ROLE OF SINGLE VOXEL PROTON MAGNETIC RESONANCE SPECTROSCOPY ON A 3 TESLA MR SCANNER IN CHARACTERISING BREAST LESIONS- A TERTIARY CARE CENTRE EXPERIENCE IN EASTERN INDIA

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ABSTRACT

BACKGROUND

To evaluate whether the detection of choline-containing compounds in single voxel MR spectroscopy of breast lesions can differentiate between benign and malignant breast lesions.

MATERIALS AND METHODS

This prospective observational study included 99 breast lesions in 77 patients (between 18 and 86 years age) who underwent 3T breast MRI including proton MR spectroscopy before biopsy. Following dynamic contrast-enhanced study, single voxel, water and fat suppressed proton MR spectroscopy was performed. The position and size of the Volume of Interest (VOI) was placed so as to include the enhancing part of the lesion and excluding as much as possible the nonenhancing gland parenchyma, adjoining fat or necrotic part of the lesion. Choline peak at 3.2 ppm was qualitatively evaluated. MRI BIRADS scoring was done for each lesion. Sensitivity and specificity of the (1) H-MRS were calculated. Final histopathological diagnosis was taken as the gold standard.

RESULTS

According to histopathology, 53 lesions were malignant and 46 were benign. The qualitative approach based on presence or absence of choline peak yielded 88.68% [95% CI 76.97% to 95.73%] sensitivity and 76.09% [95% CI 61.23 to 87.41%] specificity for differentiating malignant and benign lesions (p<0.0001).

CONCLUSION

In vivo proton, MR spectroscopy can be used as an adjunctive tool for characterising breast lesions. However, the detection of choline-containing compounds is not specific for malignancy. Benign breast lesions may also demonstrate choline peak.

KEYWORDS

3 Tesla, Single Voxel, Proton Magnetic Resonance Spectroscopy, Breast Cancer.


BACKGROUND

Breast cancer is one of the most common cancer among women worldwide and second most malignancy among Indian women after cervical cancer in rural population.¹ The age standardised incidence rate of breast cancer varies between 9 to 32 per 1,00,000 women in India and has become the country with the largest estimated number of breast cancer deaths worldwide.¹ Early diagnosis is essential for successful treatment and x-ray mammography, ultrasonography and MRI are the currently used methods for detection and characterisation of breast lesions.

3-Tesla MRI is now increasingly being used for characterisation of breast lesions due to its better spatial resolution, higher signal to noise ratio and shorter image acquisition time.²,³ Apart from Dynamic Contrast-Enhanced MRI (DCE-MRI), which is based on tumour angiogenesis, characterisation of suspicious breast lesions can also be based upon the evaluation of changes in tissue metabolism and cellular chemistry as detected by proton magnetic resonance spectroscopy.⁴,⁵

The major components of cell membrane are choline-containing compounds required for structural stability and proliferation of cells.⁶ Many studies have shown elevated total choline compounds in neoplastic tissues, which may be due to increased membrane turnover by replicating cells.⁷,⁸ Using in vivo proton magnetic resonance spectroscopy (1 H-MRS), the choline signal can be measured. In the MR spectra, the choline peak is found resonating at 3.2 ppm.
with the main contribution from phosphocholine.\textsuperscript{9,10} The aim of present study is to determine whether the detection of choline-containing compounds in single voxel MR spectroscopy of breast lesions can differentiate between benign and malignant breast lesions.

**SUBJECTS AND METHODS**

**Study Population**
This is a prospective observational study conducted in the Department of Radiodiagnosis in collaboration with the Department of General Surgery and Department of Pathology of IPGMER and SSKM Hospital, Kolkata. The study was approved by the “Institutional Ethical Committee.” 88 women with 99 suspicious breast lesions who underwent MRI breast in our hospital between January 2015 and October 2016 were included in the study.

**Inclusion Criteria**
Female patients with suspicious breast lesions assessed by clinical/physical examination and/or ultrasonography and/or mammography.

**Exclusion Criteria**
1. Less than 1 cm size contrast-enhancing masses.
2. Previous or current neoadjuvant chemotherapy or radiation therapy.
3. Previous interventional or surgical breast related procedures in the three months preceding the examination.
4. Male patients presenting with breast lumps.
5. Patients without histopathological confirmation of the breast lesion.
6. Any patient who had general contraindications to MRI were excluded such as:
7. Patients having history of allergic manifestation to contrast or other drug.
8. Patients with implanted cardiac pacemaker, aneurysm clips, cochlear or other such device contraindicated for MRI examination.
10. Unwillingness to be part of the study.

