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PROTON-MR-SPECTROSCOPY OF THE BREAST: IS IT A RELIABLE IMAGING MODALİTY FOR CHARACTERIZING THE BI-RADS 3 AND 4 LESIONS BEFORE THE BIOPSY?

Hasan Aydın1, Emine Öztürk1, Volkan Kızılgöz1, Hakan Güzel2, Baki Hekimoğlu1.

Dışkapı Yıldırım Beyazıt Research Hospital, Radiology Department1. ANKARA

Dışkapı Yıldırım Beyazıt Research Hospital, General Surgery Department2. ANKARA

Abstract

Aim; Our aim is to evaluate the diagnostic performance of pre and post contrast proton MR spectroscopy (H-MRS) in patients with breast imaging-reporting data system (BI-RADS) 3 and 4 lesions.

Materials and Methods; After institutional review board approval and informed consent taken from all the patients; breast MR imaging and unenhanced-enhanced spectroscopy was performed in 55 patients with BI-RADS 3 and 4 lesions. We had 4 DCIS, 5 malignant tumours, 1 borderline phylloides tumour, 3 mastititis and 42 benign masses in both groups. Diagnostic interpretation was based on the BI-RADS category depending upon the Ultrasonographic-Mammographic and MRI findings. Statistical analysis of BI-RADS 3 and 4 masses were performed by Fischer's exact test and Pearson chi square test.

Results; For the evaluation of BI-RADS 3 mass lesions, pre and post-contrast spectroscopy had about 100% sensitivity and specificity. According to the BI-RADS 4 lesions; H-MRS before and after contrast admistration, presented 81-73 % sensitivity with 100 % specificity for both acquisitons. Pre and post-contrast H-MRS, had 91-85% sensitivity and 56-44% specificity for all BIRADS-3 and 4 lesions of 55 patients. Pre-contrast MR-Spectroscopy had significant statistical differences with regard to histopathology for all BI-RADS 3 and 4 lesions ($p<0.05$), however post-contrast spectroscopy did not have any statistical differences from the biopsy ($p>0.05$).

Conclusion; H-MRS, especially the one performed before the contrast application, was useful for characterizing the BI-RADS 3 and 4 breast lesions, further improve the sensitivity and specificity of breast MR imaging and influence patient treatment options.

Key words: MR Spectroscopy; breast; contrast agents; biopsy.

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Authors **:**

1) **Hasan Aydın M.D.[1] (principal author)**
2) **Emine Öztürk M.D.[1]**
3) **Volkan Kızılgöz M.D.[1]**
4) **Hakan Güzel M.D.[2]**
5) **Baki Hekimoğlu M.D.[1]**

Institution **:**

1- Dışkapı Yıldırım Beyazıt Education and Research Hospital / Radiology Department

2- Dışkapı Yıldırım Beyazıt Education and Research Hospital / General Surgery Department

Adress: Dışkapı Y.B. Eğitim ve Araştırma Hastanesi İrfan Baştuğ Caddesi Altındağ/Ankara-Turkey Postal Code :06110 Tel: 0090-312 5962616

Author Tel: Dr.Hasan Aydın: 0090-532 3484530, 0090-312 3220006, Dr.Emine Öztürk: 0090-533 4229271, Dr.Volkan Kızılgöz: 0090-505 7994013

Author e-mail: dr.hasanaydin@hotmail.com, ozturkemn@yahoo.com, volkankizilgoz@gmail.com

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Data analysis : H.A.E.Ö.

İnterpretation : H.A,E.Ö,V.K.

Manuscript drafting : H.A,V.K,E.Ö

Literature research : H.A,E.Ö,B.H.

Clinical studies : H.A,E.Ö,H.G.

Statistical analysis : H.A.

Manuscript editing : H,A,E.Ö,V.K

Abbreviated author names:

H.A : Hasan Aydın

E.Ö : Emine Öztürk

V.K : Volkan Kızılgöz

H.G : Hakan Güzel

B.H : Baki Hekimoğlu

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Principal Author's **:**

Address : Dışkapı Y.B. Eğitim ve Araştırma Hastanesi İrfan Baştuğ Caddesi Altındağ/Ankara-Turkey Postal Code :06110

Phone : 0090-532 3484530, 0090-312 3220006

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E-Mail : dr.hasanaydin@hotmail.com

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INTRODUCTION

Traditional approaches to assess breast lesions are robust screening methods, such as ultrasonography (US) and mammography (1,2). Mammography provides a widely available, reliable and cost-effective screening tool, however has decreased efficacy in patients with dense breasts, patients with silicone implant and patients that have previous surgery (3). US classification of benign and malignant breast lesions is of low specificity about 30% and ultimately requires histology for confirmation (1-3).

