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ORIGINAL ARTICLE

The Contribution of MR Spectroscopy to the Diagnosis of BIRADS 4 and 5 Breast Lesions

ABSTRACT

Objectives: Breast cancer is the most frequently diagnosed type of cancer worldwide. Magnetic resonance spectroscopy (MRS) is a diagnostic method that non-invasively measures metabolite levels in tissues and analyzes their biochemical composition. In this study, we aimed to examine the choline metabolite levels in patients with BIRADS category 4 and 5 breast lesions through MRS performed before biopsy.

Methods: We included 30 female patients with lesions detected in examinations, ultrasonography, or mammography and performed dynamic contrast-enhanced breast magnetic resonance imaging (MRI), diffusion-weighted imaging, and MRS. We compared the conventional findings of breast masses on MRI with histopathological results and choline level measurements separately.

Results: Although the median choline level in the malignant group was clinically found to be higher compared to the benign group, there was no significant difference between the groups (p=0.473). The area under the ROC curve was 0.580 (95% Confidence Interval: 0.369–0.792), indicating that choline levels were not statistically significantly predictive (p=0.454). Among all cases, there was no correlation between choline levels and tumor diameter, minimum, mean, and maximum ADC measurements (p>0.05). The choline levels in the HER-2 positive group were higher compared to the HER-2 negative group (p=0.009).

Conclusion: Although the choline level was found to be higher in malignant breast lesions, there was no statistically significant correlation. It is evident that interpreting MRS data in conjunction with morphological data is much more valuable than evaluating it alone.

Keywords: Breast, cancer, radiology, spectroscopy

Breast cancer is the most frequently diagnosed cancer type worldwide, with over 2 million individuals receiving this diagnosis annually. It is also the most prevalent cancer across all anatomical regions. Breast cancer accounts for approximately 7% of annual cancer-related deaths and ranks fifth in mortality rates among all cancers, following lung, colorectal, liver, and stomach cancers (1).

Advancements in breast cancer screening have facilitated early diagnosis, enabling the initiation of treatment at earlier stages; this is a critical factor influencing prognosis. Regular self-examination of the breasts, clinical examinations, and the appropriate application of radiological diagnostic methods within a well-structured algorithm enhance the likelihood of early diagnosis (2).

Mammography is the standard imaging modality for breast cancer diagnosis and screening. The sensitivity of mammography for diagnosing breast cancer has been reported to range from 69% to 90% in various studies. However, mammography also has a false-negative rate of 10–15%. Sensitivity increases with age, as younger women often have dense breast tissue rich in glandular tissue, which reduces mammography sensitivity (3). Ultrasonography and magnetic resonance imaging (MRI) are the other principal imaging methods for breast and axillary examination besides mammography. MRI is recognized as the most sensitive method for breast examination (4).

MRI is a non-ionizing radiation technique characterized by high contrast resolution. In addition to conventional breast examination methods, MRI can be performed for diag-

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nostic purposes due to its capability for multiplanar and dynamic contrast imaging. Emerging techniques enable rapid sequences and functional examinations, leveraging advancements in stronger gradients and computer programs that quickly analyze data. These improvements have led to shorter acquisition times, enhanced image quality, and minimized motion artifacts. Diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) are among these rapid MRI applications (5).

Diffusion MR has proven effective in determining local cancer spread and detecting metastatic axillary lymph nodes. Cancers with initially low apparent diffusion coefficient (ADC) values tend to respond better to chemotherapy. Furthermore, an increase in ADC values, indicating chemotherapy effectiveness, can occur before any reductions in tumor size are noted (6,7).

MRS is a diagnostic method that non-invasively measures metabolite levels in tissues and analyzes their biochemical composition. The objective is to measure and differentiate signals from small quantities of metabolites that resonate between water and fat. The principal metabolites detectable in breast MRS include N-acetyl aspartate (NAA), choline, and creatine. Elevated levels of choline (3.2 ppm), which indicate membrane metabolism, have been associated with breast cancer. An increase in choline levels is thought to serve as a biomarker reflecting tumor aggressiveness. Studies utilizing 1.5 Tesla machines report an average sensitivity of 80–90% and specificity of 80–90% for distinguishing malignant from benign lesions. Incorporating the MRS technique alongside dynamic contrast MRI has reportedly enhanced the specificity of this method from around 70% to as high as 92% (8,9).

In this study, we aimed to examine choline metabolite levels in patients with BIRADS category 4 and 5 breast lesions via MRS performed prior to biopsy. We investigated the effectiveness of MRS in distinguishing between malignant and benign lesions by comparing findings with patients' pathology results.

