Published in final edited form as:

NMR Biomed. 2011 April ; 24(3): 316–324. doi:10.1002/nbm.1595.

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

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Abstract

This study was to investigate the association between tCho and the clinical characteristics and biomarker status of breast cancer. Sixty-two patients with breast cancer which was 1.5 cm or larger in size on MR images were studied. The tCho concentration was correlated with the MR imaging features, the contrast enhancement kinetics, clinical variables, and biomarkers. Pair-wise two-tailed Spearman's non-parametric test was used for the statistical analysis. The tCho was higher in high grade than moderate/low grade tumor ($p=0.04$) and in tumors with higher Ktrans and kep ($p<0.001$ for both). The association of tCho with age ($p=0.05$) and triple negative biomarker ($p=0.09$) approached significance. tCho was not detected in 17 patients, including 15 invasive ductal cancer and 2 infiltrating lobular cancer. Fifteen of the 17 patients had moderate to low grade cancers, and 11 had HER-2 negative cancer, suggesting these two factors might lead to false negative choline. Higher tCho in high grade tumors and tumors with higher Ktrans and kep indicates choline is associated with cell proliferation and tumor angiogenesis. Higher choline level in younger women may be due to their more aggressive tumor type. The results presented here may aid in better interpretation of ¹H MRS for diagnosis of breast lesions.

INTRODUCTION

Choline-containing compounds are the major components of cell membrane required for structural stability and cell proliferation (1). Many studies have shown that tCho peak is elevated in neoplastic tissues. The increased tCho in neoplastic tissues may be due to increased membrane turnover by replicating cells. However, the precise mechanisms that produce an elevated tCho concentration have not been fully understood yet. The level of tCho can be modulated by numerous changes in enzymatic activity and fluxes in biosynthetic and catabolic pathways in which choline compounds serve as both precursors and catabolites (2). The choline signal can be measured using in vivo proton magnetic resonance spectroscopy (¹H MRS). The choline peak is found in the MR spectra resonating at 3.2 ppm, with the main contribution from phosphocholine (3).

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¹H MRS has become an adjunct to dynamic contrast enhanced MRI (DCE-MRI) in the clinical evaluation of breast lesions. Malignant lesions are more likely to show high levels of choline-containing compounds compared to benign or normal breast tissues, and this observation may serve as the basis for differentiating between malignant and benign breast lesions. Prior studies performed at 1.5T MR have reported sensitivities of 70–100% (average 89%) and specificity of 67–100% (average 87%) for breast MRS (4–11). Katz-Brull et al. analyzed five studies and reported an overall sensitivity of 83% and specificity of 85% (12). Despite of the promising results demonstrated in these studies, ¹H MRS has a false-negative rate of approximately 4–18% and a false-positive rate of 14–18% (4–6,13), and can only be used to provide additional information for characterization of the detected lesion.

The underlying mechanisms for the elevated level of choline-containing compounds in breast cancer have been extensively investigated. Since choline level represents a proliferative marker, many biological factors may affect its concentration within the tumor. It would be of interest to evaluate the biological parameters of benign and malignant lesions that might affect the outcome of ¹H MRS. It has been reported that the degree of elevated choline-containing compounds is related to the grade of the tumor, with higher levels in high-grade than in low-grade lesions (14,15). The relationship between the presence of choline containing compound and other commonly analyzed breast cancer biomarkers, such as estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER-2 receptor), was less studied (16–18).

The false-negative results in breast cancer based on total choline concentration (tCho) measured by proton magnetic resonance spectroscopy may be in part related to other characteristic parameters. The purpose of this study was to conduct a systematic analysis of the relationship between the choline concentration measured by ¹H MRS and the known diagnostic and prognostic markers of breast cancer, including the clinical characteristics, tumor phenotype and biomarker status of breast cancer.

MATERIALS AND METHODS

Patients

The subjects were identified from a retrospective review of our research breast MRI database of all patients who received a scan protocol including DCE-MRI and the single-voxel ¹H MRS sequence from 2003 to 2006. The inclusion criteria were patients with biopsy confirmed diagnosis of malignant lesions that measured 1.5 cm or larger on MR images. The ¹H MRS voxel size used in this study was 1.5cm to 2.0cm in one dimension.. If fibroglandular tissues are contained in the MRS voxel, that will lead to a lower choline; if fatty tissues are contained in the MRS voxel that may further degrade the spectral quality. Therefore, lesions smaller than 1.5cm were excluded to minimize the impact of partial volume effect.