All the patients signed a written informed consent form in their own local language before inclusion in the study. In premenopausal women, MR imaging was done during the second week of menstrual cycle. Postmenopausal women who were under treatment with hormone replacement therapy were excluded from the study. MRI included both dynamic contrast-enhanced study and proton MR spectroscopy.

**MRI Acquisition and Post Processing**
Bilateral breast MRI was performed using 3.0T MR (Signa HDx 3.0T, GE Medical Systems) scanner. The patient was positioned in prone position and a dedicated 16-channel bilateral breast coil. The study protocol included: an axial T1, T2, STIR sequences, sagittal T2FS, an axial vibrant multiphase 3D T1-weighted dynamic gradient-echo sequence obtained after 10 mL IV bolus injection of gadolinium DTPA at the rate of 2.5 mL/sec followed by a 20 mL saline flush. Dynamic study comprised of one precontrast and 7 postcontrast series, each phase of 1 minute 21 seconds duration. Automated subtracted images were obtained for each of seven phases. A single voxel water and fat-suppressed proton MR spectroscopy (axial breast in GE Signa HDx 3T) was acquired using the following technical parameters- TR/TE 2000/155; FOV 20x20; scan time 8 minutes.

**MRI Interpretation**
T2 and STIR images were first examined to detect the presence or absence of any lesion or cyst. Morphological assessment was done on postcontrast axial and reformatted vibrant multiphase images. Kinetic curve was obtained by FuncTool software using multiphase axial vibrant and subtracted images. MRI BIRADS classification was done for each lesion based on both morphology and kinetic curve assessment.

In MR spectroscopy, the Volume of Interest (VOI) position and size were chosen to encompass enhancing part of the lesion excluding as much as possible the nonenhancing gland parenchyma, surrounding fat or necrotic part of the lesion. A peak at 3.2 ppm was considered positive and if no peak was seen then considered negative. The interpretation was done by a radiologist with more than 10 years’ experience in breast MR imaging.

**Reference Standard**
All lesions with a MR BIRADS category 3, 4 or 5 underwent surgical excision (n=64) or followed with 14-gauge core needle biopsy under ultrasound guidance (n=35). Histopathological diagnosis was taken as the gold standard.

**Statistical Analysis**
Sensitivity, specificity and accuracy of the (1) H-MRS were calculated.

**RESULTS AND ANALYSIS**
Single-voxel\textsuperscript{1} H-MRS was performed for 99 breast lesions. Histologically, 53 lesions were malignant; 46 were benign. According to the final histopathological reports, the malignant lesions were invasive ductal carcinoma (n=33) (Figure 4A and 4B), invasive ductal carcinoma with ductal carcinoma in situ (n=3), inflammatory intraductal carcinoma (n=8), invasive lobular carcinoma (n=2), pure mucinous carcinoma (n=2) (Figure 3A and 3B), mixed mucinous carcinoma (n=1), malignant phyllodes (n=1), papillary carcinoma (n=1) and invasive metaplastic carcinoma (n=2) while the benign lesions included fibroadenoma (n=14), idiopathic granulomatous mastitis (n=6), benign phyllodes (n=3), fibrocystic disease of breast (n=6), fibroadenolipoma (n=3), benign proliferative lesion (n=1), ductal adenoma (n=3), tubular adenoma (n=1), lactating adenoma (n=1) hyalinised fibroadenoma (n=1), fibroadenosis with epitheliosis (n=1) and intraductal papilloma (n=6).
The qualitative approach based on presence or absence of choline peak yielded 88.68% [95% CI 76.97% to 95.73%] sensitivity and 76.09% [95% CI 61.23 to 87.41%] specificity for differentiating malignant and benign lesions (p<0.0001). Out of 99 lesions, 58 lesions showed choline peak and 41 lesions did not show choline peak at 3.2 ppm. Out of the 41 lesions showing no choline peak, 35 lesions were benign (true negative) and 6 lesions (false negative) were malignant by histology. Similarly, out of 58 lesions showing choline peak, 47 were malignant (true positive) and 11 (false positive) were benign by histology.