METHODS

Following the approval of the ethics committee for our study (Ethics Committee Decision Date: 10.05.2017, Decision Number: 2017-05/1), we conducted our research between May 2017 and January 2018 at the Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology Health Application and Research Center, Department of Radiodiagnostics. Patients presenting with complaints of breast pain and palpable masses underwent physical examinations, breast ultrasonography, or mammographic examinations. The study included 30 female patients with detected BIRADS 4 and 5 lesions, for whom we performed dynamic contrast-enhanced breast MRI, DWI, and MRS with 3 Tesla MRI prior to biopsy. Histopathological diagnoses were established by pathologists using either tru-cut biopsy or surgical specimens.

Eligible participants for the study were women aged 18 and older, suspected of having lesions through physical examination, ultrasonography, and mammography, who were planned for MRI and biopsy. It was required that there be no contraindications for MRI.

To mitigate potential effects of the menstrual cycle on ADC values in premenopausal cases, breast MRI was performed between days 7–17 of the cycle. Breast MRI examinations were conducted using a 3 Tesla MRI device (Magnetom-Skyra, Siemens, Erlangen, Germany) available in our clinic. As part of the standard breast MRI examination protocol, we obtained axial plane TSE T1 fat-suppressed and T2-weighted fat-suppressed sagittal-axial images, along with pre-contrast and dynamic post-contrast gradient echo 3D T1-weighted images in the axial plane. According to the breast MRI examination protocol, we administered a gadolinium-based contrast agent at a routine dose of 0.1–0.2 mmol/kg via venous access in the antecubital region. In the dynamic study, images were captured in the axial plane at 60-second intervals, repeated five times post-contrast injection using a T1-weighted 3D FLASH sequence. The parameters for TSE T1-weighted sequences included TR: 550 ms, TE: 8 ms, matrix: 256 x 256, section thickness 3 mm, and section interval 0.3 mm. For the TSE T2-weighted sequence, parameters were TR: 5000 ms, TE: 110 ms, matrix: 256 x 256, section thickness 3 mm, and section interval 0.3 mm.

For the dynamic contrast study, parameters were programmed as TR: 5.16 ms, TE: 2.38 ms, flip angle: 10 degrees, matrix: 256 x 256, section thickness 1.10 mm, and section interval 0.3 mm. Additionally, sagittal images with TSE T1A were obtained using a small FOV of approximately 18–36 cm, with variations according to breast size. Utilizing the standard subtraction program available on the Siemens MRI console, subtracted series were generated to reveal the contrast profile by pixel-wise subtraction of pre-contrast images from their corresponding post-contrast images. We transferred images to the workstation and plotted time/signal curves for the lesions from dynamic contrast images; the lesions were evaluated quantitatively and qualitatively according to their contrast uptake dynamics.

DWI was routinely conducted before obtaining dynamic images in both breasts using a standard breast coil in the axial plane to avoid the negative effects of the contrast agent. DWI parameters were adjusted using a single-shot SE sequence with TR: 7500 ms, TE: 84 ms, matrix: 256 x 256, section thickness 4 mm, and section interval 2 mm. For each section, three different b-values of 0, 400, and 800 s/mm^2 were employed. The standard measurement area (ROI) on the workstation was utilized to identify the area where diffusion restriction values of the lesion would be quantitatively evaluated on the ADC map.

For accurate lesion localization, MRS images were routinely obtained after dynamic images using a standard breast coil in the axial plane. We employed fast spin echo (FSE) T2A images and post-contrast T1A images to define the region to be selected. In single voxel examinations, we selected a voxel size of approximately 1x1x1 cm^3 from suitable sections in the axial plane. The voxel was typically positioned to fully encompass the pathology of either the solid or necrotic components of the tumor area. We favored the PRESS (Point-resolved surface coil spectroscopy) sequence (TR=1500 TE=135) for spectrum acquisition, ensuring a high signal-to-noise ratio (SNR). The examination time was set at 5–10 minutes. Gradient shimming was applied to suppress water signals, and data were automatically processed using packaged software.

We assessed breast MRI images in conjunction with mammography and ultrasound findings by two radiologists. In the breast MRI evaluation, we considered not only the morphological characteristics of each lesion but also the contrast enhancement pattern, kinetic characteristics, presence of diffusion restriction, mean ADC value, and choline peak.