A total of 62 patients were identified. Table 1 summarizes the number of patients in each category: tumor type (invasive ductal carcinoma (IDC) or infiltrating lobular cancer (ILC)), tumor grade (I, II, III), tumor morphology (mass or non-mass), HER-2 (positive or negative), estrogen receptor (ER) (positive or negative), progesterone receptor (PR) (positive or negative), Hormonal receptor (positive or negative), or Triple Negative (TN) (yes or no). All these 62 subjects received pre-therapy ¹H MRS. Either surgery (N=29) or neoadjuvant chemotherapy (N=33) were performed after the MRI/MRS study. Patient age ranged from 31 to 78 with a mean age of 54. Forty-one patients were ≤ 55 and twenty-one were >55. The analyzed clinical variables and biomarkers included: patient age, tumor histological type, tumor grade, ER, PR, and HER-2. The association between choline and the lesion features appeared on MRI, including mass lesions versus non-mass-like

enhancements and the contrast enhancement pharmacokinetic parameters, were also analyzed. This study was approved by the institutional review board and all participants gave written informed consent.

MRI Protocol

The MRI study was performed using a 1.5T Phillips Eclipse MR scanner with a standard bilateral breast coil (Philips Medical Systems, Cleveland, OH, USA). The imaging protocol consisted of high-resolution precontrast T1 weighted imaging, bilateral DCE-MRI, and MRS. After the localizer scan to define the location of the breasts, sagittal view unilateral precontrast T1-weighted images were acquired using a spin-echo pulse sequence. A three-dimensional (3D) spoiled gradient-recalled echo (SPGR) radio frequency Fourier-acquired steady-state (RF-FAST) pulse sequence with 16 frames (repetitions) was then utilized for bilateral dynamic imaging. A total of 32 axial slices with 4-mm thickness were used to acquire dynamic data from both breasts. The following imaging parameters were used: TR = 8.1 msec, TE = 4.0 msec, flip angle = 20°, matrix size = 256 × 128, and FOV = 38 cm. The scan time was 42 seconds per acquisition. The sequence was repeated 16 times for dynamic acquisitions, including four pre-contrast sets and 12 post-contrast sets. The contrast agent (Omniscan, 0.1 mmol/kg) was manually injected at the beginning of the fifth acquisition, and was timed to finish in 12 seconds in order to standardize the bolus length for all patients. Immediately following the contrast, 10 cc saline was injected to flush in all contrast medium.

¹H MRS Protocol and Analysis

After completing the DCE-MRI, the acquisition of MR spectrum was performed using the localized single-voxel technique with the point-resolved spectroscopic sequence (PRESS) (19). The spectroscopic voxel was placed by a spectroscopist (HM Baek) on the subtraction images at one-minute post injection generated on the scanner console (using DCE frame #6 – frame #3). The voxel size was from 3.4 cm³ (1.5×1.5×1.5 cm) to 8.0 cm³ (2×2×2 cm). It was carefully positioned to maximize coverage of the enhanced lesion on the subtraction images, and minimize the inclusion of adipose tissue on pre-contrast non-fat-saturated (non-fat-sat) images. Voxel shimming was performed for optimization of field homogeneity, and the typical line width of the water peak (full-width at half-maximum [FWHM]) was 8 to 17 Hz. The water suppression was performed by using three-pulse chemical shift selective (CHESS) RF pulses (20), and fat signal was independently attenuated by using frequency-selective lipid suppression technique. The PRESS sequence parameters were as follows: TE = 270 msec, TR = 2000 msec, data points = 2048, spectral bandwidth = 1953 Hz, and acquisition averages = 128. A fully relaxed, unsuppressed spectrum (24 averages) was also acquired to measure the water and lipid peaks as the internal reference for calculating absolute Cho concentration (in mmol/kg) (21,22). 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 (22).

Analysis of Enhancement Time Course

The enhancement kinetics of the lesion was measured from a hot spot region of interest (ROI). A computer algorithm was used to search an area of 3×3 pixels on one image slice within the whole tumor that showed the strongest enhancement on subtraction images at two minutes post-injection as the hot spot ROI. The maximum intensity projection (MIP) was used as the reference. The percent enhancement time course was calculated by subtracting the pre-contrast signal intensity (mean of first four frames) from each of the subsequent 12 post-contrast signal intensities and then normalized to the pre-contrast signal intensity to calculate the enhancement percentage. The enhancement kinetics was further analyzed based on the two-compartmental pharmacokinetic model described by Tofts et al. (23,24) to obtain

transfer constant and rate constant, K_{trans} and k_{ep} (representing the uptake rate and washout rate, respectively).

