Section (2)

2-4 Imaging Findings of Breast Cancer

The female breast cancer has been investigated by different modalities which includes mammography, ultrasound and MRI in order to detect the early presence of cancer. Magnetic resonance (MR) imaging has been increasingly used for accurate diagnosis of both primary and recurrent breast cancers, particularly in cases in which mammography and breast sonography are inconclusive or yield discrepancies. In addition, MR imaging may improve the analysis of the local extent of breast cancer by revealing multifocal and multicenter tumor growth in patients scheduled for conservative breast surgery. Although the high sensitivity of breast MR imaging has proved to be advantageous for preoperative patients, the limited specificity of this imaging method continues to be a significant problem, particularly in patients referred for further clarification and delineation of inconclusive findings obtained using conventional breast imaging techniques (Philadelpho,2011).

Several studies has investigated the role of advanced MR imaging techniques, such as magnetic resonance spectroscopy (MRS) and diffusion-weighted imaging (DWI), in improvement of the specificity of MR imaging for the evaluation of breast lesions

2-4-1 MR Spectroscopy

Proton MR spectroscopy (^{1}H MRS) has emerged as a powerful, non-invasive method for studying tumor biochemistry and has the potential to improve the specificity of contrast-enhanced breast MRI to 67– 100% (Robinson, 1997- Jacobs, 2005) . Several in vivo studies proved that ^{1}H MRS discriminate between benign and malignant lesions of the breast by detecting the presence of choline metabolites, a marker of increased cell-membrane turnover in tumors (Bartella, 2006). ^{1}H MRS has been reported to be a reliable method because it is based on the appearance of a single spectroscopic peak, that of phosphocholine, in the spectrum at a frequency of 3.2 ppm. (Castillo, 1999- Gary, 2003).   However, results of previous studies also demonstrated that the choline levels may not be as greatly elevated in some breast cancers as they are in others, and sometimes are not detected at all, resulting in false-negative diagnoses (Patricia, 2008).

Proton MR Spectroscopy with Choline Peak as Malignancy Marker Improves Positive Predictive Value for Breast Cancer Diagnosis: Preliminary Study. This research done by Lia Bartella MD, et al. The purpose for the study was to prospectively evaluate the diagnostic performance of magnetic resonance (MR) spectroscopy in patients with suspicious lesions or biopsy-proved cancers at MR imaging by using histologic findings as the reference standard.

breast MR spectroscopy was performed in patients with suspicious or biopsy-proved malignant lesions measuring 1 cm or larger at MR imaging. Single-voxel MR spectroscopy data were collected from a single rectangular volume of interest that encompassed the lesion. MR spectroscopy findings were defined as positive if the signal-to-noise ratio of the choline resonance peak was greater than or equal to 2 and as negative in all other cases. MR spectroscopy findings were then compared with histologic findings.

Lia and her colleagues reported that, a total of 56 patients (age range, 20–77 years) with 57 lesions were imaged. The median lesion size at MR imaging was 2.3 cm (range, 1–15 cm). Histologically, 31 (54%) of 57 lesions were malignant, and 26 (46%) were benign. A choline peak was present in 34 of 57 lesions (including all

cancers) and in three of 26 benign lesions, giving MR spectroscopy a sensitivity of 100% and a specificity of 88%. In 40 lesions of unknown histologic type, the use of MR spectroscopy as an adjunct to MR imaging would have significantly ($P < .01$) increased the positive predictive value of biopsy from 35% to 82%. If biopsy had been performed only on those lesions with a choline peak at MR spectroscopy, biopsy may have been spared in 23 (58%) of 40 lesions, and none of the cancers would have been missed.

The researcher concluded that Proton MR Spectroscopy was successfully incorporated into breast MR imaging studies for lesions measuring 1 cm or larger. This technique may be useful in reducing the number of lesions detected at MR imaging that require biopsy

Characterization of Lesions of the Breast with Proton MR Spectroscopy: Comparison of Carcinomas, Benign Lesions, and Phyllodes Tumors. Another study conducted by Gary M. K. Tse et al. Their aim for the study was to evaluate the possible relationship between spectroscopy results and the tumor proliferative index, angiogenesis, and HER2/neu *oncogene* overexpression. 19 breast carcinomas was evaluated, 21 benign breast lesions (including 18 fibroadenomas, one fibrocystic change, one hamartoma, and one papilloma), and six phyllodes tumors (four benign, two of borderline malignancy) using proton MR spectroscopy. All lesions were larger than 1.5 cm. Tumor Ki-67 proliferative index, tumor angiogenesis, and HER2/neu oncogene overexpression were evaluated by immunohistochemistry of the histologic material.