Contrast-enhanced MR imaging of the breast has been shown to have potential benefits in the differential diagnosis of breast abnormalities and getting increasingly important role in the clinical setting for the screening of breast cancer (4,5). Although reported sensitivity of breast MR imaging has been as high as 94-100%, reported specificity has been much more variable, between 37-97% and of low specificity (4,6,7). To improve the specificity of breast MR imaging, detailed assessment of lesion morphology using 3D-MRI and of kinetic patterns using dynamic protocols or combining both strategies have been focused (4,6). In addition to morphologic and kinetic analyses, molecular information has been expected to be useful for the diagnosis of breast masses; in vivo proton-MR-Spectroscopy via providing the cellular chemical information, has the potential to further improve the diagnostic accuracy specificity of MR breast examinations (4-6,8).

H-MRS allows non-invasive molecular analysis of biologic tissues and has been suggested as an adjunct to MR examination to improve the specificity of distinguishing benign from malignant breast masses classified according to BI-RADS category (2,8,9). The diagnostic value of H-MRS is typically based on the elevation of choline compounds such as phosphocholine and glycerophosphocholine, which are the markers of active tumour and aid in the discrimination between benign and malignant breast lesions mainly the BI-RADS 3-5 masses (5,8,9). The purpose of this research is prospectively evaluate the diagnostic performance of MR-Spectroscopy in the categorization of BI-RADS 3 and 4 breast tumours before the histopathological analysis.

MATERİALS AND METHODS

The ethics committee at our institution approved the study and informed consent was taken from all participants prior to the examination. Our study consisted of 55 patients; age ranged from 18-79, mean about 48. Between November 2010 to May 2011, 33 BI-RADS3 and 22 BI-RADS 4 masses were evaluated by dynamic MR imaging and H-MRS. Inclusion criteria for consecutive patients were: 18 years of age or older women, breast lesions ≥ 5 mm in size interpreted either by diagnostic MR imaging or proved by biopsy. Exclusion criteria were inability to undergo or complete the MR imaging, presence of a breast hematoma from recent surgery or biopsy, general contraindications to MRI or to the administration of gadolinium-based contrast agents. Examinations were tried to be scheduled during the second week of menstrual cycle for the pre-menopausal women (5,8,9), none of the enrolled postmenopausal women was under the hormonal replacement therapy. Patients were referred to the MR imaging and H-MRS examination by either mammography or US findings or both of them.

Analysis of data set: Categorization and classification of breast lesions according to the BI-RADS strategy were made by the US-mammographic findings and via the dynamic breast MR scan; lesions of smooth marginated, macrolobulated and well circumscribed nodular lesions under US and/or mammography associated with macrocalcifications and finally without rapid washout pattern or showing neither washout nor initial rapid rise under dynamic contrast-enhanced breast MR imaging, were classified as BI-RADS 3 masses; lesions with irregular marginated, microlobulated nodular lesions under US, associated with segmentally distributed or clustered and clumped or showing linear-branching ductal pattern microcalcifications under mammography and with rapid washout pattern, rapid early uptake or showing non washout but initial rapid contrast rise under dynamic contrast-enhanced breast MR imaging, were classified as BI-RADS 4 masses (6,10,11).

All the BI-RADS 4 lesions and 16 of the BI-RADS 3 masses in this study were identified by histopathology using either excisional or needle biopsy, remaining BI-RADS 3 lesions were under 2 years or more US-mammographic follow up and considered as benign masses. BI-RAD 3 masses evaluated with biopsy, were re-categorized as BI-RADS 4 lesions then the research had 38 BIRADS-4 lesions and 17 BI-RADS 3 lesions. 2 ductal carcinoma in situ (DCIS), one enfectious mastititis and 1 borderline phylloides tumour was accounted from the BI-RADS 3 group, the others were proposed to be benign according to the biopsy and 2 DCIS, 5 malignant lesions; 3 invasive ductal and 2 lobular carcinoma, 2 granulomatous mastititis were diagnosed in BI-RADS 4 group, remaining ones were proved to be benign with biopsy. Borderline-phylloides tumour and 3 mastitis were considered as benign in BIRADS-4 group.We had 4 DCIS, 5 malignant tumours, 1 borderline phylloides tumour, 3 mastititis and 42 benign masses in both BI-RADS 3 and 4 groups.