Interpretation of MRI Features Based on BI-RADS lexicon

The presentation of the lesion on MR Images was analyzed by a radiologist (JH Chen) with extensive experience in body imaging and breast MR imaging. Morphological and enhancement kinetic features were evaluated in concordance with the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) lexicon (25). Morphological diagnosis included mass-type with well-defined tumor boundaries (including a foci < 5 mm and a mass ≥ 5 mm), and non-mass-like enhancement lesions that enhance in an area that is neither a mass nor a blood vessel. Tumor size was measured based on the longest dimension and the longest perpendicular dimension shown on MIP.

Analysis of Tumor Grade and Biomarkers

The tumor grade and biomarker status were examined by pathologists at our institution using the standard clinical protocol. The modified Bloom and Richardson tumor grade of I, II, and III (indicating low, moderate, and high grade) were used in the analysis. The ER and PR status were considered negative if immunoperoxidase staining of tumor cell nuclei in the biopsy specimen was less than 5%. The expression of HER-2 protein in the tumor was measured using immunohistochemical (IHC) analysis on a scale from 0 to 3+. A score of 3+ on IHC indicates positive HER-2; and scores of 0 to 1+ indicates negative HER-2. Patients with score of 2+ were further examined using fluorescence in situ hybridization (FISH). A tumor is designated as “positive” for Her-2 gene amplification if gene-to-chromosome ratio is > 2.0 . When ER or PR is positive, the cancer was hormonal receptor positive; and when ER, PR, and HER-2 are all negative, the cancer was triple-negative.

Statistics

The association between all considered variables, including the choline concentration (tCho), clinical characteristics, tumor phenotypes, and biomarker status, was evaluated. Age and choline concentration were continuous variables. The enhancement kinetic parameters K_{trans} and k_{ep} were also continuous variables. The tumor type is separated as IDC or ILC. The tumor grade is categorized as I (low), II (moderate) and III (high). The tumor morphology was separated into mass lesions or non-mass lesions (NML). The biomarkers, including ER, PR, HER-2, hormonal receptor and triple negative were categorized as positive or negative. The pair-wise association was analyzed by using two-tailed Spearman's non-parametric test with pair-wise deletion of missing data. For non-parametric correlation, it treated all the data based on its own rank in the whole dataset. It does not require numerical value or any assumption about its distribution. On the other hand, parametric correlation (Pearson's correlation) can be used for numerical values comparison and it requires the dataset should be normally distributed.

For correlation coefficient r and p -value: correlation coefficient r quantifies the correlation value about two variables, and p -value measures the probability of independency of the two variables. If absolute r is in range of (0, 0.3), it indicates two variables are poorly correlated. If absolute r is in range of (0.3, 0.5), it indicates two variables are moderately correlated. If absolute r is in range of (0.5, 1), it indicates two variables are highly correlated. For p , if $p < 0.05$, two variables are correlated. If $p > 0.05$, two variables are not correlated.

To interpret the study results, we first checked p -value to see whether these two variables are correlated ($p < 0.05$) or not ($p \geq 0.05$). Then we checked the correlation coefficient r to see how much they correlated ($r < 0.3$, poor correlation, $0.3 < r < 0.5$ moderate, $r > 0.5$ high

correlation). When p was small ($p < 0.05$) and r was small (absolute $r < 0.3$), it highly indicates the data sample is diversely distributed (distribution and/or small sample size).

RESULTS

The results of pair-wise association among all analyzed variables are shown in Table 2. ER and PR were highly correlated ($r = 0.87$, $p < 0.001$), which was the strongest correlation among all analyses, a well-known fact. Patients with IDC were more likely to present mass lesion ($r = -0.43$, $p < 0.001$). Younger patients were more likely to have higher choline ($p = 0.05$), and present triple-negative cancer ($r = 0.32$, $p = 0.02$). HER-2 positive cancer was more likely to be high grade ($r = 0.36$, $p = 0.01$).

