Correlation of molecular biomarker (ER, PR, HER2/neu status) with total choline concentration and tumor volume in breast cancer patients: Using an MRI and in vivo Proton MRS

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Objectives: To determine the association of Chol and tumor volume in invasive breast cancer patients with molecular subtypes based on expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptors (HER2).

Introduction: Breast cancer is a heterogeneous disease comprising of five molecular subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2), basal like and normal like. Luminal tumors are characterized by expression of the estrogen receptor (ER), which is usually accompanied by progesterone receptor (PR) expression. Nearly 70% of breast cancers are ER+/PR+ which have a better prognosis and more treatment options than ER- cancers (1). Expression of protein kinase HER2 is up-regulated in HER2 over-expressing tumors (~20%). These molecular features of breast cancer play an important role in treatment management. Thus, early diagnosis and understanding of the molecular features of breast tumors is essential for successful treatment and in order to increase the patient survival. In-vivo magnetic resonance spectroscopy (MRS) is a unique tool that detects total choline (tCho) in malignant breast tissues and its presence has been reported to differentiate malignancy and 1H MRS in a clinical setting has been reported to increase the specificity of MRI. However, variations in tCho concentration and observation of tCho peak in normal and benign lesions reduces the diagnostic value of in vivo MRS and thus understanding the reasons for these variations might help increase the diagnostic specificity. Therefore, in the present study, we determined the absolute concentration of tCho and tumor volume in different molecular subtypes (ER, PR and HER2) of invasive breast cancer patients to get an insight into the association of tCho and tumor volume with the molecular heterogeneity of breast lesions.

Material and Methods: A total of 73 (mean age = 45.5 ± 11.4; range: 25 – 70 years) women for whom ER, PR, HER2 status available were included in the analysis. Written informed consent was obtained from each patient and controls and the study was approved by the Institutional ethical committee. Patients with the clinically palpable lump were subjected to FNAC for confirmation of malignancy followed by core needle biopsy. Biopsied tissue was subjected to histology and immune-histochemical examinations to determine the expression of hormonal receptors like ER, PR and HER2. Patients with HER2 expression scores 0 and 1+ were categorized as HER2-negative (HER2-) and those with the scores of 3+ were categorized as HER2/neu-positive (HER2+). 26 patients with the score of 2+ were excluded from the analysis since their data of fluorescence in situ hybridization was not available. Thus, 13 patients fall under the category of HER2- (a) n = 13 3.8 ± 1.2(1.7 – 6.3) HER2/neu- (b) n = 34 4.4 ± 2.9(1.0 – 11.8) HER2/neu+ (a) n = 13 3.8 ± 1.2(1.7 – 6.3) HER2/neu+ (b) n = 34 4.4 ± 2.9(1.0 – 11.8) HER2/neu+ (c) n = 35 5.0 ± 2.9(1.0 – 11.8) HER2/neu+ (c) n = 35 5.0 ± 2.9(1.0 – 11.8) HER2/neu+ (d) n = 38 4.3 ± 2.8(1.0 – 16.1) HER2/neu+ (d) n = 38 4.3 ± 2.8(1.0 – 16.1) PR+(a) n = 37 5.0 ± 2.9(1.0 – 11.8) PR+(a) n = 37 5.0 ± 2.9(1.0 – 11.8) PR+(b) n = 36 4.7 ± 2.9(1.0 – 16.1) PR+(b) n = 36 4.7 ± 2.9(1.0 – 16.1) 5 denotes p<0.05 for tumor volume between (c) and (d).

Discussion: In the current study concentration of total tCho levels measured showed a wide variation with the different sub types of tumor but no significant difference was observed among various molecular subtypes. The wide range of tCho concentration observed might be attributed to the heterogeneous nature of the breast lesions or other molecular features of breast cancer. Further tumor volume was found to be significantly larger in ER- group than in ER+ group. Chen et al. reported larger tumor volumes with markedly higher micro-vessel density in ER- cancers with no difference in Cho levels (3). Koukourakis et al. reported an inverse association of micro-vascular density with ER expression (4). The higher proliferative activity associated with ER- cancers may be one reason for larger tumor volumes observed in our patients (5). Our data demonstrated the potential of quantitative 1H MRS and MR imaging in characterizing malignant based on different sub-types.