For morphological characteristics, we evaluated the diameter of the mass (calculating the average of two perpendicular diameters), its

shape (oval, round, irregular), and edge characteristics (well-defined, poorly defined, irregular, or spiculated). We assessed the presence of homogeneous or heterogeneous enhancement patterns, along with peripheral rim enhancement and the existence of non-enhancing internal septa within the contrast enhancement patterns.

Lesions were evaluated quantitatively and qualitatively according to their contrast uptake dynamics. We obtained the maximum contrast uptake rate, amount, and time-signal intensity curves utilizing the region-of-interest (ROI) technique over the lesion. A significant increase in signal intensity of at least 90% within the first two minutes post-contrast was defined as significant, followed by an examination of the signal intensity curve's shape. The persistent curve (Type 1) was identified as one that continued to increase in contrast over time; the plateau curve (Type 2) was defined as achieving maximum signal intensity at 2–3 minutes after contrast injection and maintaining this level, and the wash-out curve (Type 3) was characterized by peaking at 2–3 minutes and subsequently decreasing in signal intensity.

Post-processing operations were performed on the dynamic, DWI, and spectroscopic examinations sent to the workstation. Prior to evaluating DWI, we located each lesion based on conventional sequences. Utilizing dynamic images, we created subtracted maximum intensity projection (MIP) and multiplanar reconstruction (MPR) images, placing ROIs in areas of greatest enhancement using post-processing software to derive time-dependent enhancement curves. Choline resonance was identified from MRS data at 3.2 ppm based on previous studies of breast lesions. We calculated the integral value of the choline peak from the acquired spectra.

Following MRI, histopathological evaluations were conducted using thick-needle biopsy or surgical specimens with ultrasound guidance on all lesions. The specimens were assessed by our hospital's pathology clinic. Immunohistochemical statuses of ER, PR, HER-2, and Ki-67 were evaluated for lesions diagnosed with breast cancer. A staining level of 1% or greater was considered positive for ER and PR. HER-2 status was assessed using the CB-11 monoclonal HER-2 antibody, with tumor cell membrane scoring as follows: scores of 0 for difficult-to-detect incomplete membranous staining (<10%), score 1 for >10% incomplete membranous staining, score 2 for >10% weak-moderate complete membranous staining or complete strong membranous staining (⩽10%), and score 3 for >10% strong complete membranous staining. The Mib-1 monoclonal antibody was used to evaluate Ki-67 status, recording the percentage of positive nuclear staining.

Conventional findings of breast masses on MRI were compared with histopathological results and choline level measurements separately.

Statistical Analysis

We evaluated the distribution of continuous numerical variables for normality using the Shapiro-Wilk test. The homogeneity of variance assumption was investigated using the Levene test. Descriptive statistics were presented as mean ± standard deviation or median (minimum–maximum) for continuous numerical variables, and frequency and percentage for categorical variables.

The significance of differences in mean values between groups was assessed using Student's t-test. Categorical variables were evaluated for differences using the Continuity Corrected Chi-Square test.

Spearman's rank correlation test was employed to investigate statistically significant correlations between choline measurements and tumor diameter, ADC, nuclear pleomorphism, mitosis, tubules, Ki-67, and CerbB2.

Given that the assumptions of parametric test statistics were not satisfied between groups, we utilized the Mann-Whitney U test to assess differences for continuous numerical variables when the number of independent groups was two; for more than two independent groups, the Kruskal-Wallis test was employed.

The discriminatory power of choline measurements in distinguishing between benign and malignant groups was evaluated by calculating the area under the ROC curve and the 95% confidence interval.

Data analysis was performed using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) software. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

In our study, we identified a total of 30 solid lesions in 30 female patients using dynamic contrast-enhanced breast MRI and MRS. The mean age of the participants was 38.7 years (range: 24–67). According to the histopathology results, the mean age of the 14 patients with benign diagnoses was 36.1 years, whereas the mean age of the 16 patients with malignant diagnoses was 49.5 years.

The mean age of the malignant group was statistically significantly higher compared to the benign group ($p<0.001$). The median maximum diameter was also statistically significantly larger in the malignant group ($p=0.005$).

The minimum ADC level was lower in the malignant group compared to the benign group, though this difference did not reach statistical significance ($p=0.093$). Conversely, the mean and maximum ADC levels were statistically significantly lower in the malignant group compared to the benign group ($p<0.001$) (Table 1).

