Role of Proton MR Spectroscopy in Differentiation of Benign and Malignant Breast Lesions

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Abstract

Aim: To determine the optimal cutoff value of choline (Cho) concentration in quantitative multivoxel magnetic resonance (MR) spectroscopic data to differentiate benign from malignant breast lesions.

Material and Methods: The study was institutional review board approved, and informed consent was obtained from each patient. Between July 2012 and July 2013, multivoxel MR spectroscopy was performed in 40 consecutive patients with 40 breast lesions assessed as BIRADS 3 to 5 and larger than 1cm in diameter at mammography and US.

Two-dimensional point-resolved spatially localized spectroscopy chemical shift imaging was first performed without signal suppression (TR/TE, 1450/30ms) as reference measurement and was performed subsequently with suppression of water and fat signals (1500/135) to detect Cho. Differences in mean and highest Cho concentration in the breast lesions were tested for significance by using the independent sample t-test.

The final diagnosis was confirmed with pathologic findings.

Results: Twenty four out of 40 breast lesions were malignant. The mean Cho concentration varied between 0.5 and 1.4mmol/L (0.94mmol/L±0.28 [standard deviation]) in benign lesions and between 1.4 and 8.5mmol/L (3.15mmol/L±1.5) in malignant lesions. The highest Cho concentrations in benign and malignant lesions were 0.6-1.7mmol/L (1.29mmol/L±0.33) and 1.8-10.6mmol/L (4.5mmol/L±1.99), respectively. Mean and highest Cho concentrations in benign and malignant breast lesions differed significantly (p<0.001 for both).

Using the highest choline concentration cut off value of >1.7 resulted in 100% sensitivity, specificity and accuracy for differentiation of benign and malignant breast lesions.

Conclusion: Quantitative single multivoxel MR spectroscopy can be applied to differentiate benign from malignant breast lesions. The use of highest Cho concentration of 1.7mmol/L or lower as a cutoff. Further larger studies will be needed to confirm these results.

Key Words: Magnetic resonance (MR) – Optimal cutoff value – Breast lesions.

Introduction

MAGNETIC resonance (MR) spectroscopy is a noninvasive diagnostic modality that can measure chemical information from a selected region in the body. It can provide tumor metabolic information [1].

MR spectroscopy has been increasingly applied for the evaluation of breast lesions and therapy response monitoring [2-29]. The diagnostic value of MR spectroscopy is generally based on the detection of elevated levels of choline-containing compounds (Cho), which are markers of an active malignant breast tumor [30].

High levels of choline-containing metabolites (referred to as total choline or (Cho) are mainly due to the increase of phospholipid metabolism and cellular membranes proliferation [31].

MR spectroscopy can be performed as a single-[2-22] or multivoxel [23-29] technique. The single-voxel technique has limitations in terms of lesion coverage, which may affect the sensitivity of the assessment of Cho from just one voxel in view of tumor heterogeneity [23,27]. Multivoxel MR spectroscopy, referred to as spectroscopic imaging or chemical shift imaging, acquires spectroscopic information from a large volume of interest subdivided into an array of voxels measured in a single measurement [23-29]. Therefore, the multivoxel MR spectroscopic technique is suitable for analyzing the regional distribution of tumor metabolites and studying tissue heterogeneity. Another advantage of multivoxel MR spectroscopy is the possibility of metabolic mapping of breast lesions [27].
Several single-voxel MR spectroscopic studies conducted at 1.5 T have shown the results of the single-voxel technique for differentiating between malignant and benign breast lesions on the basis of the detection of Cho (peak visibility or Cho signal-to-noise ratio) [2-22]. However, in some studies Cho signals were also detected in benign lesions and normal breast tissues [6,12,14]. Therefore, the presence of a Cho-related peak at breast MR spectroscopy is not sufficient for a noninvasive diagnosis of malignancy. Quantification of the peak of Cho is required to determine the accurate levels of Cho [30].