The measured tCho level had a wide range 0.08 – 9.99 (1.9 ± 2.3 mmol/kg), but the high variation was consistent with the previously published value, e.g., 1.38 – 10 mmol/kg by Bolan et al. (21). Higher tCho showed significant correlation with higher tumor grade ($r = 0.38$, $p = 0.04$) (Figures 1 and 2). The association of tCho with age and triple negative status approached significant level ($p = 0.05$ and $p = 0.09$, respectively) (Figure 3). Analysis of DCE pharmacokinetic parameters found that higher Ktrans was associated with younger age ($r = -0.3$, $p = 0.02$) and higher tumor grade ($r = 0.32$, $p = 0.02$); higher Ktrans and Kep were associated with higher choline level ($r = 0.54$ $p < 0.001$; $r = 0.53$ $p < 0.001$) and triple negative tumor ($r = -0.36$ $p = 0.01$; $r = -0.36$ $p = 0.01$). The results of tCho, Ktrans, and Kep in different tumor types, tumor grades, MR phenotypes, and biomarkers status were listed in Table 3.

Seventeen patients showed false negative results of tCho in our study, including 15 IDC and 2 ILC. Eleven patients were HER-2 negative (Figure 4), four patients were HER-2 positive (Figure 5 and Figure 6), and the other two patients' HER-2 results were not available. Of these 17 patients, 15 had moderate to low grade cancers and 2 had high grade tumor (Figure 4), 4 had extensive DCIS, and 5 had non-mass-like enhancement lesions. The results suggested that negative HER-2 (when in combination with positive estrogen receptor) and low tumor grade were two likely factors leading to false negative choline.

DISCUSSION

The addition of single-voxel 1H MRS could improve the diagnostic specificity of DCE-MRI (9,22). Bartella et al. found that the use of 1H MRS could significantly increase the positive predicting value (PPV) of biopsy from 35% to 82% and obviate biopsy in 57% of the 40 lesions with unknown histologic features (11). Huang et al. also showed that the addition of 1H MRS to a conventional MRI protocol increased the specificity from 62.5% to 87.5% (10).

Although 1H MRS has shown promising results for evaluating breast cancer, a number of false-negative findings in various in situ and invasive lesions have been reported (4,5,7). The failure to detect choline in some breast cancers might be related to insufficient sensitivity, such as for small or less aggressive tumors. Other problems, including patient motion, contamination by hemorrhage (5), the inclusion of fatty tissue (6), and tumor cells growing with many intervening stromal cells and inflammatory cells (26) could also lead to false negative results. In studies to characterize the dependence of breast 1H MRS sensitivity on the lesion size, the sensitivity in three different size groups (< 2.5 , 2.5–4.9, and ≥ 5 cm) increased from 72% to 90% to 100% (5–7). In this study we only selected patients with tumor size larger than 1.5 cm. In small lesions, the MRS voxel size may be larger than the tumor size. If fibroglandular tissues are contained in the MRS voxel, that will lead to a lower choline; if fatty tissues are contained in the MRS voxel that may further degrade the spectral quality. Therefore, in either scenario, the spectrum suffers from contamination of

normal tissues, and it does not reflect the true characteristics of the cancerous tissues. Many biological factors likely to affect the measurement of choline by ^1H MRS need to be investigated to understand the intrinsic limitation of ^1H MRS for characterization of breast lesions.

In our study, higher tCho level were correlated with higher K_{trans} and k_{ep} ($p < 0.001$ for both). However, note that the hot spot size was 3×3 pixels on one slice (4 mm), with a total of 9 pixels. The MRS voxel was much bigger than the DCE hot spot. Therefore, these datasets are not meant for spatial correlation, rather are for characterizing different properties of the tumor (that is, vascular and metabolic) for investigation of their associations. We have published two other studies (27,28) comparing the DCE and MRS results analyzed from spatially co-registered tissues. Su et al. reported a study correlating pharmacokinetic parameters in DCE-MRI with choline measured by ^1H MRS using chemical-shift imaging method in 14 patients (27). It was shown that by averaging over all Cho-positive voxels, there was a significant linear correlation between Cho with percent enhancement at 2 min after injection ($r = 0.75$, $p = 0.002$), pharmacokinetic parameters K_{trans} ($r = 0.74$, $p = 0.003$), and k_{ep} ($r = 0.76$, $p = 0.002$). Baek et al. studied 32 patients using single-voxel ^1H MRS (28) and found a significant correlation between tCho and the pharmacokinetic parameter k_{ep} ($r = 0.62$, $p < 0.0001$), indicating that tissues with a high Cho level have higher wash-out rates in DCE MRI. A sub-cohort of twenty subjects reported in that study were analyzed in this work. The results suggested that overall there is a correlation between Choline metabolism and angiogenesis activity. The findings that higher K_{trans} and k_{ep} were significantly associated with younger age and triple negative cancer suggested that angiogenesis was higher in more aggressive breast cancer.