Table 1. Demographic and diffusion characteristics of cases according to benign and malignant groups

	Benign (n=14)	Malign (n=16)	p
Age	36.1±8.3	49.5±10.2	**<0.001**
Diameter	13.5 (10-45)	22 (13-40)	**0.005**
BIRADS	4 (4-4)	5 (4-5)	**<0.001**
ADC (minimum)	0.796 (0.58-1.58)	0.681 (0.51-0.97)	0.093
ADC (mean)	1.134 (0.81-2.13)	0.804 (0.74-1.23)	**<0.001**
ADC (maximum)	1.432 (1-2.44)	1.026 (0.82-1.56)	**<0.001**

Table 2. MRI characteristics of lesions and association with LAP according to benign and malignant groups

	Benign (n=14)	Malign (n=16)
Lesion border		
Sharp border	13 (92.9%)	2 (12.5%)
Irregular border	1 (7.1%)	6 (37.5%)
Spiculated border	0 (0%)	8 (50.0%)
Kinetic curves		
Type 1	2 (14.3%)	0 (0%)
Type 2	10 (71.4%)	2 (12.5%)
Type 3	2 (14.3%)	14 (87.5%)
Type 1 signal		
Hyperintense	1 (7.1%)	0 (0%)
Hypointense	9 (64.3%)	16 (100%)
Isointense	4 (28.6%)	0 (0%)
Type 2 signal		
Hyperintense	9 (64.3%)	1 (6.25%)
Hypointense	1 (7.1%)	9 (56.25%)
Isointense	4 (28.6%)	6 (37.5%)
Staining		
Unpainted	1 (7.15%)	0 (0%)
Homogeneous	10 (71.4%)	6 (37.5%)
Heterogeneous	1 (7.15%)	10 (62.5%)
Peripheral	2 (14.3%)	0 (0%)
Lymphadenopathy		
Negative	14 (100%)	11 (68.75%)
Positive	0 (0%)	5 (31.25%)

Table 3. Choline levels according to various histopathological features in the malignant group

	n (%)	Choline	p
Perineural invasion			0.958
Negative	6 (37.5%)	1.07 (0.21-6.42)	
Positive	10 (62.5%)	1.63 (0.04-4.70)	
Lymphovascular invasion			0.958
Negative	6 (37.5%)	1.07 (0.21-6.42)	
Positive	10 (62.5%)	1.63 (0.04-4.70)	
ER			0.267
Negative	2 (12.5%)	0.71 (0.51-0.92)	
Positive	14 (87.5%)	1.33 (0.04-6.42)	
PR			0.681
Negative	7 (43.7%)	0.92 (0.21-4.52)	
Positive	9 (56.3%)	1.16 (0.04-6.42)	
Her-2 (cerbB2)			**0.009**
Negative	11 (68.7%)	0.92 (0.04-4.52)	
Positive	5 (31.3%)	4.35 (1.49-6.42)	
Intrinsic subtype			0.534
Luminal A	3 (18.8%)	1.08 (1.07-1.77)	
Luminal B	11 (68.7%)	1.49 (0.04-6.42)	
Triple negative	2 (12.5%)	0.71 (0.51-0.92)	

The frequency distributions of other MRI characteristics of the cases based on benign and malignant classifications are shown in Table 2.

Although the median choline level in the malignant group was clinically higher than in the benign group, the difference did not achieve statistical significance (p=0.473). The area under the ROC curve (AUC) for distinguishing between the benign and malignant groups based on choline measurements was 0.580 (95% Confidence Interval: 0.369–0.792), indicating that choline levels did not demonstrate statistically significant predictive capability (p=0.454).

The median choline level in the benign group was 0.94; when cases were divided into two groups based on this median value, there was no statistically significant difference in the frequency of choline levels being above (or below) 0.94 between the benign and malignant groups (p=0.749).

Moreover, using weighted average choline levels, we categorized the benign group into quartiles. Those with choline levels below 0.17 constituted the 1st quartile, those between 0.17 and 0.94 constituted the 2nd quartile, those between 0.94 and 2.12 constituted the 3rd quartile, and those above 2.12 constituted the 4th quartile. Statistically significant differences in the frequency distributions of choline levels between the benign and malignant groups according to this classification were not observed (p=0.448).

Among all cases, no correlation was found between choline levels and tumor diameter, minimum ADC, mean ADC, and maximum ADC measurements (p>0.05). Additionally, no statistically significant differences in choline levels were observed according to BIRADS staging (p=0.723), kinetic curve types (p=0.739), or staining patterns (p=0.728) across all cases. No significant differences in choline levels were found between lymphadenopathy (LAP) negative and LAP positive groups (p=0.746).

Among malignant cases, no statistically significant differences in choline levels were found between the group with perineural invasion and the group without perineural invasion (p=0.958). Similarly, no significant difference in choline levels was found between the group with lymphovascular invasion and the group without (p=0.958).