Previous multivoxel MR spectroscopic studies have been far from quantitative, with the use of the Cho signal-to-noise ratio as a measure of tumor activity [23,25,26,29]. One recent study [27] presented a quantitative multivoxel MR spectroscopic method for the examination and metabolic mapping of disease in the human breast. With the use of literature values for T1 and T2 relaxation times of Cho and water in fibroglandular breast tissue and tumors, the concentration of Cho can be determined in different tumor compartments and surrounding tissues with two brief multivoxel MR spectroscopic measurements [27].

Aim of the study:

The purpose of this study was to determine the cutoff value of Cho concentration in quantitative multivoxel MR spectroscopy to differentiate benign from malignant breast lesions.

Material and Methods

Between July 2012 and July 2013, this prospective study was conducted at Mansoura University Hospital. Forty consecutive patients (mean age: 55 years; age range: 30-80 years) assessed as Breast Imaging Reporting and Data System (BI-RADS) 3 to 5 and larger than 1 cm in diameter at mammography and breast ultrasound, underwent multivoxel MR spectroscopy. Forty breast lesions were included. Patients were excluded if they had undergone neoadjuvant chemotherapy, radiation therapy, or previous surgical or interventional procedures in the breast harbor the lesion during the previous 3 months, or if metallic clips were present from previous surgery or needle biopsy in the breast harboring the lesion. In case of more than one lesion in the patient, the largest lesion was chosen for analysis.

The final diagnosis of the breast lesions was confirmed by using histologic or cytologic findings after biopsy or surgery. Informed consent was obtained from each patient prior to the study. The clinicians and patients were not informed of the results from MR spectroscopy.

MRI and multi-voxel proton MR spectroscopy:

Multi-voxel proton MRS was performed using a 1.5-T MRI scanner (Magnetom Avanto, Siemens Healthcare). The dedicated four-channel phased-array breast coil was used. Bilateral breast imaging was performed with the following protocol: An axial STIR sequence (TR/TE, 4400/74ms; inversion time, 130ms; 4-mm thickness without an interslice gap; FOV, 360x360mm²; matrix size, 224x448; acquisition time, 134 seconds), a 3D T1-weighted FLASH dynamic gradient-echo sequence (TR/TE, 5.0/2.4ms; flip angle, 20°; 1-mm thickness without an interslice gap; 1x1x1mm³ isotropic voxel; one un-enhanced and four post-contrast-enhanced acquisitions, administration of an IV bolus injection of 0.2mL/kg gadopentetate dimeglumine (Magnevist) using an MRI-compatible power injector with a flow of 2mL/s followed by a 20-mL saline flush. Post-processing consisted of standard subtraction (enhanced minus un-enhanced images) for all the dynamic phases and maximum-intensity-projection images.

Proton MRS spectra were acquired using the protocol of Sijens et al. [27]. This protocol included two-dimensional chemical shift imaging with double-spin-echo point-resolved spatially localized spectroscopy with phase-encoding gradients between the section-selective 90° pulse and the first section-selective optimized 180° pulse. Two-dimensional chemical shift imaging of the breast was performed twice, first without suppression of water and fat signals (1500/30ms) to serve as a reference measurement. The echo time was kept small to minimize loss of water and fat peak intensities due to T2 relaxation, and the repetition time was set at 1500ms to limit the acquisition time to 4 minutes 46 seconds. The second measurement was with suppression of water and fat signals (1500/135ms) to be able to detect Cho. The same repetition time and a longer echo time (135ms) were used to be able to pre-saturate the water signal and to reduce the effect of residual fat signals on the spectral baseline (acquisition time, 4 minutes 46 seconds). The total MR spectroscopic acquisition time therefore was less than 10 minutes.