Lesions with a higher tCho level were more likely to show a higher tumor grade ($p = 0.04$). Smith et al. (15) measured the content of the choline-related metabolites in chemical extracts of 46 human breast carcinoma using ^31P NMR spectroscopy and found that the phosphocholine content was higher in high grade tumors when compared with low grade tumors. In our study high grade breast cancer more likely occurs in estrogen negative breast cancer ($p = 0.04$). Negative ER in breast cancer is considered as a less favorable prognostic indicator. Compared to its ER positive counterpart, the cells are more likely to be poorly-differentiated, and more aggressive. ER-negative tumors were characterized by a higher proliferative activity, and a significant association between Choline kinase overexpression with high histologic tumor grade and ER negative status has been reported (29). The association was possibly mediated through higher cell proliferation (5).

Despite that HER-2 positive cancer was more likely to be high tumor grade ($P = 0.01$), tCho did not showed a significant difference between HER-2 positive and negative cancer. In our study ^1H MRS showed 17 false negative diagnoses. Of them, 15 were moderate or low grade tumors and 11 were HER-2 negative cancers. It was therefore suggested that HER-2 negative cancer with moderate or low grade was more likely to be tCho negative (9). HER2 receptor mediates signaling to cancer cells and stimulates proliferation (30,31). HER2/neu is over-expressed in 20%–25% of invasive breast cancers and associated with an aggressive tumor, an early relapse and reduced survival rate (32–34). HER-2 positive breast cancer is in general more aggressive than HER-2 negative cancer. In one study by Aboagye et al., overexpression of HER-2 in a tumor cell line resulted in a dramatic increase of choline compounds (35).

Younger patients were more likely to have higher choline ($p = 0.05$). Breast cancer in young patients is known to be more aggressive and associated with higher recurrence rate and mortality (34). In a large series of 3,722 patients, Chung et al. (36) demonstrated that women < 40 years have the worst 5-year breast cancer-specific survival compared to all other older

age groups. Tumors in young women were more likely to be advanced stage, high grade, ER/PR negative, and lymph-node positive (37). Young age was thus considered a poor prognostic factor and recommended for aggressive chemotherapy irrespective of other demographic, clinical, and biological characteristics (38). The accurate diagnosis of malignant breast tumors in younger women is of special importance for two reasons. First, the sensitivity of the mammographic examination in these patients (with denser breast) is lower (39–41), which makes MRI/MRS a suitable adjunct imaging modality in these women. Second, the diagnosis of benign lesion in young women is slightly higher than in the entire population, and the addition of 1H MRS may improve the diagnostic specificity. Using 1H MRS, malignant tumors in young patient population can be diagnosed correctly with high sensitivity (100%) and specificity (89%–100%) (5–7). The denser breasts in young women may yield a better spectral quality for the analysis of choline. Given all these reasons, including 1H MRS in the scan protocol for young women may provide very useful information.

It was noted that triple negative cancer was more likely to have high tCho than non-TN cancer ($p = 0.09$). All of the 11 TN tumors in this study showed positive choline peaks. TN tumors, accounting for 12%–26% of all types of breast cancers, were known to be more aggressive (42–47). Histologically, TN cancers were poorly differentiated, mainly of high histologic grade and with high mitotic index (42,48).

In our study, mass lesions vs. non-mass-like enhancement did not show significant difference of tCho ($p = 0.79$). Since non-mass-like enhancement lesions typically grow in an infiltrative pattern, measurement of their tCho level needs to be taken cautiously to avoid measurement contamination from the normal tissues that are intermingled with cancerous tissues within the MRS voxel. In a study by Bartella et al. (49), 1H MRS significantly increased the PPV of biopsy for MR imaging–detected lesions with non-mass enhancement from 20% to 63% and has obviated biopsy in 68% of lesions. In their study, all 12 non-mass-like enhancement cancers showed positive choline. From their illustrated cases, most of them presented as focal non-mass-like lesions rather than diffusely infiltrative lesions. This might be the reason why their results showed 100% sensitivity. In our study, cases of diffuse non-mass-like-enhancement lesions were included, which may account for the lower choline detection rate.