They reported that Spectroscopy findings were positive in 17 (89%) of 19 carcinomas but negative for all benign lesions and phyllodes tumors (sensitivity, 89%; specificity, 100%). Significantly higher levels were obtained for all biologic parameters in carcinomas compared with benign lesions and phyllodes tumors. *HER2/neu* oncogene overexpression was present in 37% of carcinomas but not in other lesions. The two false-negative findings of breast carcinoma showed similar Ki-67 proliferative index and microvessel density compared with the remaining carcinomas, but both cases were negative for HER2/neu overexpression.

The researchers concluded that Proton MR Spectroscopy is useful in the in vivo characterization of breast masses when the lesion exceeds 1.5 cm in maximal dimension. Spectroscopy is unable to reveal benign breast lesions and phyllodes tumors of benign and borderline malignancy. We suggest that a false-negative spectroscopic result may be related to an absence of *HER2/neu* overexpression in carcinoma of the breast.

[1]H MR Spectroscopy and Diffusion-Weighted Imaging of the Breast: Are They Useful Tools for Characterizing Breast Lesions Before Biopsy? A study done by Mitsuhiro Tozaki and Eisuke Fukuma, the aim of the study was to determine whether proton (H1) MR spectroscopy and diffusion-weighted imaging might be useful tools for characterizing breast lesion before biopsy.

Single-voxel ^{1}H MRS and diffusion-weighted imaging were performed in 171 suspicious or highly suspicious lesions. Using the residual water signal as a reference (4.7 ppm), a choline peak at 3.22–3.23 ppm was defined as malignant. If a high-signal-intensity lesion was detected in high-b-value (b = 1,500 s/mm^2) images, that lesion was defined as positive for malignancy. Among the patients with positive results on diffusion-weighted imaging, the apparent diffusion coefficient (ADC) values of the mass or focus were calculated from two different gradient factors (b_1 = 500 s/mm^2 and b^2 = 1,500 s/mm^2).

They reported that; the diagnostic sensitivity and specificity of ^{1}H MRS were 44% (40/91) and 85% (68/80), respectively (p < 0.001). If ^{1}H MRS was applied for mass lesions larger than 15 mm, the diagnostic sensitivity and specificity were 82% (28/34) and 69% (11/16), respectively. Of the high-b-value images, 24 benign lesions and eight nonmass ductal carcinoma in situ were visually negative. With the use of a cutoff ADC value of 1.13 × 10^{-3} mm^2/s, a specificity of 67% (43/64) and sensitivity of 97% (61/63) was obtained on diffusion-weighted imaging.

The authors concluded that ^{1}H MRS was useful for characterizing breast lesions measuring 15 mm or larger, and diffusion-weighted imaging was useful for characterizing lesions of any size. However, these two techniques still have potential pitfalls in relation to the diagnosis of nonmass breast lesions.

MRI and ^{1}H MRS of The Breast: Presence of a Choline Peak as Malignancy Marker is Related to k21 Value of the Tumor in Patients with Invasive Ductal Carcinoma….. A research done by Patricia R. Geraghty, MD, et al. to assess which specific morphologic features, enhancement patterns, or pharmacokinetic parameters on breast Magnetic Resonance Imaging (MRI) could predict a false-negative outcome of Proton MR Spectroscopy (^{1}H MRS) exam in patients with invasive breast cancer. Sixteen patients with invasive ductal carcinoma of the breast were prospec-tively included and underwent both, contrast-enhanced breast MRI and ^{1}H MRS examination of the breast. The MR images were reviewed and the lesions morphologic features, enhancement patterns and pharmacokinetic parameters (k21-value) were scored according to the ACR BI-RADS-MRI lexicon criteria. For the in vivo MRS studies, each spectrum was evaluated for the presence of choline based on consensus reading. Breast MRI and ^{1}H MRS data were compared to histopathologic findings. In vivo ^{1}H MRS detected a choline peak in 14/16 (88%) cancers. A false-negative ^{1}H MRS study occurred in 2/16 (14%) cancer patients. K21 values differed between both groups: the 14 choline positive cancers had k21 values ranging from 0.01 to 0.20/second (mean 0.083/second), whereas the two choline-negative cancers showed k21 values of 0.03 and 0.05/second, respectively (mean 0.040/second). Also enhancement kinetics did differ between both groups; typically both cancers that were choline-negative showed a late phase plateau (100%), whereas this was only shown in 51/4 (36%) of the choline positive cases. There was no difference between both groups with regard to morphologic features on MRI.

This study showed that false-negative ^{1}H MRS examinations do occur in breast cancer patients, and that the presence of a choline peak on ^{1}H MRS as malignancy marker is related to the k21 value of the invasive tumor being imaged.