The field of view was 10x 1 0cm to roughly cover the transverse cross section of the examined breast and was subdivided into 144 phase-encode steps at the used section thickness of 1cm. In this hybrid chemical shift imaging technique, the volume of interest, on which the automated adjustments of B0 field (shimming), frequency, transmitter gain, and receiver attenuation were performed, was smaller than the field of view (3x3x1cm) to end up with essentially measuring the watery part of the breast.
(glandular breast tissue and/or disease). The band-width was 1300Hz. Unwanted water and lipid signals were suppressed with band-selective inversion with gradient dephasing [27].

**Data analysis:**

The MR spectroscopic measurements were performed in breast lesions (BIRADS 3-5) larger than 1 cm in diameter, at mammography and ultrasound, that were localized on diffusion- and T2-weighted MR images; the results of MR spectroscopy then were projected on the transverse T2-weighted MR imaging series. A standard software package (Syngo; Siemens) was used for post-processing MR spectroscopic data. The number of peaks fitted included the chemical shift ranges restricted to 2.9-3.1ppm for creatine, 3.1-3.4ppm for Cho, 4.5-5.0ppm for water, and 1.0-1.5ppm for the main resonance of fat.

Lesion voxels were defined as voxels matching the lesion location at MR imaging and having a water signal larger than the fat signal. A radiologist (GE) with 6 years of experience in breast MRS performed the spectral analysis.

**Pathologic analysis:**

Pathologic findings at biopsy and definitive surgery served as the reference standard. The pathology report on each patient was reviewed, paying special attention to parameters such as pathologic subtype, histologic grade and size.

**Results**

Mean size of all the 40 breast lesions was 2.45±0.78cm. Twenty four of the 40 lesions were malignant and 16 lesions were benign. Malignant lesions had a mean size of 2.65±0.85, while mean size of benign lesions was 2.14±0.56cm.

The 40 lesions had a mean choline peak at 3.2±0.7ppm. The 24 malignant lesions had a mean choline peak at 3.16±0.44ppm, whereas the 16 benign lesions had a mean choline peak of 3.25±0.73ppm.

In spite of the overlap in the mean choline peak for benign and malignant lesions (3.16-3.36 and 3.08-3.24ppm respectively), the difference between the mean choline peak of malignant and benign lesions was statistically significant ($p<0.001$). Using the mean choline peak cut off value at ≤3.21ppm resulted in 87.5% sensitivity, 68.8% specificity and 80% accuracy for the differentiation of malignant lesions.

For malignant lesions, after application of water and fat suppression, Cho peak was intense in voxels containing malignant tumor and was negligible outside the lesion. For benign lesions, the Cho peak was not nearly as prominent as in malignant tumors, although, as seen on the metabolic map, still exceeded the levels of Cho in voxels outside the lesion.

<table>
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<th>Mean size</th>
<th>Choline_peak</th>
<th>Mean choline concentration</th>
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Role of Proton MR Spectroscopy in Differentiation of Benign

The mean choline concentration of the 40 lesions was 2.27±1.6mmol/L. In the 24 malignant lesions, the mean choline concentration was 3.15±1.5mmol/L. In the 16 benign lesions, mean choline concentration was 0.94±0.28mmol/L.

The mean highest choline concentration of the 40 lesions was 3.22±2.22mmol/L. The mean highest choline concentration in malignant lesions was 4.5±1.99mmol/L, while in benign lesions, it was 1.29±0.33mmol/L.

Furthermore, with regard to the highest Cho concentration, there was no overlap between the values for benign (0.6-1.7mmol/L) and malignant (1.8-10.6mmol/L) lesions. with regard to the mean benign and malignant Cho concentration, the ranges overlapped at 1.4mmol/L (0.5-1.4 vs 1.4-8.5 mmol/L, respectively).

The difference in mean choline concentration and mean highest choline concentration was statistically significant (p<0.001 for both). By using the mean choline concentration cut off value of >1.4 resulted in 91.7% sensitivity, 100% specificity and 95% accuracy for the differentiation between malignant and benign lesions. Using the highest choline concentration cut off value of >1.7 resulted in 100% sensitivity, specificity and accuracy for characterization of malignant lesions.