IDC and ILC did not show a significant different tCho level ($p = 0.84$) in our study. 1H MRS was found equally sensitive in other types of invasive carcinomas compared to the more common IDC (50). Ductal carcinoma in-situ (DCIS) and IDC with an extensive in situ component, however, are likely to be negative for choline at 1H MRS (51). Conversely, it is known that some fibroadenomas may present high levels of tCho in vitro (52) and in vivo (4,5,11), which might be related to their high activity of cell proliferation.

Since in this study the MRS was performed after injection of Gd contrast, the effect of Gd on the measured spectra was a concern. Bolan et al. (53) reported that the post-contrast tCho peak was 10% less compared with the pre-contrast value, and Bonnie et al. (54) found that Gd increased linewidth (~17%) and decreased area (~15%) of the tCho peak. More recently, Lenkinski et al. (55) reported that only the three negatively-charged chelates: Magnevist, Multihance, and Dotarem, broadened the Cho peak in phantoms and reduced the area of the tCho peak in vivo by an average of about 40%. Therefore, these studies demonstrate that contrast agents can affect MRS measurements. However, it is not yet clear if the effects of contrast agents would significantly bias MRS measurements.

The small number of subjects and the exclusion of tumors smaller than 1.5 cm were limitations of this study. With the 1H MRS voxel size of 1.5–2.0cm, it was still possible that

adjacent normal breast tissues were included in the 1H MRS voxel, leading to partial volume effect and reduced choline concentration.

CONCLUSION

In this study, we have shown that higher tCho concentration was significantly correlated with higher tumor grade and higher Ktrans and kep (higher angiogenesis). Women of younger age also tended to have higher choline level, which is expected based on that younger patients are likely to have more aggressive tumors; also their denser breasts may yield a better spectral quality for the analysis of choline. The results presented here may provide further understanding about the role of 1H MRS in characterization of different breast lesions, and that will aid in better interpretation of 1H MRS for diagnosis of breast lesions.

Acknowledgments

This work was supported in part by NIH/NCI R01 CA127927, R01 CA90437, R03 CA136071, and California BCRP # 9WB-0020, 12FB-0031 and 14GB-0148.

Abbreviations

1H MRS	proton magnetic resonance spectroscopy
DCE-MRI	dynamic contrast enhanced MRI
HER-2 receptor	human epidermal growth factor receptor 2
tCho	total choline concentration
ER	estrogen receptor
PR	progesterone receptor
TN	Triple Negative
IDC	invasive ductal carcinoma
ILC	infiltrating lobular cancer
3D	three-dimensional
SPGR	spoiled gradient-recalled echo
RF-FAST	Fourier-acquired steady-state
PRESS	point-resolved spectroscopic sequence
CHESS	chemical shift selective
ROI	region of interest
MIP	maximum intensity projection
ACR BI-RADS	American College of Radiology Breast Imaging Reporting and Data System
IHC	immunohistochemical
FISH	fluorescence in situ hybridization
NML	non-mass lesions
PPV	positive predicting value
DCIS	Ductal carcinoma in-situ

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Figure 1.

A 62 y/o woman with a 3.4×3.3cm high grade invasive ductal cancer in her right breast. The 1H MRS showed a high choline peak (6.97 mmol/kg) at the 3.2ppm location. The biomarkers information was not available in this patient.

Figure 2.

A 66 y/o woman with a 2.7×2.6cm moderate grade, Her-2 negative, ER-positive invasive ductal cancer in the left breast. The 1H MRS showed a low choline peak (1.79 mmol/kg) at the 3.2ppm location.

Figure 3.

A 35 y/o woman with a 3.5×2.7cm high grade, triple negative invasive ductal cancer in the right breast. The 1H MRS showed a choline peak (4.33 mmol/kg) at the 3.2ppm location.

Figure 4.

A 32 y/o woman status post breast augmentation with a 3.5×2.0 cm ill-defined margin heterogeneously enhanced invasive ductal cancer in her left breast. The tumor was high grade, Her-2 negative, and hormonal positive. The choline peak was not detectable in the ¹H MRS spectra.