All the MR imaging and H-MRS examinations were performed on a 1.5 T 8 channel Philips Nova Achievva system, Netherland with 33 mlt\min. maximum gradient strength and a 150 mt per millisecond slew rate. A double breast coil, 4 channel breast array coil with parallel acquisition was used for bilateral breast MR imaging and H-MRS. IV contrast agent used for dynamic breast MR scans was Gadobutrol (Gadovist, Bayer-Schering Farma, Germany), administered by

means of automatic enjection, 0.1-0.3 mmol/kg and followed by a 20-ml saline flush. MR imaging was performed in the transverse and sagittal planes. Axial and sagittal T1W SE (TR/TE; 550/10, 3 mm slice thickness, 512 matrix and 340x340 mm FOV, duration of each scan about 1.35 min.), axial and sagittal fat-saturated (FS) T2W TSE (TR/TE; 5000/120, 3 mm slice thickness, 512 matrix and 340x340 mm FOV, duration of each scan about 3.05 min.), axial and sagittal 3D-T1W Thrive gradient-echo sequence (TR/TE; 7.0/3.4, 1 mm slice thickness, 512 matrix ,12 degree flip angle, duration of scan about 1.03 min.) were performed in the pre-contrast sessions. Pre-contrast scans continued about 11.5 minutes. Dynamic MR imaging was performed for both breasts in the same planes by using 3D- FS Thrive sequence consisted of one unhanced and 6 contrast-enhanced scans continueing about 1 min for each acquisitions, temporal subtraction for all dynamic phases were also applied. Dynamic breast examination continued about 6.10 minutes.

A single-voxel H-MRS was performed by using a point-resolved spectroscopy sequence (PRESS) after the end of pre-contrast and contrast enhanced breast MR imaging sequences. The parameters of H-MRS were as follows: TR/TE;1500 / 135-270 msec, voxel size; 0.5-2.5 mm3 depending upon the size of lesion, 256 acquisitions, 1000 Hz spectral width and 1024-2048 data points, display and analysis of metabolite limits from 0-7 ppm and acquisition time for each scan was 4.5 min. Automatic shimming and 10-20 Hz full width at maximum (FWHM) were also achieved. Spectral suppression for water and lipid metabolites and also base-line correction was not applied. For voxel placement, axial or sagittal MR images were used as scout images and voxel of interest (VOI) was placed to include the entire lesion. 3 major metabolites; lipid (0.8-1.35 ppm), H2O (4.6-5 ppm) and choline (3-3.4 ppm) were examined in the spectroscopic sequences, chemical shifts were referenced to the water peak at approximately 4.75 ppm. (1,12-14). In the discrimination of benign and malignant breast masses, choline peak was chosen as reported in the previous studies, a threshold signal-to-noise ratio of 2 and more in either or both TE values, was believed to indicate the presence of choline in at least one spectra and the mass was characterized as malignant with regard to that pre or post-contrast spectrum (2,4-6,8,9,15-21). Pre and post contrast spectroscopic sequences with TE; 135 and 270 msec were about 18 min.long. In some of the cases of BI-RADS 4 group, the tumour was difficult to identify and clearly separated from the normal breast tissue so contrast-enhanced H-MRS was performed first and the patients were re-examined 1-2 days later with a non-contrast enhanced MRI and spectroscopy where the VOI could easily be placed with the guidance of previously obtained contrast-enhanced MR imaging and spectroscopic studies.

Both MR images and spectroscopic studies were reviewed by one radiologist who had 4 years experience in the breast imaging modalities. He was blinded and unaware of the results of the histopathology. As mentioned before, diagnostic interpretation was based on the BI-RADS category depending upon the US-Mammographic and MR findings. Statistical analysis of BI-RADS 3 and 4 masses according to the unhanced and enhanced H-MRS were performed by Fischer's exact test and Pearson chi square statistics with applying upon the SPSS 11.5 written form (SPSS-Inc, Chicago-IL). Sensitivity, specificity, positive predictive value (PPV) and negative-predictive value (NPV) were calculated with regard to the biopsy results and breast MRI findings in the follow-up BI-RADS 3 patients without histopathological analysis. $P<0.05$ was considered to indicate a statistically significant difference.

RESULTS

Table 1 summarizes the BI-RADS 3 and 4 breast masses of all 55 patients, including age of the patients, mass localization, pre and post-contrast H-MRS findings and biopsy results.

When we correlate the unenhanced and post-contrast H-MRS results for the 17 BIRADS-3 masses with the biopsy yields, it has %100 sensitivity and specificity ($p= 0.059$) with PPV and NPV: 1.00 in the diagnosis of breast lesions(Figure 1, 2), both pre and post-contrast spectroscopic sequences have no significant statistical differences from the histopathologic analysis for the characterization of BIRADS-3 mass group ($p>0.05$). When we combine the results of pre and post-contrast H-MRS for the BI-RADS 3 masses; they have also %100 sensitivity and specificity with PPV: and NPV: 1.00($p=0.059$) without any significant statistical differences from the biopsy results ($p>0.05$).