The benign lesions showing choline peak in MR spectroscopy included tubular adenoma (n=1), ductal adenoma (n=1), fibrocystic disease of breast (n=1), fibroadenolipoma (n=2) (Figure 2A and 2B), benign proliferative lesion (n=1), ductal papilloma (n=1), fibroadenoma (n=1), idiopathic granulomatous mastitis (n=2) (Figure 1A and 1B), benign phylloides (n=1). In invasive ductal carcinoma, the results of (1) H-MRS were negative in 5 cases (Figure 5A and 5B). Also, one case of pure mucinous carcinoma didn't demonstrate choline peak in the study.

Figure 1A- A 47-year-old lady with idiopathic granulomatous mastitis in right breast. Single voxel MR spectroscopy images are shown.

Figure 1A- Position of volume of interest is shown on sagittal reference plane.

Figure 1B- MR spectrum shows total choline-containing compound peak at 3.2 ppm. This lesion is false positive finding for MR spectroscopy.
Figure 2A and 2B, single voxel MR spectroscopy in a 40-year-old lady with benign phylloides in right breast showing choline resonance peak at 3.2 ppm. This lesion is false positive for MR spectroscopy.

Figure 3A and 3B- A 42-year-old lady with invasive ductal carcinoma in right breast. Single voxel spectrum shows no positive choline resonance peak. This lesion is false-negative finding for MR spectroscopy.

Figure 4A and 4B- Single voxel proton MR spectroscopy in a 60-year-old postmenopausal lady with invasive ductal carcinoma in left breast.
  Position of volume of interest is shown on sagittal reference plane.
  MR spectrum shows total choline-containing compound peak at 3.2 ppm. This lesion is true positive finding for MR spectroscopy.
Figure 5A and 5B- A 52-year-old postmenopausal lady with pure mucinous carcinoma in right breast. Single voxel MR spectroscopy images are shown.

Figure 5A- Position of volume of interest is shown on axial reference plane.

Figure 5B- MR spectrum shows total choline-containing compound peak at 3.2 ppm. This lesion is true positive finding for MR spectroscopy.

DISCUSSION
The diagnostic value of in vivo breast MR spectroscopy is typically based on the detection of elevated level of tCho, which is a marker of active tumour. The study of Roebuck et al.4 showed the potential of utilising tCho as a biomarker of breast malignancy in 1998. The qualitative approach was based on whether a distinct resonance at approximately 3.2 ppm is present or not. No objective statistical analysis of the spectrum in terms of SNR or tCho signal amplitude was performed by this method. Most of the qualitative MR spectroscopy studies are done on 1.5 Tesla MR Scanner. Less number of studies are done in the Indian population where the occurrence of breast malignancy is very high. In our study, we have demonstrated the importance of in-vivo 3-Tesla single voxel water and fat-suppressed proton magnetic resonance spectroscopy of the breast as a tool in characterising breast lesions in a noninvasive manner by detecting increased levels of composite choline compounds.

The sensitivity (88.68%) result of (1) H-MRS obtained in our study are consistent with those (sensitivity=83%-100%) reported in previous studies.11-14 One of the major reasons for relatively high sensitivity in our study is the exclusion of enhancing lesions, which are less than one centimetre in size.

However, the specificity (76.09%) was significantly lower than that reported in previous studies (specificity=83%-100%),11-14 which may be attributed to the various benign pathologies showing choline peak at 3.2 ppm in (1) H-MRS study.

The failure to detect choline in some breast cancers might be related to contamination by haemorrhage.12 The inclusion of fatty tissue11 and tumour cells growing with many intervening stromal cells and inflammatory cells.15 In small lesions, the MRS voxel size maybe larger than the tumour size leading to inclusion of fibroglandular and fatty tissues in the MRS voxel, partial volume effect and reduced choline concentration.

LIMITATIONS
For MR spectroscopy, a lesion has to be more than 1 cc in volume to provide proper results. Hence, we could not obviate the need of biopsy in these cases. The single voxel technique, which is the most commonly used technique allows only one lesion to be examined at a time. In addition, smaller number of cases are the other limitations of our study. Studies of MR spectroscopy may improve the specificity.

CONCLUSION
In vivo, qualitative proton MR spectroscopy along with MR breast imaging can be used as an adjunctive tool for characterising breast lesions. However, the detection of choline-containing compounds is not specific for malignancy. Various benign breast lesions may also demonstrate choline peak. Larger multicentric trials are needed in establishing this technique in routine practice.

REFERENCES