ER positivity did not demonstrate a statistically significant impact on choline measurements (p=0.267). Additionally, no statistically significant association was observed between PR positivity and choline measurements (p=0.681).

However, choline levels in HER-2 positive cases were statistically significantly higher than in HER-2 negative cases (p=0.009). Among malignant cases, no statistically significant differences in choline levels were evident regarding intrinsic subtypes (p=0.534).

As depicted in Table 3, the choline levels according to various histopathological features of cases in the malignant group were shown.

Table 4. Correlation coefficients and significance levels between choline levels and histopathological characteristics within malignant cases

	n	Correlation coefficient	p
Nuclear pleomorphism	16	0.132	0.626
Mitosis	16	0.374	0.153
Tubule	16	0.117	0.667
Ki-67	16	-0.438	0.090
CerbB2 (Her-2)	16	0.690	**0.003**

Within the malignant cases, no correlation was identified between choline levels and nuclear pleomorphism, mitosis, and tubules (p>0.05).

While a decrease in choline level was noted as the Ki-67 staining percentage increased, the correlation between these variables was not statistically significant (r=-0.438 and p=0.090). In contrast, an increase in CerbB2 positivity corresponded with a statistically significant increase in choline levels (r=0.690 and p=0.003) (Table 4).

DISCUSSION

In our study, when evaluating the sizes of the lesions, the average diameter of benign lesions was calculated as 13.5 mm (range: 10–45), while the average diameter of malignant lesions was 22 mm (range: 13–40). The median diameter of lesions was statistically significantly larger in the malignant group (p=0.005). However, it is evident that lesion size alone is not a definitive criterion for malignancy diagnosis.

When examining the relationship between choline levels and tumor diameter among all cases, an increase in choline levels was noted with an increase in lesion diameter; however, this correlation did not reach statistical significance (p=0.951). Chen et al. (10) identified a relationship between choline density in solid lesions and tumor size. Similarly, Katz-Brull et al. (11) subdivided patients into three groups based on lesion size (<2.5 cm, 2.5–4.9 cm, and ≥5 cm), reporting that as lesion size increased, choline levels also increased, with sensitivity for diagnosing malignancy rising from 72% to 90%, and then to 100% (p=0.025).

Smaller diameter lesions are often interpreted as benign due to insufficient choline signal for detection. Utilizing MRI machines with magnetic field strengths greater than 1.5 Tesla has elevated the sensitivity for detecting choline. In our study, the utilization of a 3 Tesla machine enhanced our sensitivity in detecting choline signals. However, the inconsistency of our data with the literature may stem from the relatively small patient population in our study.

In dynamic contrast-enhanced breast MRI, breast lesions can be qualitatively evaluated post-contrast agent administration, facilitating the plotting of time versus signal intensity curves. According to this methodology, three types of curves are identified. Type 1 persistent curves are typically associated with benign lesions (83% benign vs. 9% malignant). The sensitivity for benign lesions is reported at 52.2%, with specificity at 71%. For malignant lesions, plateau curves (Type 2) exhibit sensitivities of 42.6% and specificities of 75%. Type 3 wash-out curves are generally not seen in benign lesions (specificity 90.4%), but sensitivity is notably low (20.5%) (12). In our study, 14.3% of benign lesions exhibited Type 1 kinetics, 71.4% exhibited Type 2 kinetics, and 14.3% exhibited Type 3 kinetics; conversely, 12.5% of malignant lesions exhibited Type 2 kinetics, while 87.5% exhibited Type 3 kinetics.

A study by Kuhl et al. (13) compared the staining kinetics of a total of 266 lesions with their pathology results, revealing that among diagnosed benign lesions, 83% exhibited Type 1 kinetics, 11.5% exhibited Type 2, and 5.5% exhibited Type 3 patterns. Among malignant lesions, 57.4% exhibited Type 3 kinetics, while 33.6% exhibited Type 2, and 8.9% exhibited Type 1 patterns. This population demonstrated an 87% likelihood of malignancy for those showing Type 3 kinetics, compared to only 6% for those showing Type 1.

While the contrast kinetics of benign and malignant lesions in our study aligned with the literature, no statistically significant differences were found when evaluating their relationship with choline levels (p=0.739).

Upon examining diffusion-weighted series, we observed a statistically significant correlation between lesion histopathology and ADC values, consistent with existing literature. The mean and maximum ADC levels were lower in the malignant group compared to the benign group (p<0.001) (14,15).