For the diagnosis of BI-RADS 4 breast masses; Non-enhanced H-MRS results correlated with the biopsy yields, have 81% sensitivity and %100 specificity ($p= 0.211$) with PPV: 1.00 and NPV: 0.13 (Table 2a-figure 3), pre-contrast spectroscopic imaging has no significant statistical differences from the biopsy results in the depiction of these lesions ($p>0.05$), at the same time contrast-enhanced H-MRS for the BIRADS-4 group, has a %73 sensitivity, %100 specificity with PPV: 1.00 and NPV: 0.09($p=0.289$) (Table 2b-figure 4), like the pre-contrast ones, post-contrast spectroscopy imaging has also no significant statistical differences from the histopathologic analysis for the characterization of BIRADS-4 mass group ($p>0.05$). When we combine the results of pre and post-contrast H-MRS for the BI-RADS 4 masses, they have % 76.6 sensitivity, %80 specificity with PPV:0.79 and NPV: 0.40 ($p=0.245$) (Table 3), and both sequences have no significant statistical differences in the diagnosis of BI-RADS 4 mass group from the histopathological analysis either ($p>0.05$).

For the all 55 lesions of both 17 BIRADS-3 and 38 BI-RADS 4 mass groups; H-MRS without contrast, has %91 sensitivity and %56 specificity ($p= 0.003$) with PPV: 0.91 and NPV: 0.56 with regard to the biopsy yields (Table 4a), contrast-enhanced H-MRS imaging for BIRADS 3 and 4 groups, has %85 sensitivity, %44 specificity with PPV: 0.89 and NPV: 0.36 ($p=0.067$) (Table 4b), pre contrast H-MRS have significant statistical differences from the histopathological analysis in the evaluation of both BI-RADS 3 and 4 group lesions ($p<0.05$) but however post contrast spectroscopic imaging has no significant statistical differences from the biopsy results($p>0.05$). When we combine the results of pre and post-contrast H-MRS for the diagnosis of BI-RADS 3 and 4 masses, they have all together %89 sensitivity, %60 specificity with PPV: 0.82 and NPV: 0.31 ($p=0.034$) (Table 5), and the combination of these sequences have significant statistical differences in the diagnosis of BI-RADS 3 and 4 mass groups from the pathological analysis ($p<0.05$).

DISCUSSION

Proton-MR-Spectroscopy provides a complementary technique to breast MR imaging, usually performed with a single-voxel technique and may serve as an adjunct to breast MRI (5,8,9,16-21). Breast MRI is not a currently routine screening method for breast disease, however has a growing role in identifying the lesions and determining the extent of disease (3,7,11,22). Although the architectural and dynamic contrast uptake criteria are the chief measures available for breast MR interpretation, additional measures of metabolism may be efficient with MR Spectroscopy and it provides biochemical measure of tumor metabolism (3,5,8,9,18,20,22-24). Our experience showed that single-voxel H-MRS of the breast was clinically feasible, could be performed after a standard unenhanced and contrast-enhanced breast study in an examination time of approximately 40 min. By using single voxel spectroscopic technique for lesion characterization, we were able to confirm majority of benign and malignant BI-RADS 3 and 4 lesions found by MR imaging. Previous investigators had reported sensitivities of 70-100% and specificities of 67-100% (Table 6). They all suggested that H-MRS might supplement breast MR imaging, reducing the number of biopsies especially in the diagnosis of benign ones (5,9,18,20). In our patients; the sensitivity of spectroscopy, enhanced plus unenhanced series for all 55 BI-RADS 3 and 4 masses was 89%, specificity was 60 %. For BI-RADS 3 lesions; H-MRS had % 100 sensitivity and specificity, for BI-RADS 4 masses; it was about % 76.6 sensitivity and % 80 specificity. In the BI-RADS 4 group; the sensitivity of pre-contrast spectroscopic studies was more than the post-contrast H-MRS results, the specificity was almost the same in BI-RADS 3 and 4 groups for both methods. For the all 55 patients, the specificity was also higher in the pre-contrast spectroscopic series. In our research, one DCIS and one lobular ca. from BI-RADS 4 group was misdiagnosed as benign with both spectroscopic studies, the other malignant and DCIS cases were truely interpreted by either one or both spectroscopic methods. As we had 4 DCIS and 5 malignant cases in this study, there was seven true positive cases.

In the previous reports; the elevation of composite choline levels about the threshold of choline signal-to noise ratio 2 or more, was used to discriminate between benign and malignant breast masses, elevated levels of choline metabolites had been reported in many studies of excised human breast tumours (3,5,8,9,15-21). The use of long echo times (≥135 msec.) typically led to an improved visibility of the choline compounds because of a decreased overlap with the lipid signal that had no diagnostic value in breast tumours. Therefore, breast H-MRS examination should be performed with a long echo time (135-270 msec.) to increase the viability of composite choline signal as we performed in our research (2,12,18,19). In this research, we also applied two H-MRS acquisitions (unenhanced and enhanced) by using two echos, 135 and 270 msec. and the composite choline alterations were almost the same in both long echo techniques. The diagnosis made by breast H-MRS depend on the presence of choline signal; composite choline detection (malignant) or not (benign) that was acquired for the measurement of sensitivity, specificity, PPV and NPV of all researchs but in some cases such as fibrocystic mastopathy, phylloides tumours, tubular adenomas and normal lactating breast parenchyma might also show increased choline signals that can easily interfere the results of these studies, especially affect the specificity and NPV of the reports (1-3,12,22,25).

