict axillary node status in human breast cancer, in vivo

A. McIntosh[1,2], P. J. Bolan[1,2], S. Meisamy[1,2], A. Styczynski[2,3], L. I. Everson[1], M. T. Nelson[1], T. H. Emory[1], T. M. Tuttle[4], D. Yee[5,6], M. Garwood[1,2]

[1]Radiology, University of Minnesota, Minneapolis, Minnesota, United States, [2]Center for Magnetic Resonance Research, Minneapolis, Minnesota, United States, [3]Biomedical Engineering, University of Minnesota, Minneapolis, Minnesota, United States, [4]Surgery, University of Minnesota, Minneapolis, Minnesota, United States, [5]Medicine, University of Minnesota, Minneapolis, Minnesota, United States, [6]Fairview-University Cancer Center, University of Minnesota, Minneapolis, Minnesota, United States

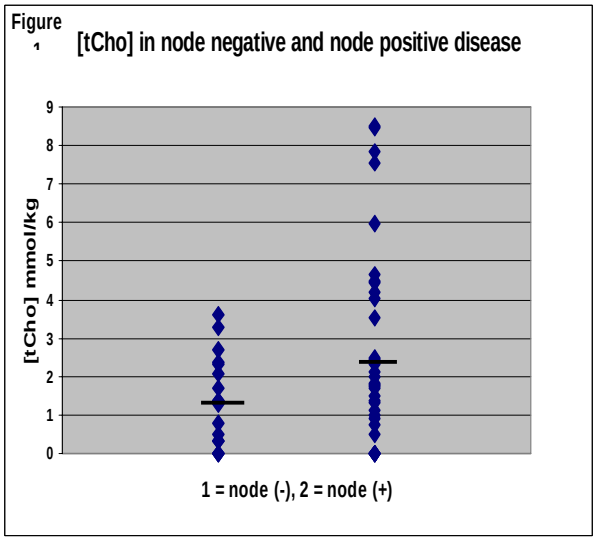
Purpose: To determine whether the concentration of total choline-containing compounds, [tCho], in human breast cancer as measured by high-field proton magnetic resonance spectroscopy (^{1}H MRS), *in vivo*, can be used to independently predict axillary node disease.

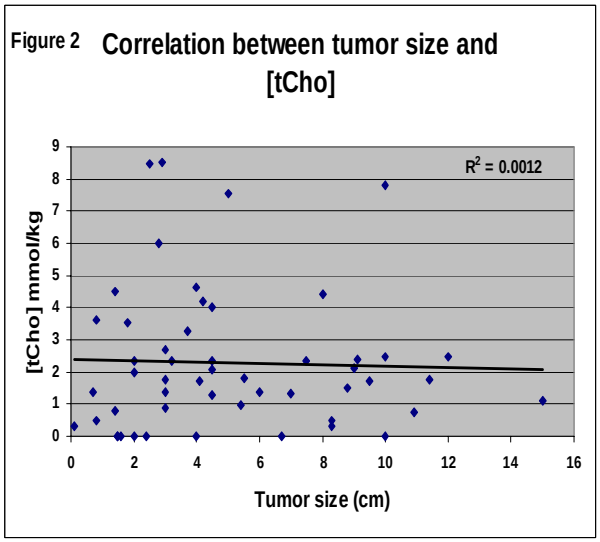
Introduction: Breast cancer will be diagnosed in approximately 220,000 American women and will result in approximately 40,000 deaths in 2004 [1]. The most important prognostic factor in breast cancer is lymph node status [2]. Lymph node status cannot be reliably predicted by physical exam and breast imaging alone. Many studies have shown the biochemical differences between benign and malignant breast disease. One previous study evaluated MRS of axillary nodes to determine metastatic status, using a qualitative method [3]. MRI is currently being evaluated for use in diagnosing breast disease, especially in high risk women [4, 5]. Additionally, MRS has revealed biochemical changes in human breast cancer following treatment with neoadjuvant chemotherapy [6-8]. To the best of our knowledge, no study has found an association between quantitative, *in vivo* tumor [tCho] and lymph node status or disease stage. Here, new data derived from analyses of results from our ongoing ^{1}H MRS studies of breast cancer are presented.

Materials and Methods: Forty eight patients diagnosed with biopsy-confirmed invasive breast cancer were evaluated with contrast-enhanced (Gd-DTPA), fat-suppressed, T_1-weighted MRI and localized ^{1}H MRS using a 4 Tesla research system. MR data were acquired using two different single-breast quadrature transmit-receive radiofrequency surface coils to accommodate different breast sizes. Single voxel ^{1}H spectra were acquired using localization by adiabatic selective refocusing (LASER) [9]. Spectra were analyzed and quantified to produce a [tCho] measurement in units mmol tCho/kg of water [10]. Nodal status was based on pathologic investigation. Staging of disease and tumor size was based on physical examination by the oncologist or surgeon, pathologic evaluation, and imaging with ultrasound and/or mammography. Analysis of variance, logistic regression, linear regression, and chi square analyses were used to determine association between [tCho], grade, stage, tumor size, and hormone receptor status and to determine the ability of these parameters to predict nodal status.

Results: Of the forty eight patients evaluated, there were seven cases of stage-1, 16 of stage-2, 21 of stage-3, and 4 of stage-4 disease. There were 13 node negative, and 35 node positive subjects. Statistical analysis revealed a significantly lower average [tCho] in stages 0-1 (mean 1.1 mmol/kg) tumors than in stages 2-4 (mean 2.3 mmol/kg), $p < 0.05$. Nodal status was also found to be statistically significant: node-negative disease had a lower [tCho] (mean 1.3 mmol/kg) than node-positive disease (mean 2.7 mmol/kg), p=0.01(Figure 1). No correlation was found between tumor size and [tCho] (R^2= 0.0012, p= 0.68) (Figure 2). Significant associations between grade, hormone receptor status, and nodal status were also not found. As would be expected, tumor size did have a significant association with nodal status. Specifically, a tumor size <2 cm was significantly more likely to be node-negative than a larger tumor (p = 0.02). Although it did not reach significance, there was evidence that [tCho] could be used as an independent predictor of nodal status (p=0.11). In this population, higher [tCho] values were associated with node-positive disease independent of tumor size, grade, and hormone receptor status. Of note, no subjects in our study population with a [tCho] greater than 4 mmol/kg had node-negative disease.

Conclusions: These data show that in our study group, node-positive breast cancers had a higher average [tCho] than node-negative disease. From our analysis, the association of [tCho] and nodal status does not appear to be a simple function of tumor size. Based on this preliminary work, [tCho] may be a useful parameter in predicting breast cancer nodal status. With continued accrual of subjects, statistical significance might be reached. Noted in the results was the fact that no subject with a [tCho] greater than 4 mmol/kg had node-negative disease. Once statistical significance is reached, receiver operating characteristic analysis can be used to determine a [tCho] level which will optimize sensitivity and specificity. Furthermore, work is ongoing to find pathologic correlation between [tCho] and an *in vivo* biomarker, which is necessary for these findings to have clinical utility.





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