In Vivo Proton MR Spectroscopy of the Breast Using the Total Choline Peak Integral as a Marker of Malignancy…

A study made by Francesco Sardanelli and his colleagues. Their aim of study was to use the total choline-containing compound (tCho) peak integral as a marker of malignancy in breast MR spectroscopy (MRS).

Forty-eight single-voxel water- and fat-suppressed 1.5-T MRS measurements were performed in 42 patients, obtaining both absolute tCho peak integral and tCho peak integral normalized for the volume of interest (VOI). Our reference standard was histology for lesions with BI-RADS category 4 and 5 and histology or at least a 2-year follow-up for findings with BI-RADS 2 and 3 and normal glands. Receiver operating characteristic (ROC) analysis, Mann-Whitney U test, and Spearman's rank correlation were used.

Three of 48 measurements (6%) failed. Of the remaining 45 spectra, 18 nonmalignant tissues showed no tCho peak, eight nonmalignant tissues showed a tCho peak integral from 0.99 to 9.03 arbitrary units (AU), and 19 malignant lesions showed a tCho peak integral from 1.26 to 19.80 AU. The diameter of nonmalignant tissues was 16.9 ± 7.4 mm; that of malignant lesions was 15.3 ± 6.9 mm (p = 0.308). At ROC analysis, the optimal threshold was 1.90 AU for absolute tCho peak, with 0.895 (17/19) sensitivity, 0.923 (24/26) specificity, and an AUC (area under the curve) of 0.917 (95% CI, 0.822–1.000); the optimal threshold was 0.85 AU/mL for the normalized tCho peak integral with 0.842 (16/19) sensitivity, 0.885 (23/26) specificity, and an AUC of 0.941 (0.879–1.000) (p = 0.470). A negative correlation (p = 0.011) was found between the VOI and the normalized tCho peak integral of malignant tissues.

The researcher concluded that Breast MRS using tCho peak integral reaches a high level of diagnostic performance.

2-4-2 Diffusion -Weighted Imaging

Diffusion weighted MR imaging (DW-MRI) provides unique information about the state of the molecular translational motion of water. This allows inference about local tissue architecture which is a sensitive early indicator of abnormality and cellularity. The mean or average diffusivity in tissue is quantified by an index called the Apparent Diffusion Coefficient (ADC).

Quantitative Diffusion-Weighted Imaging as an Adjunct to Conventional Breast MRI for Improved Positive Predictive Value.....This study done by Savannah c. Partridge and his colleagues. The aim of the study was to investigate whether adding diffusion-weighted imaging (DWI) to dynamic contrast-enhanced MRI (DCE-MRI) could improve the positive predictive value (PPV) of breast MRI.

The retrospective study included 70 women with 83 suspicious breast lesions on DCE-MRI (BI-RADS 4 or 5) who underwent subsequent biopsy. DWI was acquired during clinical breast MRI using $b = 0$ and 600 s/mm^2. Apparent diffusion coefficient (ADC) values were compared for benign and malignant lesions. PPV was calculated for DCE-MRI alone (based on biopsy recommendations) and DCE-MRI plus DWI (adding an ADC threshold) for the same set of lesions. Results were further compared by lesion type (mass, nonmasslike enhancement) and size.

Of the 83 suspicious lesions, 52 were benign and 31 were malignant (11 ductal carcinoma in situ [DCIS], 20 invasive carcinoma). Both DCIS (mean ADC, $1.31 \pm 0.24 \times 10^{-3}$ mm^2/s) and invasive carcinoma (mean ADC, $1.29 \pm 0.29 \times 10^{-3}$ mm^2/s) exhibited lower mean ADC than benign lesions ($1.70 \pm 0.44 \times 10^{-3}$ mm^2/s, $p < 0.001$). Applying an ADC threshold of 1.81×10^{-3} mm^2/s for 100% sensitivity produced a PPV of 47% versus 37% for DCE-MRI alone, which would have avoided biopsy for 33% (17/52) of benign lesions without missing any cancers. DWI increased PPV similarly for masses and nonmasslike enhancement and preferentially improved PPV for smaller (≤ 1 cm) versus larger lesions.

They concluded that DWI shows potential for improving the PPV of breast MRI for lesions of varied types and sizes. However, considerable overlap in ADC of benign and malignant lesions necessitates validation of these findings in larger studies.

Apparent Diffusion Coefficient in Invasive Ductal Breast Carcinoma: Correlation with Detailed Histologic Features and the Enhancement Ratio on Dynamic Contrast-Enhanced MR Images…. A study done by Poka Namoto Matsubayashi et al To investigate the correlation of Apperent Diffusion Coefficient (ADC) values in invasive ductal breast carcinomas with detailed histologic features and enhancement ratios on dynamic contrast-enhanced MRI.

