Multimodality assessment of Breast tumor physiology and metabolism

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Introduction:

Angiogenesis is a central component of tumor growth and proliferation[1]. Microscopically, tumor cell proliferation has been shown to correlate with neovascular proliferation. Quantitative assessment of tumor vascularity is often an important diagnostic feature in discriminating between benign and malignant entities. Recently, novel therapeutic agents have been developed, which affect tumor growth and spread on the basis of their ability to target tumor angiogenesis. A diagnostic modality must therefore accurately depict baseline lesion vascularity, and ideally assess alterations in tumor vascularity and function with precision.

Contrast enhanced MRI and Doppler sonography are two imaging-based modalities that allow for a non-invasive determination of tumor vascularity. Sehgal et al[2] reported six vascularity measures derived from color analysis of color and power Doppler images of 42 breast lesions with 23 malignancies. On average the malignant lesions were 1.3-2 times more vascular than the benign lesions. The malignant lesions also demonstrated more internal (geographic) heterogeneity in vascularity. There have been a number of reports on the use of contrast enhanced MRI to distinguish benign from malignant breast lesions [3, 4, 5]. Contrast enhanced MR imaging of the breast is exquisitely sensitive to invasive carcinomas based on its ability to define areas of high vascularity associated with tumor angiogenesis. Time course analysis of signal intensity changes of breast lesions after the bolus injection of the Gad-chelate has been used to evaluate the likelihood of malignancy. Accuracy of such analyses for determining lesion malignancy varies from 66-93%.

In this study, we investigate the relationship CE-MRI and Doppler US vascularity assessment (qualitative and quantitative) of focal breast lesions in a population of women with suspicious breast lesions.

Methods and Materials:

Patient Selection:

Patients with suspicious or known malignant breast lesions were prospectively enrolled in a clinical trial of multi-modality breast imaging. The primary goal of this study was to evaluate separately and together the diagnostic and staging accuracy of multi-modality breast assessment. Patients were subjected to multimodality imaging, including digital mammography, whole breast ultrasound, and CE-MRI, all performed sequentially on the same day. In addition, women with biopsy proven malignancy prior to enrollment were imaged with whole body FDG-PET for the purposes of both local staging and evaluation of metastatic spread of disease.

The study design was approved by our local Institutional Review Board.

Ultrasound Imaging:

Bilateral whole breast sonography (including gray scale, color flow, and power Doppler imaging) was performed using a state of the art ATL3000 (ATL, Bothell, WA) ultrasound scanner currently in use in our institution. The breasts were first scanned in the radial and anti-radial planes so that the entire volume of breast tissue is imaged. Representative images were obtained of each of the four quadrants of each breast. Special attention was paid to the region of the index lesion that led to study entry. All suspicious lesions identified were imaged in two orthogonal planes on gray scale. Radial coordinates (the oíclock site) and the distance of lesions from the areolar margin were recorded. These lesions were then interrogated by both color flow and power Doppler imaging. In color Doppler mode of the scanner the flow velocity will be recorded on videotape without aliasing at the lowest possible wall filter. The Doppler gain was increased until background noise appeared across the image and backed off until few random specks were visible. The term noise refers to appearance of color in the image without apparent flow.

Grey scale and Doppler Ultrasound Interpretation:

Ultrasound interpretation was performed in real-time by one of several expert breast radiologists at our institution. Sonographic interpretations included analysis of the gray scale features of suspicious lesions based on the features reported by Stavros et al [6]. In addition, lesion vascularity, based on its appearance in color and power Doppler imaging, was assessed on a three-point scale as: avascular, intermediately vascular, or hypervascular.

Quantitative Doppler Ultrasound Analysis:

Quantitation of power Doppler measures was performed through the method of Sehgal [2]. The Color and Power Doppler images were digitized from the videotapes at 24 bit resolution. Five to seven images were obtained in contiguous planes covering the entire volume of the detected mass. The images were analyzed by software developed in house in our laboratory to measure the flow indices viz., mean color level (MCL), percentage area of flow (PAF), vascular density (VD) and color-weighted fractional area (CWFA), from each color and power Doppler image.

Magnetic Resonance Imaging:

Breast MR Examinations were performed on a 1.5-Tesla scanner (LX© [General Electric, Milwaukee, WI} echo speed or Sonata© [Siemens, Erlangen, Germany]) with the use of a dedicated surface breast coil array. Bilateral breast imaging was performed in the prone positioning with the breasts dependent in the breast coil. The imaging protocol evolved over the course of the study. However in all cases it included bilateral fat suppressed T2 weighted images in the sagittal plane (4,000/85 [repetition time msec/ echo time msec], 512x256) and a slab interleaved 3D fat suppressed spoiled gradient echo prior to and 3-6 times after the injection of contrast. The spoiled gradient echo sequence had a minimum spatial resolution of 0.78 mm, slice thickness of a 2-3.5mm, and a time resolution of 45-120 seconds minutes. Sequential post contrast acquisitions were acquired for approx.6 minutes following a rapid bolus injection of 0.1 mmol/kg gadopentetate dimeglumine

(Omniscan©; Nycomed, Princeton, NJ) followed by a 20 ml saline flush. Subtraction images were obtained by subtracting the pre-contrast images from the first post contrast Image on a pixel-by-pixel basis.