Our study highlighted a statistically significant relationship between lesion histopathology and mean and maximum ADC values; however, no statistically significant difference in minimum ADC values was observed between the malignant and benign groups (p=0.093). In parallel, when comparing mean and maximum ADC values with choline levels, p-values of 0.769 and 0.814 were documented, signifying no correlation between these variables. These discrepancies may be attributed to the limited patient population in our study compared to previous literature.

By measuring the total choline peak integral, we calculated the average choline level in the benign group to be 0.94 (0.08–4.54) AU, in contrast to 1.12 (0.04–6.42) AU in the malignant group. Metabolic variations due to cellular proliferation in malignantly transformed cells lead to alterations in the concentrations of choline-containing molecules, particularly phosphocholine. Consequently, the choline levels detected through MR spectroscopy are positively correlated with the metabolic proliferative activity of malignant cells (16).

Breast cancer cells reportedly exhibit higher levels of phosphocholine than normal breast epithelial cells (11). In a study conducted by Roebuck et al. (17) in 1998, elevated choline was qualitatively identified for the first time in vivo as a biomarker for breast malignancies. This study, featuring 17 lesions, reported 70% sensitivity, 86% specificity, and 88% positive predictive value for elevated choline levels in malignancy detection. Numerous studies emphasize the advantages of incorporating supplementary MR methods, such as MRS, to enhance the specificity of breast malignancy detection via routine breast MRI examinations (18–20).

In our study, while the median choline level in the malignant group was higher than that of the benign group, the difference was not statistically significant (p=0.473). The AUC for distinguishing between benign and malignant groups based on choline measurements was 0.580 (95% Confidence Interval: 0.369–0.792), indicating the absence of statistically significant predictive power for choline levels (p=0.454).

Several factors may account for the lack of correlation between choline levels and histopathological outcomes. Firstly, performing MRS necessitates an MRI machine with at least 1.5 Tesla. It is widely acknowledged that higher spatial and spectral resolution is achievable with 3 Tesla machines. Furthermore, in literature utilizing machines with higher magnetic field strengths, choline peaks have been identified even in benign lesions and normal breast tissue (21).

In a study assessing 43 asymptomatic volunteers during lactation, resonances were observed within the choline spectral region (3.2 ppm) in all three breastfeeding mothers (22). Additionally, 40 other volunteers exhibited three false positive choline peaks. In our study, the use of a 3 Tesla machine likely increased the probability of detecting choline peaks, even in benign lesions, matching observations made in the literature. Prior literature has also reported choline peaks in benign lesions, including fibroadenomas and fibrocystic changes, as well as atypical ductal hyperplasia and atypical chronic inflammatory alterations (23,24).

Inclusion criteria restricted our study to mass lesions greater than 10 mm in diameter, excluding non-mass lesions and those measuring less than 10 mm. Consequently, this may have augmented the likelihood of obtaining pathological diagnoses for benign lesions such as fibrocystic changes, fibroadenomas, atypia-containing ductal hyperplasia, and chronic inflammatory changes, further facilitating the detection of choline peaks in benign lesions.

Nevertheless, the literature indicates a significant increase in sensitivity for detecting choline in malignant lesions over 2 cm (25). However, in our cohort, 62.5% of the malignant lesions measured less than 2 cm in diameter, potentially diminishing the rate of observed choline peaks among malignant lesions.

One notable limitation of breast MRS is that voxel placement for MR spectroscopy typically occurs after the contrast series to ensure accurate placement. Literature suggests that the accumulation of the contrast agent may influence spectroscopic examination (26). In our study, MRS voxel placement was also executed after the contrast series to facilitate precise lesion localization, a factor that could adversely impact our measurements.

Prognostic factors and markers (Ki-67, ER, PR, HER-2) are frequently employed in clinical practice for breast cancer management. Presently, the status of axillary lymph nodes represents the most critical prognostic factor utilized to predict breast cancer outcomes (27). In our study, we examined the relationships between lymphovascular invasion and LAP positivity and choline levels but did not yield significant findings (p=0.958).

Although MRS was not performed on lymph nodes, we sought to ascertain correlations between choline peak levels and LAP positive patients, discovering no significant associations.

Ki-67 is instrumental in evaluating cell proliferation in lymph node-negative patients, while ER and PR status relate to the response to hormone replacement therapy, and HER-2 status pertains to the response to Herceptin (28,29). In our study, no statistically significant differences were noted between Ki-67 staining percentages, ER and PR positivity, and choline measurements (p=0.090, p=0.267, p=0.681, respectively). However, it was noteworthy that choline levels in the HER-2 positive group were significantly higher than those in the HER-2 negative group (p=0.009). Given that HER-2 positive tumors exhibit more aggressive behavior, heightened levels of choline, indicative of cell metabolism and angiogenesis, may be particularly significant in these cases. Various studies have established associations between choline-containing metabolite presence and HER2/neu expression, as well as aggressive tumor phenotypes (25,30).

