The Association between Choline Concentration Measured by 1H MR Spectroscopy with Clinical Characteristics and Biomarkers of Breast Cancer

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Introduction:

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) of the breast is an adjunct to the Magnetic Resonance Imaging (MRI) to improve the specificity in distinguishing benign from malignant breast tumors. The diagnostic value of ^{1}H-MRS is typically based on the detection of elevated level of choline containing compounds (tCho), which is a marker of cell proliferation thus indicating the level of aggressiveness in cell division. However, *in vivo* breast ^{1}H-MRS has shown a variable sensitivity (46% - 100%) from study to study [1]. Since choline level represents a proliferative marker, many biological factors may affect its concentration within the tumor. Since this issue has not been studied using a systematic approach we set out to investigate the association between choline and the clinical characteristics and biomarker status of breast cancer. Choline was measured using single-voxel technique with an internal reference method to calculate the absolute concentration in mmol/kg. The other considered lesion characteristics measured on MRI included lesion phenotype (presenting as mass lesions or non-mass type enhancements), and the contrast enhancement kinetic pattern (showing washout or not). Clinical variables considered included: patient age, tumor histological type, tumor grade, biomarker status (ER-estrogen receptor, PR-progesterone receptor, and HER-2). In order to minimize the impact of partial volume effect, which is known to affect the spectral quality thus compromising the accuracy of choline concentration measurements, lesions smaller than 1.5cm were excluded from this study.

Methods:

In a review of our research breast MRI database from 2003 to 2006, a total of 63 patients who were studied with the ^{1}H MRS scan protocol were included in this analysis. All patients had histologically proven breast cancer, and they were referred to participate in this research study for pre-operative staging. Some patients received immediate surgery and some received neoadjuvant chemotherapy. The examinations were performed on a Philips Eclipse 1.5 T MR system with the standard bilateral breast coil. The dynamic contrast enhanced (DCE) MR images were acquired first, and then the single-voxel ^{1}H MRS study was performed using the Point-Resolved spectroscopy (PRESS) sequence. The voxel size was from 3.4 to 8.0 mL (1.5-2 cm^3), placed over the enhanced lesion detected on DCE-MRI. The water suppression by done by CHESS, and frequency-selective lipid suppression (FATSAT) was used for fat suppression. The acquisition parameters were TR/TE= 2000/270 ms with 128 averages. An unsuppressed spectrum was also acquired to measure the water peak (24 averages) to serve as reference. The MR spectrum was analyzed by one spectroscopist. The absolute tCho levels were quantified by using a Gaussian line-shape fitting model and the unsuppressed water signal was used as an internal reference [2]. The tumor morphology was evaluated by a radiologist based on the Breast Imaging Reporting and Data System (BI-RADS) breast MRI lexicon published by the American College of Radiology. The lesion phenotype was separated into mass lesions with well-defined tumor boundaries or non-mass lesions (NML) showing enhancements without clear borders. The enhancement kinetic curves were separated into the washout pattern, or no-washout pattern (including plateau and persistent pattern). The available biomarkers, ER, PR, and HER-2, were included in the analysis. Also when ER or PR is positive, the patient is considered as hormonal receptor positive; and when ER, PR, and HER-2 are all negative, the patient has triple-negative cancer. The association between the choline concentration (tCho) and all considered variables, also pair-wise among all variables, were analyzed by using two-tailed Spearman's non-parametric test.

Results:

The results are summarized in Table 1.The measured tCho level had a wide range 0.08 – 9.99 (2.7 ± 2.3 mmol/kg), consistent with the previously published value (e.g., 1.38 – 10 mmol/kg) by Bolan et al. [3]. The significant associations are highlighted in yellow ($p < 0.05$). ER and PR were highly correlated ($p<0.001$), which was the strongest correlation among all analyses, a well-known fact. Patients with IDC were more likely to present mass lesion ($p<0.017$). We found that younger patients were more likely to present triple-negative cancer ($p<0.036$), and were more likely to have higher choline ($p<0.045$). The HER-2 positive cancer was more likely to be IDC (invasive ductal cancer, $p<0.043$) and have higher tumor grade ($p<0.043$). Although tCho did not show significant correlation with any cancer characteristics, the p values in 3 analyses approached significant level ($p < 0.1$, highlighted in pink). Triple negative cancer was more likely to have high tCho than non-TN cancer ($p<0.06$). Lesions with higher tCho had a higher grade ($p<0.07$), and were more likely to present washout DCE kinetic pattern ($p<0.09$). Other associations among clinical variables that approached significance level (highlighted in blue) included: younger age was associated with higher grade ($p<0.08$), IDC had higher tumor grade than non-IDC ($p<0.08$), and compared to ER- cancer ER+ cancer was more likely to have lower grade ($p<0.07$).

	Age (Years)	tCho (mmol/kg)	Morphology Mass/NML	DCE washout /no	Type IDC or not	Tumor Grade (1-3)	ER (+/-)	PR (+/-)	HER-2 (+/-)	Hormonal R (+/-)	Triple Neg (yes or no)
Age	(1)	(-0.27) 0.045	(-0.13) 0.36	(-0.08) 0.62	(0.11) 0.42	(-0.24) 0.08	(0.17) 0.25	(0.06) 0.68	(-0.1) 0.94	(0.17) 0.25	(0.3) 0.036
tCho		(1)	(-0.07) 0.6	(-0.25) 0.09	(0.04) 0.79	(0.25) 0.07	(-0.05) 0.7	(-0.25) 0.87	(-0.09) 0.52	(-0.09) 0.53	(-0.26) 0.06
Morphology			(1)	(0.1) 0.5	(0.3) 0.017	(-0.22) 0.1	(0.07) 0.64	(0.07) 0.64	(-0.1) 0.49	(0.04) 0.77	(0.03) 0.85
DCE kinetics				(1)	(0.17) 0.26	(-0.18) 0.26	(0.17) 0.29	(0.23) 0.2	(-0.15) 0.36	(0.16) 0.32	(0.12) 0.46
Tumor Type					(1)	(-0.24) 0.08	(0.19) 0.19	(0.23) 0.13	(-0.28) 0.043	(-0.09) 0.53	(0.05) 0.73
Tumor Grade						(1)	(-0.26) 0.07	(-0.2) 0.21	(0.29) 0.043	(-0.21) 0.15	(-0.27) 0.06
ER							(1)	(0.86) 0.001	(-0.15) 0.3	N/A	N/A
PR								(1)	(-0.16) 0.31	N/A	N/A
HER-2									(1)	(-0.18) 0.21	N/A
Hormonal R										(1)	N/A
Triple Neg											(1)

Table1. The data format presented in the cell is: (r, correlation coefficient) and p value. Age, tCho are continuous variables; morphology, DCE, tumor type, ER, PR, HER-2, HR, and triple negative are dichotomized variables, and the tumor grade is categorized variables (1-3).

Discussion:

The primary aim of this study was to investigate the association between tCho measured by single-voxel MRS and other clinical characteristics in different breast lesions. The only significant finding of tCho was with age, which is expected based on that choline is a tissue proliferation marker, and that younger patients are more likely to have proliferative breast tissues, also they have denser breasts that will yield a better spectral quality for the analysis of choline. The other correlation of tCho approaching significance level is with DCE washout pattern (higher angiogenesis), higher tumor grade, and in patients with triple negative breast cancer. Since these characteristics are associated with more aggressive disease, thus are expected to show a higher proliferation thus higher choline. We also found other well-known relationships such as a high correlation between ER and PR ($p < 0.001$), and that mass lesions are more likely to show washout DCE pattern ($p<0.017$). The results presented here may provide further understanding about the role of MRS in characterization of different breast lesions, and that will aid in better interpretation of MRS for diagnosis of breast lesions.

References: [1]. Meisamy S, et al. Radiology 23:465-475(2005). [2]. Baek et al., MAGMA 19:96-104 (2006). [3]. Bolan et al., Magn Reson Med 50: 1134-1143 (2003).

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