Magnetic Resonance Imaging Interpretation:

MRI interpretation was performed by one of two radiologists with extensive experience in breast MRI interpretation. All enhancing lesions were identified and categorized on the basis of morphologic features for focal masses or regional enhancements described in Nunes et al [8]. Qualitative assessment of enhancing morphology included assessment for the presence or absence of rim enhancement and non-enhancing septations. Dynamic enhancement patterns were assessed through visualization of serial enhanced images with and without baseline (pre-gadolinium) image subtraction, and rated on a three point scale: gradually enhancing, early enhancing with plateau phase, or early enhancing with delayed wash-out. Degree of overall enhancement was also graded on a three-point scale as: mild (equivalent to background parenchymal enhancement, moderately enhancing (slightly more enhancing than background parenchyma) or markedly enhancing.

Quantitative Magnetic Resonance Imaging Analysis:

Lesion region of interest (ROIs) were drawn on the pre-gadolinium images, and on the post-gadolinium images at 1, 2.5, and 5, minutes following gadolinium injection. Maximal percent enhancement was calculated as: max $[(S^i-S^0)/S^0] \times 100$, where S^0 = baseline signal intensity and S^i = signal intensity at time I after gadolinium administration. Signal enhancement ratio (SER) was calculated per Hylton et al. [7] as $(S^a-S^0)/(S^b-S^0)$, where S^a and S^b = signal intensity at 2.5 and 5 minutes post gadolinium administration, respectively.

Multi-modality Interpretation and Consensus:

Two radiologists were assigned for interpretation of the US and imaging findings separately, as per the multi-modality imaging assessment program. A third radiologist evaluated the digital mammography. The two radiologists interpreting US and MRI had access to the results of prior film-screen mammography results. All radiologists had access to any additional pertinent clinical data (e.g. site of palpable abnormalities). Care was taken to ensure any assigned radiologist was not previously involved with or familiar with the research subjectís prior studies on any given day. Each modality was initially interpreted blinded to the results of the other experimental modalities. For each modality all clinically significant findings were recorded, characterized, measured and rated on a BI-RADS {Breast Imaging Reporting and Data System} assessment scale and on a 100 point likelihood of malignancy scale. After the blinded interpretations were complete, conference of the study readers and research coordinators was held to review the modality-specific results for each patient. A consistent lesion indexing scheme was developed for each patient such that all finding on the all modalities could be mapped onto the same lesions indexing scheme. A consensus BI-RADS assessment was the assigned to each fining, with assessments of 4 and 5 carrying biopsy recommendations.

Statistical methods:

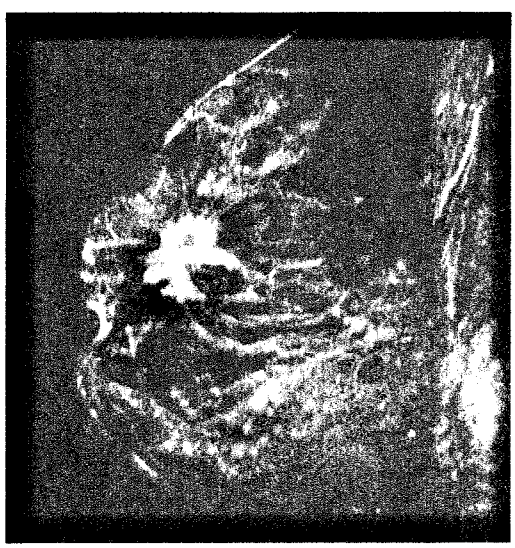
The per lesion agreement for the three qualitative measures of lesion vascularity (US vascularity, MR degree of enhancement, and MR dynamic curve shape were assessed by pair wise comparison using the Gamma statistic, G. The correlation between qualitative and quantitative assessments was assessed by analysis of variance. Correlation between quantitative vascularity assessments was obtained by means of the Pearson correlation. Discrimination between benign and malignant lesions by quantitative imaging analysis values was assessed by the Studentís t-test. For all analyses, significance was assessed at the p=0.05 level.