CONCLUSION

Research into breast MRS is rapidly advancing; however, the clinical application of this technique for breast lesions has not yet become routine due to several limitations. Despite the existence of numerous studies indicating a correlation between breast malignant lesions and choline levels, no consensus has emerged regarding specific cut-off values for measuring and evaluating choline due to variations in measurement protocols.

There is a clear increase in choline levels resulting from heightened angiogenesis and cellular activity in malignant lesions; however, the concurrent detection of increased choline levels in certain benign lesions and even normal breast tissue, particularly with high Tesla machines, represents a significant limitation of the method.

Moreover, as MRS is acutely sensitive to magnetic field inhomogeneities, achieving objective results in patients with hematomas or metallic clips is another critical constraint of this technique.

In conclusion, while MRI demonstrates high sensitivity for detecting breast lesions, its specificity is comparatively low. A range of modalities, including dynamic studies, contrast kinetics, and diffusion-weighted assessments, are employed to improve MRI specificity in imaging breast lesions. In our study, we aimed to determine whether MRS could enhance specificity in differentiating between benign and malignant choline peaks. While higher choline levels were identified in malignant breast lesions, the correlation was not statistically significant. Integrating MR spectroscopic data with morphological analyses proves considerably more valuable than evaluating each individually.

Additionally, a significant finding of our study is the positive correlation between choline peak levels and HER-2 expression. Given their aggressive nature, HER-2 positive tumors may utilize heightened choline levels, reflective of cell metabolism and angiogenesis, as a valuable prognostic parameter in guiding treatment selection.