Figure 5.

A 50 y/o woman with a 4.1×2.1cm regional enhancement of infiltrative lobular cancer in her left breast. The tumor was low grade, Her-2 positive, and hormonal negative. The choline peak was not detectable in the 1H MRS spectra.

Figure 6.

A 58 y/o woman with a 2.8×2.2cm ill-defined margin heterogeneously enhanced invasive ductal cancer in her left breast. The tumor was moderate grade, Her-2 positive, and hormonal negative. The choline peak was not detectable in the 1H MRS spectra.

Table 1

Clinical and Imaging Characteristics of the 62 Women

	Case number	Percentage (%)
Tumor type (N=62)		
IDC	55	89%
ILC	7	11%
Tumor grade (N=57, 5 unknown)		
I	9	16%
II	28	49%
III	20	35%
Tumor morphology (N=62)		
Mass	43	69%
Non-mass	19	31%
HER-2 (N=55, 7 unknown)		
Positive	18	34%
Negative	37	66%
ER (N=54, 8 unknown)		
Positive	34	63%
Negative	20	37%
PR (N=47, 15 unknown)		
Positive	26	55%
Negative	21	45%
Hormonal receptor (N=54, 8 unknown)		
Positive	35	65%
Negative	19	35%
Triple negative tumor (N=56)		
Yes	11	20%
No	45	80%

Table 2

Correlation of Age, MRI Features, and Clinical Characteristics

	MRI features						Clinical characteristics				
	Correlation r (P-value)	Cho level	Tumor Type	Tumor Grade	Morphology	Ktrans	Kep	Her2	ER	PR	Triple Negative
Age		-0.25 (0.05)	0.26 (0.04*)	-0.26 (0.04*)	0.01 (0.94)	-0.30 (0.02*)	-0.29 (0.02*)	-0.07 (0.62)	0.23 (0.09)	0.14 (0.36)	0.32 (0.02*)
Cho Level			0.03 (0.84)	0.38 (0.04*)	0.03 (0.79)	0.54 (<0.001*)	0.53 (<0.001*)	-0.03 (0.85)	-0.11 (0.41)	0.08 (0.56)	-0.23 (0.09)
Tumor Type				-0.28 (0.03*)	-0.43 (<0.001*)	-0.19 (0.13)	-0.24 (0.06)	-0.22 (0.10)	0.24 (0.08)	0.27 (0.07)	0.15 (0.26)
Tumor Grade					0.24 (0.07)	0.32 (0.02*)	0.29 (0.03*)	0.36 (0.01*)	-0.27 (0.04*)	-0.22 (0.13)	-0.22 (0.11)
Morphology						0.10 (0.45)	0.17 (0.18)	0.09 (0.50)	-0.04 (0.78)	-0.02 (0.87)	-0.009 (0.95)
Ktrans							0.95 (<0.001*)	-0.02 (0.89)	-0.25 (0.07)	-0.24 (0.11)	-0.36 (0.01*)
Kep								0.06 (0.67)	-0.28 (0.04*)	-0.29 (0.04*)	-0.36 (0.01*)
Her2									-0.14 (0.31)	-0.17 (0.26)	0.35 (0.007*)
ER										0.87 (<0.001*)	0.66 (<0.001*)
PR											0.62 (<0.001)

The data format presented in the cell is: r, correlation coefficient and (p value).

Age, tCho, Kirans, KeP are continuous variables; morphology, tumor type, ER, PR, HER-2, HR, and triple negative are dichotomized variables, and the tumor grade is a categorized variable (1-3).

Table 3
Measurements of tCho, Ktrans, and Kep in different tumor type, tumor grade, MR phenotypes, and biomarker status

	Tumor type		Tumor grade			Morphology		HER-2		ER		PR		Triple	
	IDC	ILC	I	II	III	Mass	Non-mass	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos
tCho (mmol/kg)	1.87	2.12	1.88	1.53	2.31	2.02	1.51	1.14	1.20	1.75	1.81	1.83	1.79	2.13	1.64
Ktrans (min ⁻¹)	0.13	0.06	0.06	0.13	0.15	0.12	0.11	0.13	0.10	0.15	0.10	0.15	0.11	0.17	0.10
Kep (min ⁻¹)	0.71	0.35	0.41	0.67	0.84	0.70	0.59	0.72	0.57	0.82	0.55	0.82	0.57	0.98	0.55