Results:

A total of 23 focal lesions in 19 women were studied by both quantitative Doppler US and CE-MRI. Sixteen of these were invasive malignancies, and seven were benign lesions. Of the malignancies, all were invasive cancers. Eleven were ductal carcinoma, two were mixed ductal and lobular cancers, one was a pure lobular carcinoma, and two were medullary carcinomas (multifocal in a single patient). Of the benign lesions, three were fibrocystic change, two were fibroadenomas, one was a fibroepithelial lesion, and one was a benign intraductal papilloma.

Figure 1 demonstrates Doppler US and CE-Mri images for a highly vascular lesion (patient was diagnosed with invasive ductal carcinoma).

A)



B)

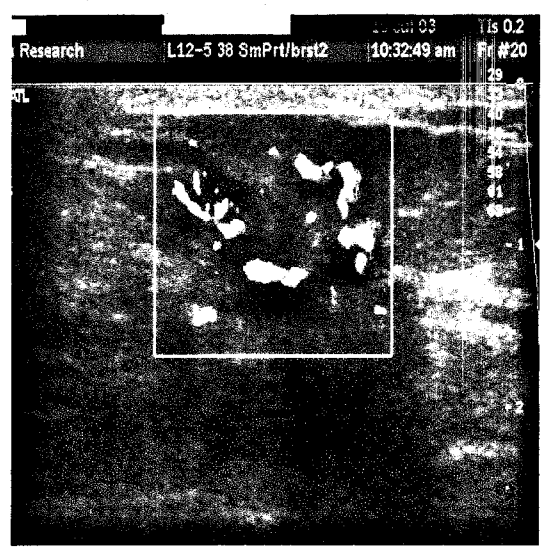


Figure 1: Contrast MRI (subtraction image, A) and Doppler (color flow) US image (B) of index lesion in patient with invasive ductal carcinoma. Extensive lesion vascularity is demonstrated on both Doppler and contrast enhanced imaging.

Lesion Evaluation by Qualitative and Quantitative Doppler US

Of the 23 lesions, eight were graded as avascular by the ultrasound radiologist (5 benign and 3 malignant), eight were graded as intermediate vascular (2 benign and 6 malignant), and seven were graded as hypervascular (all seven malignant). Results are summarized in Table 1.

There was a high correlation between the qualitative grading of tumor vascularity by the US reader, and the PAF. Lesions graded as avascular had a median PAF of 0.19, those graded as intermediately vascular had a median PAF of 2.39, and those graded as hypervascular had a median PAF of 3.98. These difference were statistically significant ($p=0.028$).

The mean PAF of malignant lesions was 3.87. Only two malignancies had PAF values less than 0.50. The mean PAF for benign lesions was 1.69. Two benign lesions, both fibroadenomas, had relatively large PAF values of 3.53 and 7.51. The remaining benign lesions all had PAF values less than 0.40. However, the differences in mean PAF values for benign and malignant lesions did not reach statistical significance ($p=0.09$).

Lesion Evaluation by CE-MRI

Enhancement Kinetics:

Qualitative MRI kinetic assessments for the 23 focal lesions were as follows: five lesions were gradually enhancing, seven were plateau enhancing, and eleven demonstrated washout kinetics. Of the eleven lesions with washout kinetics, 10 were malignant and 1 was benign. For the seven lesions with plateau kinetics, three were malignant and four were benign. For the five lesions with gradual enhancement, three were malignant and two were benign. Results are summarized in Table 2.

Qualitative assessments of enhancement kinetics were compared with quantitative analysis of SER. The median SER value for washout lesions was 1.07. This was higher than the median SER for lesions that were judged to possess plateau kinetics (median SER = 0.91) and for those judged to possess gradually enhancing kinetics (median SER = 0.96). Seven of the eleven lesions judged to possess washout kinetics had SER values greater than 1.0, while 3 of the remaining 4 had SER values between 0.95 and 0.99. However, several lesions judged to be plateau or gradually enhancing also had SER values greater than 1.0. These SER values for the three different classes of lesions, as graded by reader assessment of MR kinetics did not reach statistical significance ($p=0.19$).

The mean SER for malignant lesions was 1.00. The mean SER for benign lesions was 0.87. This trend did not reach statistical significance (p=0.06).

Degree of Enhancement:
None of the 23 lesions were rated as minimally enhancing (i.e. enhancing to the same degree as background glandular tissue) by the MRI reader. Thirteen lesions were rated as moderately enhancing, and ten lesions were rated as markedly enhancing. For the 13 moderately enhancing lesions, there were six benign lesions and seven malignancies. For the markedly enhancing lesions, there was one benign lesion (a fibroadenoma) and nine malignancies. These results are summarized in Table 3.

There was slight correlation between qualitative assessment of lesion enhancement and quantitation of maximal percent enhancement. For the thirteen lesions deemed moderately enhancing the median value for maximal percent enhancement was 88%. Markedly enhancing lesions had a median value of maximal enhancement of 117%. However, this difference did not reach statistical significance (p=0.49).