Voxel sizes in the spectrograms were handled owing to the sizes of the tumours within the range of 5-20 mm^3, at least 5 mm^3 voxels were placed to the tumours in the single-voxel pattern. In the previous studies, many authors presented that the voxel size differences among tumours could contribute and influence the results of H-MRS as they couldn't use the voxel sizes lower than 10 mm^3 due to technical problems (5,8,15,20) but as our voxel diameters were quite fitting to the tumours and might be as lower as 5 mm^3 in size, we proposed that our H-MRS results were not influenced by the voxel size differences among tumour volumes.

The sensitivity of breast H-MRS is defined as the percentage of malignant lesions diagnosed correctly. These are the true positive cases, malignant lesions showing the composite choline signal, the factors that limit the sensitivity of H-MRS may be determined by reviewing the false-negative cases (malignant lesions not showing the choline signal) (2,12,13). False-negative cases had been reported in the studies of Cecil et al (3) (four cases), Yeung et al (19), Tse et al (22) and Kvistad et al (17) (two cases), Roebuck et al (18) (three cases), Jagannathan et al (20) (six cases), on the other hand Bartella et al (5) and Huang et al (21) didn't mention any false-negative cases in their studies (Table 6). Most of the authors explained these false-negative cases due to technical problems, previous biopsies, patients discomfort, the size of the lesions and mislocalization of the masses via H-MRS (3,17-20,22). In our paper, we had four false negative cases in BI-RADS 4 group, two lesions were believed to be benign under the influence of both pre and post-contrast H-MRS but histopathology yielded them as DCIS and invasive ductal ca. Remaining two cases were assumed to be benign with pre-contrast series but presented malignancy in the post-contrast spectroscopy, biopsy results were the same with the enhanced H-MRS: one DCIS and ductal ca. .

The specificity of breast H-MRS is defined as percentage of benign lesions dignosed correctly. Benign lesions without the composite choline signal accepted as true negative cases. The factors that limit the specificity of H-MRS may be determined by presenting the false-positive cases (benign lesions showing the choline peak) (2,12,13). Like the false-negative ones, there were also false-positive cases reported in the several studies: Cecil et al (3), Kvistad et al (17) and Jagannathan et al (20) (two cases), Yeung et al (19) and Roebuck et al (18) (one case), Bartella et al (5) (three cases), Huang et al (21) (four cases), however Tse et al (22) had no false-positive case in his research (Table 6). Fibroadenomas, fibrocystic diseases and tubular adenomas were diagnosed as false malignant in these studies due to the presence of choline peak and most of the authors postulated that these benign lesions all had high cellularity and high epithelial proliferative activity (1,3,5,17-21). In our study, we had also six false-positive cases in the BI-RADS 4 group; two cases were misdiagnosed as malignant by the non-enhanced spectroscopic results. One case was falsely diagnosed as malignant by both spectroscopic modalities, the other three cases were interpreted as false malignant due to the failure of enhanced H-MRS. Biopsy results for these lesions were; mastititis, fibroadenomas, fibrocystic changes and complicated

parenhcymal cysts. We had 46 benign lesions in both BI-RADS groups, therefore true-negative cases in this research were 40.

Through the re-categorized BI-RADS 3 lesions with biopsy; there were three cases of discrepancy between the pre and post contrast H-MRS, these three new BI-RADS 4 cases were interpreted as false malignant via the enhanced H-MRS. In the literature, Joe et al (26) showed that there were changes in both the linewidth, increase of 15-21% and area, decrease of 11-18% of the Cho peak in the same subjects with pre and postinjection of Omniscan (gadodiamide). Lenkinski et al (27) presented that negatively–charged chelates; Magnevist, Multihance, Dotarem broadened the Cho peak and reduced the area of Cho peak in vivo by an average of 40% so the use of such contrast agents may lead to an underestimation of the levels of Cho present in human breast cancers in the post-contrast H-MRS, Lenkinski et al (27) also recommend the use of neutral chelates such as Omniscan, Optimark, Prohance and Gadovist in MRI/MRS studies of the breast, their approach was that in vivo studies had smaller changes in the Cho peak after these contrast agents administration (10-15%) and the effect of such gadolinium-based neutral contrast agents on the MR-spectra of the lesion was negligible. In our opinion; 3 false positive cases throughout the 38 BI-RADS 4 lesions in this research should also be considered as negligible (7.7%) and our contrast agent, Gadovist with neutral chelates had no influence on these results.