Ethics Committee Approval: This study was conducted with the permission of the Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology Health Application and Research Center Local Ethics Committee (decision no: 2017-05/1, date: 10.05.2017).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-49. [CrossRef]
2. Alsalamh R, Al-Harbi FA, Alotaibi RT, Al-Harbi ON, Alshahrani N, Alfadhel SM, et al. Barriers to breast cancer screening in Saudi Arabia: A systematic review and meta-analysis. Cureus 2024;16(7):e65103 [CrossRef]
3. Berg WA. Tailored supplemental screening for breast cancer: What now and what next? AJR Am J Roentgenol 2009;192(2):390-9. [CrossRef]
4. Oeffinger KC, Fontham ET, Etzioni R, Herzig A, Michaelson JS, Shih YC, et al. Breast cancer screening for women at average risk: 2015 Guideline update from the American Cancer Society. JAMA 2015;314(15):1599-614. [CrossRef]
5. Woodhams R, Ramadan S, Stanwell P, Sakamoto S, Hata H, Ozaki M, et al. Diffusion-weighted imaging of the breast: Principles and clinical applications. Radiographics 2011;31(4):1059-84. [CrossRef]
6. Richard R, Thomassin I, Chapellier M, Scemama A, de Cremoux P, Varna M, et al. Diffusion-weighted MRI in pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer. Eur Radiol 2013;23(9):2420-31. [CrossRef]
7. Park SH, Moon WK, Cho N, Song IC, Chang JM, Park IA, et al. Diffusion-weighted MR imaging: Pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer. Radiology 2010;257(1):56-63. [CrossRef]
8. Jacobs MA, Barker PB, Bottomley PA, Bhujwalla Z, Bluemke DA. Proton magnetic resonance spectroscopic imaging of human breast cancer: A preliminary study. J Magn Reson Imaging 2004;19(1):68-75. [CrossRef]
9. Jacobs MA, Barker PB, Argani P, Ouwerkerk R, Bhujwalla ZM, Bluemke DA. Combined dynamic contrast enhanced breast MR and proton spectroscopic imaging: A feasibility study. J Magn Reson Imaging 2005;21(1):23-8. [CrossRef]
10. Chen JH, Mehta RS, Baek HM, Nie K, Liu H, Lin MQ, et al. Clinical characteristics and biomarkers of breast cancer associated with choline concentration measured by 1H MRS. NMR Biomed 2011;24(3):316-24. [CrossRef]
11. Katz-Brull R, Seger D, Rivenson-Segal D, Rushkin E, Degani H. Metabolic markers of breast cancer: Enhanced choline metabolism and reduced choline-ether phospholipid synthesis. Cancer Res 2002;62:1966-70.
12. Macura KJ, Ouwerkerk R, Jacobs MA, Bluemke DA. Patterns of enhancement on breast MR images: Interpretation and imaging pitfalls. Radiographics 2006;26(6):1719-34. [CrossRef]
13. Kuhl CK, Mielcareck P, Klaschik S, Leutner C, Wardelmann E, Gieseke J, et al. Dynamic breast MR imaging: Are signal intensity time course data useful for differential diagnosis of enhancing lesions? Radiology 1999;211(1):101-10. [CrossRef]
14. Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. J Magn Reson Imaging 2002;16:172-8. [CrossRef]
15. Palle L, Reddy B. Role of diffusion MRI in characterizing benign and malignant breast lesions. Indian J Radiol Imaging 2009;19(4):287-90. [CrossRef]
16. Podo F. Tumour phospholipid metabolism. NMR Biomed 1999;12(7):413-39. [CrossRef]
17. Roebuck JR, Cecil KM, Schnall MD, Lenkinski RE. Human breast lesions: Characterization with proton MR spectroscopy. Radiology 1998;209(1):269-75. [CrossRef]
18. Meisamy S, Bolan PJ, Baker EH, Pollema MG, Le CT, Kelcz F, et al. Adding in vivo quantitative 1H MR spectroscopy to improve diagnostic accuracy of breast MR imaging: Preliminary results of observer performance study at 4.0 T. Radiology 2005;236(2):465-75. [CrossRef]
19. Bolan PJ, Meisamy S, Baker EH, Lin J, Emory T, Nelson M, et al. In vivo quantification of choline compounds in the breast with 1H MR spectroscopy. Magn Reson Med 2003;50(6):1134-43. [CrossRef]
20. Huang W, Fisher PR, Dulaimy K, Tudorica LA, O'Hea B, Button TM. Detection of breast malignancy: Diagnostic MR protocol for improved specificity. Radiology 2004;232(2):585-91. [CrossRef]
21. Chen R, Gong S, Zhang W, Chen J, He S, Liu B, et al. Correlative study on MRI morphologic features, pathology, and molecular biology of breast cancer. Chin J Clin Oncol 2005;2(1):521-8. [CrossRef]
22. Stanwell P, Gluch L, Clark D, Tomanek B, Baker L, Giuffrè B, et al. Specificity of choline metabolites for in vivo diagnosis of breast cancer using 1H MRS at 1.5 T. Eur Radiol 2005;15(5):1037-43. [CrossRef]
23. Kvistad KA, Bakken IJ, Gribbestad IS, Ehrnholm B, Lundgren S, Fjøsne HE, et al. Characterization of neoplastic and normal human breast tissues with in vivo (1)H MR spectroscopy. J Magn Reson Imaging 1999;10(2):159-64. [CrossRef]
24. Bartella L, Huang W. Proton (1H) MR spectroscopy of the breast. Radiographics 2007;27-S52. [CrossRef]
25. Katz-Brull R, Lavin PT, Lenkinski RE. Clinical utility of proton magnetic resonance spectroscopy in characterizing breast lesions. J Natl Cancer Inst 2002;94(16):1197-203. [CrossRef]
26. Joe BN, Chen VY, Salibi N, Fuangtharntip P, Hildebolt CF, Bae KT. Evaluation of 1H-magnetic resonance spectroscopy of breast cancer pre- and postgadolinium administration. Invest Radiol 2005;40(7):405-11. [CrossRef]
27. Szabó BK, Aspelin P, Kristoffersen Wiberg M, Tot T, Boné B. Invasive breast cancer: Correlation of dynamic MR features with prognostic factors. Eur Radiol 2003;13(11):2425-35. [CrossRef]
28. Yaghan R, Stanton PD, Robertson KW, Going JJ, Murray GD, McArdle CS. Oestrogen receptor status predicts local recurrence following breast conservation surgery for early breast cancer. Eur J Surg Oncol 1998;24(5):424-6. [CrossRef]
29. Lovekin C, Ellis IO, Locker A, Robertson JF, Bell J, Nicholson R, et al. c-erbB-2 oncoprotein expression in primary and advanced breast cancer. Br J Cancer 1991;63(3):439-43. Erratum in: Br J Cancer 1991;64(1):202. [CrossRef]
30. Suppiah S, Rahmat K, Mohd-Shah MN, Azlan CA, Tan LK, Aziz YF, et al. Improved diagnostic accuracy in differentiating malignant and benign lesions using single-voxel proton MRS of the breast at 3 T MRI. Clin Radiol 2013;68(9): e502-10. [CrossRef]