For benign lesions, the mean value for the degree of enhancement was 113%. For malignant lesions, the mean value for degree of enhancement was 126%. This differences did not reach statistical significance (p=0.29).

Correlation between US and CE-MRI assessments of lesion vascularity

There was a strong correlation between reader assessment of lesion enhancement and kinetics on MRI (G=0.75, p=0.027). There was also a significant correlation between reader assessment of lesion vascularity on Doppler US and degree of lesion enhancement on CE-MRI (G=0.71, p=0.45). However, correlation between reader assessment of lesion vascularity of US and MR kinetics was poor (G=0.21, p=NS).

We also assessed the correlation between quantitative assessments of lesion vascularity on Doppler US and CE-MRI. Scatter plots did not reveal any clear correlation between quantitative measures (data not shown). R values for the pair wise comparison of quantitative measures of vascularity are as follows. Percentage maximal enhancement vs. Doppler PAF, R=0.07, SER vs. doppler PAF, R=0.38, and percentage maximal enhancement vs. SER, R=0.29.

US vascularity	Benign	Malignant	Total
Avascular	5	3	8
Intermediate	2	6	8
Hypervascular	0	7	7
Total	7	16	23

Table 1: Reader classification of breast lesion vascularity by US

MRI Kinetics	Benign	Malignant	Total
Persistent	2	3	5
Plateau	4	3	7
Washout	1	10	11
Total	7	16	23

Table 2: Reader classification of breast lesion vascularity by MRI enhancement kinetics

MRI Signal Intensity	Benign	Malignant	Total
Minimal	0	0	0
Moderate	6	7	13
Marked	1	9	10
Total	7	16	23

Table 3: Reader classification of maximal MR signal intensity of breast lesions.

Discussion:

Multimodality qualitative and quantitative analyses of breast lesions have shown variable degrees of correlation. The two modalities indirectly measure lesion vascularity. However, each modality assesses different aspects of tumor vascular physiology. Contrast enhanced MRI allows one to assess qualitatively the tumor perfusion. However, the kinetics of enhancement generally depends on both microvascular density and vessel permeability. Maximally lesion enhancement on MRI, conversely, is most heavily dependent on tumor extracellular space. Doppler US evaluates at the amplitude and frequency of the signals returning from intravascular flow. On Doppler US, PAF represents the area of blood flow relative to the area of the ROI. Doppler imaging relies on a minimal threshold of blood cell velocity. This leads to an image which emphasizes large diameter vessels over smaller capillaries.

In our study, PAF appeared to correlate well with qualitative reader assessment of lesion vascularity. PAF also demonstrated a trend in differentiating between benign and malignant lesions, although the difference was not statistically significant.

Numerous studies have shown that essentially all breast malignancies enhance with gadolinium. Sensitivities have been measured in the range of 95-100%, and contrast-enhanced MR imaging has been found to be highly sensitive to breast cancer as small as a few millimeters [9,10,11,12,13,14,15,16,17]. The limitation of breast MRI is low specificity, with false positive enhancements occurring frequently in benign lesions [3,4,13,17,18,19,20,21,22].

Improvements in specificity have been suggested through the incorporation of enhancement kinetics into the morphologic model of breast MRI evaluation [7, 19].

In our study, neither maximal lesion enhancement nor enhancement kinetics (SER) were able to reliably differentiate between benign and malignancy lesions, although SER demonstrated a trend toward higher values for malignant lesions.

However, these quantitative MR parameters correlated poorly with each other, and with PAF on Doppler image quantification, suggesting that different aspects of lesion physiology are being assessed by each modality.

In addition, there were discrepancies between the quantitative MRI parameters and the qualitative assessment of MRI vascularity as assessed by the MR readers in our study. Several possible explanations exist for this discrepancy. MR readers were able to assess the entire gadolinium enhancement curve, which may more accurately reflect enhancement kinetics. In addition, image evaluation enabled readers to identify hot spots or sub-regions of lesion vascularity, which have been suggested to be a more reliable indicator of malignancy than behavior of the whole-lesion enhancement curve as was used in our quantitative analysis.

Conclusions

Vascular assessments of focal breast lesions by both Doppler US and CE-MRI may aid in the distinction between malignant from benign entities. Highly vascular lesions by either modality tend to be malignant, whereas lesions with less vascularity may be malignant or benign. On a lesion per lesion basis, US and MR characterization of tumor vascularity differs, demonstrating that these modalities evaluate different aspects of tumor physiology. Methods for quantitating lesion vascularity on Doppler US are highly correlated with qualitative assessment of lesion vascularity by expert radiology readers, whereas MRI quantitative measures do not correlate as strongly with qualitative evaluations of radiology experts. This suggests the need for further refinement of methods for extracting quantitative vascular parameters from breast MRI examinations.

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