The previous single-voxel H-MRS studies also showed 82- 100% PPV (Table 6), our results were also quite similar to the literature, ranging from 79-100 % for BI-RADS 3 and 4 masses with regard to enhanced and non-enhanced H-MRS, about 82% for the combination of both spectroscopic studies for all 55 lesions of BI-RADS groups. Our NPV results of pre and post contrast spectroscopy were higher than the previous reports; ranging from 9-100%, 30% mean for all the BI-RADS 3 and 4 masses Our specificity as mentioned before was also lower than the previous reports in the literature; To our experience, lower specificity and higher NPV of both enhanced and non-enhanced H-MRS in our research might be due to large number of true-benign lesions (40) and six false-positive cases. The sensitivity of our study was quite similar to the previous reports, ranging from 76.6- 89% for both combined BI-RADS groups and unhanced H-MRS showed higher sensitivity than the post-contrast spectroscopic studies. This may be due to the alteration of composite metabolite signal, spesifically the loss of choline signal upon H-MRS sampling after contrast agent injection (3). Our research had some limitations; as a consequence of our small study population and large number of benign cases, we had relatively small sampled lesions than the ones previously reported in the literature. There were only two cases of DCIS and one phylloides tumour in the re-categorized BI-RADS 3 lesions with biopsy, 2 two DCIS cases and five malignancy in the BI-RADS 4 group: Four DCIS and five malignant cases in the BI-RADS 4 group ultimately limited the conclusions that could be drawn about MR Spectroscopy in the assessment of these lesions, further analysis in larger series with more DCIS-malignant cases and a wide variety of histologic types should be necessary. As our study consisted of the lesions ≥ 5 mm in size, we didn't have any technical failures owing to the lesion size that were mentioned in the previous papers. As all the breast MR-Spectroscopy datas were evaluated by one radiologist, inter and intraobserver variability concerning the spectroscopic results couldn't be obtained that might further affect the sensitivity and specifity of the research. Single-voxel spectroscopy technique enabled only one lesion to be evaluated at the same acquisition so if there was more than one lesion, only the more precise and bigger ones were taken into account; with further technologic advancement, advanced hardware-coils and by using multiple voxels for imaging the whole breasts, one could easily improve the clinical application of breast MR-Spectroscopy. Finally, long acquisition time of our H-MRS sequences (about 18 minutes) should reduce the spectral resolution in some cases due to the unwarranted respiratory and motion artefacts.

As a summary , MR Spectroscopy can be added as a last phase after unhanced and contrast-enhanced breast MRI with entire examination not more than 40 min, can allow higher sensitivity than the routine breast MR imaging. It may also aid in eliminating the unnecessary biopsies and surgical procedures especially in cases of benign breast diseases. Further training of radiologists to read breast H-MRS may potentially increase the specificity and diagnostic accuracy of breast diseases, further development of multivoxel spectroscopic methods may increase the choline detection but up to those days, single-voxel proton-MR-Spectroscopy will complement the lesion characterizations with the structural and dynamic MRI.

CONCLUSION

H-MRS provides a non-invasive, biochemical measure of metabolism and useful for characterizing the BI-RADS 3 and 4 breast lesions, further improve the sensitivity and specificty of breast MR imaging and influence patient treatment options. Breast MR Spectroscopy may also be useful in reducing the number of lesions that may require biopsy. It is a fast scan, well tolerated and could easily be incorporated into the breast MR imaging. Single-voxel H-MRS, especially non-enhanced spectroscopic studies with conjunction to routine breast MR imaging as shown in this research, should significantly increase the sensitivity, PPV for detecting and characterizing the BI-RADS 3 and 4 breast lesions.

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FIGURE CAPTIONS

Figure 1: Pre-contrast H-MRS imaging of a patient. Conventional imaging procedures categorised the patient as BI RADS 4. H-MRS showed no choline(BI RADS 3). Pathology revealed “mastitis”

Figure 2: Enhanced H-MRS imaging of a patient with a BI RADS 3 lesion. No choline peak observed. Pathology result was “benign”.

Figure 3: Unenhanced H-MRS depicts choline elevation. Patology result of this lesion showed malignancy.

Figure 4: Contrast enhanced H-MRS shows choline peak and the lesion categorised as BI RADS 4. Patology result of the lesion was “malignant”.