Table (2): Mean choline peak cut off value for the differentiation between benign and malignant breast lesions.

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>AUC±SE</th>
<th>95% CI</th>
<th>SENSITIVITY (95% CI)</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
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<td>≤3.21</td>
<td>0.811±0.07</td>
<td>0.656-0.917</td>
<td>87.5% (67.6-97.3%)</td>
<td>68.8 (41.3-89.0%)</td>
<td>80 (63.1-90.4)</td>
<td>80.8 (67.8-88.8)</td>
<td>78.6 (54.5-93.4)</td>
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Table (3): Highest choline concentration cut off value for differentiation between benign and malignant breast lesions.

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<th>95% CI</th>
<th>SENSITIVITY (95% CI)</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
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<td>&gt;1.7</td>
<td>1.000±0.00</td>
<td>0.912-1.000</td>
<td>100% (85.8-100%)</td>
<td>100 (79.4-100%)</td>
<td>100 (89.8-100)</td>
<td>100 (85.8-100%)</td>
<td>100 (79.4-100%)</td>
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</tbody>
</table>
Fig. (1): MRI of a female patient aged 54 years with pathologically proved invasive ductal carcinoma. (A) & (B) Axial post contrast subtraction images show two irregular speculated masses in the right breast, the 1st one show heterogenous enhance & the 2nd one shows irregular peripheral enhancement with central cystic degeneration. (C) Time intensity curve show rapid enhancement with plateau (type II curve). (D) ADC map shows restricted diffusion with low ADC value = (0.9 & 1.1x10^-3 mm^2/sec) of 1st mass & 2nd mass respectively. (E) Multivoxel spectroscopy show choline peak at 3.22ppm with mean choline concentration = 4.6 & highest choline concentration = 5.2mmol/L.

Fig. (2): MRI of a female patient aged 62 years with pathologically proved invasive ductal carcinoma. (A) Axial post contrast subtraction image shows irregular mass with speculated margins seen at the upper outer quadrant of right breast. The mass shows thick marginal enhancement. (B) Time intensity curve shows initial rapid enhancement with subsequent washout (type III curve). (C) ADC map showing ADC value = 1.1x10^-3 mm^2/sec. (D) Multi voxel spectroscopy shows choline peak at 3.19ppm with mean choline concentration = 2.9 & highest choline concentration = 3.8mmol/L.
Fig. (3): MRI of a female patient aged 44 years with pathologically proved traumatic fat necrosis. (A) & (B) Axial post contrast sub-traction images shows well defined mass with lobulated margins seen at the right breast. The mass shows peripheral enhancement with central non enhancing area. (C) Time intensity curve shows gradual increase in enhancement (type I curve). (D) DWI showing high SI areas in the lesion with ADC value = 1.3x10^{-3} mm²/sec. (E) Multi voxel spectroscopy shows choline peak at 3.32ppm with mean choline concentration = 0.7 & highest choline concentration = 1.1mmol/L.

Fig. (4): MRI of a female patient aged 53 years with pathologically proved fibroadenoma (A) & (B) Axial post contrast sub-traction images shows well defined mass with lobulated margins seen at the right breast. The mass shows heterogenous enhancement with non enhancing septae inside (C) Time intensity curve shows gradual increase in enhancement (type I curve). (D) ADC map with high ADC value = 2.6x10^{-3} mm²/sec. (E) Multi voxel spectroscopy before suppression of lipid signal shows choline peak at 3.34ppm with mean choline concentration = 0.9 & highest choline concentration = 1.3mmol/L.
Discussion

MRI is increasingly being used to examine patients with suspected breast cancer. More specifically, breast MRI has influenced the surgical staging of breast cancer by enabling the identification of multifocal and multicentric cancers of the ipsilateral or contralateral breast. Breast MRI is reported to have high sensitivity (94-100%), variable specificity (37-97%), and low positive predictive value. To improve the specificity of breast MRI, several strategies have focused on either lesion shape or enhancement kinetics. For example, higher specificity was achieved by integrating the morphologic and kinetic information obtained with MRI. In addition to imaging features, suspicious lesions may also be characterized by their cellular chemistry obtained from in vivo proton MR spectroscopy (MRS).