Dynamic MR images and diffusion-weighted images (DWIs) of invasive ductal breast carcinomas were reviewed in 25 (26 lesions) women. In each patient, DWI, T2WI, T1WI, and dynamic images were obtained. The ADC values of the 26 carcinomas were calculated with b-factors of 0 and 1000 s/mm2 using echoplanar DWI. Correlations of the ADC values were examined on dynamic MRI with enhancement ratios (early to delayed phase: E/D ratio) and detailed histologic findings for each lesion, including cellular density, the size of cancer nests, and architectural features of the stroma (broad, narrow, and delicate) between cancer nests. *Results*. The mean ADC was $0.915\pm0.151\times10\text{-}3$ mm2/sec. Cellular density was significantly correlated with ADC values (P=.0184) and E/D ratios (P=.0315). The ADC values were also significantly correlated to features of the stroma (broad to narrow, P=.0366).

 The findings suggest that DWIs reflect the growth patterns of carcinomas, including cellular density and architectural features of the stroma, and E/D ratios may also be closely correlated to cellular density.

Role of diffusion MRI in characterizing benign and malignant breast lesions..
Another study done by Lalitha Palle and Balaji Reddy.

The aim of this study was to evaluate the role of MRI based diffusion-weighted imaging (DWI) and the apparent diffusion coefficient (ADC) for characterizing breast lesions in Indian patients.

Materials and Methods:

This prospective analysis was performed between October 2006 and June 2008. It includes 200 patients between the ages of 16 and 80 years with solid breast lesions greater than 1 cm in diameter. Of these 200 patients, 80 underwent breast MRI with contrast and DWI. One hundred and twenty patients had only DWI as they had come only for sonomammography. A total of 280 lesions were detected. ADC values were calculated for all the lesions and the highest and lowest values of ADC for benign and malignant lesions were identified. Finally, we compared our findings with those of previous studies.

Results:

Two hundred and eight lesions were categorized as benign and 72 lesions were categorized as malignant based on the ADC values. Based on previous data, lesions with ADC values from 1.3 to 1.5 mm^2/s were considered benign where as lesions with ADC values ranging between 0.85 and 1.1 mm^2/s were considered malignant. Two lesions whose ADC values were in the benign range were proven to be malignant tumors after surgery. This method of using ADC values for the detection of malignant lesions showed a sensitivity of 97.22% and a specificity of 100%. The positive predictive value was 100%.

Conclusion:

DWI is a useful technique for characterizing breast tumors, especially for lesions that cannot be adequately characterized by ultrasonography and routine magnetic resonance imaging.

ARRS 2009: Diffusion-Weighted Imaging May Improve Accuracy of Breast MRI

This study reported by Alice McCarthy. The main aim of our work is to help save women from unnecessary breast biopsies," said lead investigator R. El-Khouli, MD, who lead the study.

81 patients with 85 lesions, DWI was added to the standard MRI. A total of 60 lesions were known to be malignant. With DWI MRI, the technique correctly retrospectively correctly diagnosed 50 of these (83%). A total of 23 (92%) of 25 benign lesions were diagnosed correctly.

The investigators also calculated ratios of lesion ADC to glandular tissue ADC (L/GT). They found no difference in benign and malignant ADC and L/GT ratio between pre- and postmenopausal women.   "The ADC value of benign lesions ranged from 0.7 to 3.3×10^{-3} mm^2/sec (mean, 2 ± 0.76), while for malignant lesions it ranged from 0.4 to 1.9×10^{-3} mm^2/sec (mean, 1.1 ± 0.37) ($p<0.05$). For L/GT ratio, benign lesions ranged from 0.5 to 1.7 (mean, 1.1 ± 0.39) and malignant lesions from 0.28 to 0.98 (mean, 0.53 ± 0.15) ($p<0.05$). The area under the [receiver operating characteristic] curve for the ADC values was good (0.84), while it was excellent for L/GT ratio (0.92)," Dr. El-Khouli and colleagues write in their abstract.   DWI is quantified by a calculation called apparent diffusion coefficient (ADC) mapping, a calculated measure of water diffusion through the breast tissue. Previous studies have confirmed that ADC values do vary between malignant and benign breast masses, but overlap has been reported because benign breast changes can mimic malignancies. Further complicating ADC evaluation, ADC values of the human breast are notoriously complicated to normalize. These values are affected by the hormonal status of the female body. Among the different phases of the menstrual cycle, ADC values can vary 5.5%.