Table 1 : Patients and their data list

	Name-Age	Mass Localization	MR Spectro, Pre-C+	MR Spectro, Post-C+	Biopsy results	BIRADS-3	BIRADS-4
1	E.K,43	Left Breast	Benign	Benign		+	
2	A.Y, 39	Right Breast	Benign	Benign	Benign	+	
3	F.Y, 55	Left Breast	Benign	Malign	Benign	+	
4	R.A, 38	Right Breast	Benign	Benign		+	
5	S.Y, 49	Left Breast	Benign	Benign		+	
6	A.Ç, 67	Left Breast	Benign	Benign	Benign		+
7	G.I, 53	Left Breast	Benign	Benign		+	
8	R.C, 26	Right Breast	Benign	Benign	Granulomatous mastitis		+
9	N.M, 54	Left Breast	Benign	Benign		+	
10	F.U, 39	Left Breast	Benign	Malign	Benign	+	
11	F.K,62	Right Breast	Benign	Benign			+
12	N.Y,45	Right Breast	Benign	Benign		+	
13	N.Y,45	Left Breast	Benign	Benign		+	
14	A.Ç, 54	Right Breast	Benign	Benign			+
15	C.K, 18	Right Breast	Benign	Benign		+	
16	FG.S, 60	Right Breast	Benign	Malign	Malign, ductal ca		+
17	A.Ş, 35	Right Breast	Benign	Malign	Ductal ca in situ	+	
18	Ş.A,39	Left Breast	Malign	Benign	Benign		+
19	C.Y, 20	Right Breast	Malign	Malign	Benign	+	
20	S.K,33	Left Breast	Malign	Benign	Benign		+
21	N.Y,42	Left Breast	Benign	Benign		+	
22	G.A, 35	Right Breast	Benign	Benign	Ductal ca in situ		+
23	Z.Ç, 38	Right Breast	Benign	Benign	Phyllodes tumor	+	
24	D.A, 34	Right Breast	Benign	Benign	Benign	+	
25	F.A, 35	Right Breast	Benign	Benign		+	
26	N.C, 45	Right Breast	Benign	Benign		+	

27	S.Y,45	Left Breast	Benign	Benign	Benign		+
28	D.K, 34	Left Breast	Benign	Benign	Benign	+	
29	G.I,53	Left Breast	Benign	Benign		+	
30	Z.S,41	Left Breast	Benign	Benign	Mastitis-benign.		+
31	G.K,42	Left Breast	Benign	Benign			+
32	S.Ç, 35	Right Breast	Benign	Benign			+
33	A.B,23	Right Breast	Benign	Benign		+	
34	Z.İ, 45	Left Breast	Benign	Benign		+	
35	Ö.C,18	Right Breast	Malign	Malign	Duktal ca in situ	+	
36	Z.C, 79	Left Breast	Benign	Benign			+
37	N.A,44	Right Breast	Benign	Malign	Benign,mastitis	+	
38	N.Y,47	Right Breast	Benign	Benign		+	
39	M.Y, 54	Right Breast	Benign	Benign	Benign	+	
40	F.S,53	Right Breast	Benign	Benign	Benign		+
41	Z.Y, 40	Left Breast	Benign	Benign	Benign	+	
42	İ.Y, 36	Right Breast	Benign	Benign	Benign	+	
43	D.K, 35	Left Breast	Benign	Benign		+	
44	D.A, 36	Left Breast	Benign	Benign	Benign	+	
45	K.T,52	Right Breast	Benign	Benign	Benign	+	
46	S.A, 59	Right Breast	Benign	Benign		+	
47	Ş.A,39	Right Breast	Benign	Benign	Benign	+	
48	A.Ş, 53	Left Breast	Benign	Benign	Malign		+
49	F.E,47	Left Breast	Benign	Benign	Benign		+
50	T.D, 44	Right Breast	Malign	Malign	Duktal ca in situ		+
51	A.D, 43	Right Breast	Benign	Benign	Benign		+
52	A.Y, 39	Left Breast	Benign	Benign	Benign		+
53	H.C,53	Left Breast	Malign	Malign	Malign		+

54	N.Y 51	Left Breast	Malign	Malign	Malign		+
55	F.Ç 48	Right Breast	Malign	Malign	Malign		+

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Table 2: Correlation of pre-contrast H-MRS (table 2a) and post-contrast H-MRS (table 2b) with biopsy results

Table 2a			BIRADS-3		Total
			Negative	Positive	
Pre-C+	Benign	n	2	28	30
		%n	6,5%	93,5%	100,0%
	Malign	n	2	1	3
		%n	66,6%	33,4%	100,0%
Total		n	4	30	33
		%n	13,3%	86,7%	100,0%

P=0,033, Sensitivity= 0,93, Specificity=0,50
NPV=0.66, PPV=0,94

Table 2b			BIRADS-3		Total
			Negative	Positive	
Post-C+	Benign	n	2	25	27
		%n	7,4%	92,6%	100,0%
	Malign	n	2	4	6
		%n	33,3%	66,7%	100,0%
Total		n	4	29	33
		%n	12,1%	87,9%	100,0%

P=0,142, Sensitivity= 0,86, Specificity=0,50
NPV=0,33, PPV=0,93

Table 3: Combination of pre and post-contrast H-MRS results for BI-RADS 3 lesions with respect to biopsy

Table 3			BIRADS-3		Total
			Negative	Positive	
Biopsy results	Benign	n	2	28	30
		% n	6,7%	93,3%	100,0%
	Malign	n	1	0	1
		% n	100,0%	0,0%	100,0%
	Ductal ca in situ	n	1	1	2
		% n	50,0%	50,0%	100,0%
Total		n	4	29	33
		% n	12,1%	87,9%	100,0%

P=0,032, Sensitivity: 0.90, Specificity: 0.50,
PPV: 0.87, NPV: 0.34

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Table 4 : The results of pre-contrast H-MRS (table 4a) and post-contrast H-MRS (table 4b) for BI-RADS 4 masses compared with biopsy results.