The high spectral resolution and large spatial coverage of the multivoxel technique make it advantageous over the single-voxel technique. The external and internal reference methods that had been used in single-voxel techniques are not practical for the multivoxel technique because of the requirement of a long imaging time to measure correction factors (eg, receiver gain, partial volume effects, and T1 and T2 relaxation times, etc). Furthermore, good reference acquisition and good water and fat suppression are needed for quantification, which may not be achieved given the field inhomogeneity across the large chemical shift imaging grid.

Sijens et al., concluded that improved methods for water and fat suppression have enhanced the detectability of Cho and thus facilitated the measurement of its mean and highest concentration in both benign and malignant lesions. In our study, this was achieved by measuring a volume of interest considerably smaller than the entire chemical shift imaging grid (3x3x1 cm). Several studies conducted at 1.5 T have shown that in vivo MRS can be used to distinguish between benign and malignant tumors on the basis of the hypothesis that total choline-containing compound is detectable only in malignancies. A pooled analysis of these studies showed that total choline-containing compound detectability or SNR criterion could identify malignancies with only 81% sensitivity (range, 70-92%). These studies used slightly larger lesion to detect a total choline-containing compound signal. Recently, in the study of Baek et al., and Shin et al., using the total choline peak integral and signal-to-noise ratio resulted in 82% MRS sensitivity in invasive cancers. The sensitivity was lower in smaller lesions than in larger lesions. They concluded that, for further SNR improvement, one approach is to use the scanner at a higher magnetic field, but it may suffer from a worse field inhomogeneity problem. In the contrary, in our study, using the mean and highest choline concentration cut off value of >1.4 and >1.7 mmol/L resulted in 91.7% and 100% sensitivity for characterization of malignant lesions respectively.

In previous chemical shift imaging studies of breast tumors, the peak intensity of Cho was measured in the lesion and expressed relative to the background noise level (signal-to-noise ratio), which is a far from quantitative measurement of Cho because signal-to-noise ratio depends on multiple unpredictable factors that vary among examinations. In the study of Beak et al., which yielded the highest accuracy, at the optimal cutoff of Cho, signal-to-noise ratio greater than 3.2, the number of false-negative cases was five. The present study indicated that with the highest Cho concentration of 1.7 mmol/L or lower as a cutoff, rather than a signal-to-noise ratio, no malignant lesions were falsely scored as benign.

In the study of Dorrius et al., with the highest Cho concentration of 1.5 mmol/L or lower as a cutoff, rather than a signal-to-noise ratio, no malignant lesions were falsely scored as benign. This matches our results, as the use of the highest cho concentration of 1.7 mmol/L as a cut off value resulted in 100% sensitivity and specificity for differentiation between benign and malignant breast lesions.

Limitations:

The results of dynamic contrast enhanced MR imaging were not statistically assessed, which prohibited us from evaluating the benefit of the incorporation of MR spectroscopy into the MR imaging diagnostics of breast cancer.

Another limitation was the small number of patients, so, further larger studies are required to confirm our results.

Conclusion:

Breast lesions with a volume of 1 cm³ or greater and a Cho concentration lower than 1.7 mmol/L are benign indicates that, in this patient group, multivoxel MR spectroscopy can potentially replace invasive diagnostic work-up. However, further research is needed to verify the cut off value of 1.7 mmol/L in a prospective analysis with a larger sample size.
References