Table 4a			BIRADS-4		Total
			Negative	Positive	
Pre-C+	Benign	n	2	14	16
		%n	12,5%	87,5%	100,0%
	Malign	n	3	1	4
		%n	75,0%	25,0%	100,0%
Total		n	5	15	20
		%n	25,0%	75,0%	100,0%

P=0,032, Sensitivity: 0,93, Specificity: 0,60
NPV: 0,75, PPV: 0,88

Table 4b			BIRADS-4		Total
			Negative	Positive	
Post-C+	Benign	n	3	14	17
		%n	17,6%	82,4%	100,0%
	Malign	n	2	1	3
		%n	66,7%	33,3%	100,0%
Total		n	5	15	20
		%n	25,0%	75,0%	100,0%

P=0,140, Sensitivity: 0,93, Specificity:0,40
NPV: 0,67, PPV: 0,82

Table 5 : Combination of pre and post-contrast H-MRS results for BI-RADS 4 lesions with respect to biopsy yields

Table 5			BIRADS-4		Total
			Negative	Positive	
Biopsy results	Benign	n	3	11	14
		%n	21,4%	78,6%	100,0%
	Malign	n	1	3	4
		%n	25,0%	75,0%	100,0%
	Ductal ca in situ	n	1	1	2
		%n	50,0%	50,0%	100,0%
Total		n	5	15	20
		%n	25,0%	75,0%	100,0%

P=0,714, Sensitivity: 0,78, Specificity: 0,63
NPV: 0,25, PPV: 0,75

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Table 6 : For all the 53 lesions of BIRADS-3 and BI-RADS 4 mass groups; correlation of H-MRS with biopsy results

Table 6a			BIRADS		Total
			Negative	Positive	
Pre-C+	Benign	n	4	42	46
		%n	8,7%	91,3%	100,0%
	Malign	n	5	2	7
		%n	71,4%	28,6%	100,0%
Total		n	9	44	53
		%n	17,0%	83,0%	100,0%

P=0,001, Sensitivity: 0,95, Specificity: 0,56,
NPV=0,71, PPV=0,91

Table 6b			BIRADS		Total
			Negative	Positive	
Post-C+	Benign	n	5	39	44
		%n	11,4%	88,6%	100,0%
	Malign	n	4	5	9
		%n	44,4%	55,6%	100,0%
Total		n	9	44	53
		%n	17,0%	83,0%	100,0%

P=0,035, Sensitivity: 0,87, Specificity: 0,44,
NPV=0,44, PPV=0,87

Table 7 : The combination of pre and post-contrast H-MRS for bilateral BI-RADS 3 and 4 results correlated with biopsy

Table7			BIRADS		Total
			Negative	Positive	
Biopsy results	Benign	n	5	39	44
		%n	11,4%	88,6%	100,0%
	Malign	n	2	3	5
		%n	40,0%	60,0%	100,0%
	Ductal ca in situ	n	2	2	4
		%n	50,0%	50,0%	100,0%
Total		n	9	44	53
		%n	17,0%	83,0%	100,0%

P=0,088, Sensitivity: 0,89, Specificity: 0,60
NPV: 0,28, PPV: 0,83

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Table 8 : Results of single-voxel 1,5 T H MR spectroscopy in previous studies

Study	No.of Malignant Lesions (n=168)	No.of Benign Lesions (n=112)	Sensitivity (%)	Specificity (%)	No.of True-Positive Findings (n=149)	No.of True-Negative Findings (n=97)	No.of False-Negative Findings (n=19)	No.of False-Positive Findings (n=15)	Positive Predictive Value (%)
Roebuck et al (17)	10	7	70	86	7	6	3	1	88
Kvistad et al (16)	11	11	82	82	9	9	2	2	82
Cecil et al (3)	23	15	83	87	19	13	4	2	90
Yeung et al (18)	24	6	92	83	22	5	2	1	97
Jagannathan et al (19)	32	14	81	86	26	12	6	2	93
Tse et al (21)	19	21	89	100	17	21	2	0	100
Huang et al (20)	18	12	100	87	18	8	0	4	82
Bartella et al (5)	31	26	100	88	31	23	0	3	91
Note : Mean sensitivity, specificity and positive predictive values for all studies were 87%, 87% and 90%, respectively. Study reference numbers are in paranthesis									