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Background parenchymal enhancement in the contralateral normal breast of patients undergoing neoadjuvant chemotherapy measured by DCE-MRI

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ABSTRACT

The purpose of this study was to analyze background parenchymal enhancement (BPE) in the contralateral normal breast of cancer patients during the course of neoadjuvant chemotherapy (NAC).
Forty-five subjects were analyzed. Each patient had three MRIs, one baseline (B/L) and two follow-up (F/U) studies. The fibroglandular tissue in the contralateral normal breast was segmented using a computer-assisted algorithm. Based on the segmented fibroglandular tissue, BPE was calculated. BPE measured in baseline (B/L) and follow-up (F/U) MR studies were compared. The baseline BPE was also correlated with age and compared between pre/peri-menopausal (<55 years old) and post-menopausal women (≥55 years old). The pre-treatment BPE measured in B/L MRI was significantly higher in women <55 years old than in women ≥55 years old (20.1% ± 7.4% vs. 12.1% ± 5.1%, $p \leq 0.01$). A trend of negative correlation between BPE and age was noted ($r = -0.29$). In women <55 years old, BPE at F/U-1 (18.8% ± 6.9%) was decreased compared to B/L, and was further decreased in F/U-2 (13.3% ± 5.7%) which was significant compared to B/L and F/U-1. In women ≥55 years old, no significant difference was noted in any paired comparison among B/L, F/U-1 and F/U-2 MRI. A higher baseline BPE was associated with a greater reduction of BPE in F/U-2 MRI ($r = 0.73$). Our study showed that younger women tended to have higher BPE than older women. BPE was significantly decreased in F/U-2 MRI after NAC in women <55 years old. The reduction in BPE was most likely due to the ovarian ablation induced by chemotherapeutic agents.

1. Introduction

Contrast enhancement in normal fibroglandular breast tissue of women, namely background parenchymal enhancement (BPE), is commonly observed in dynamic contrast-enhanced (DCE)-MRI. Multiple factors, including age, menstrual or menopausal status, and the use of hormones can affect breast glandular tissue enhancements [1–5]. A marked BPE is more commonly seen in younger women, and the degree of BPE naturally decreases with age [5,6]. BPE can be measured qualitatively by visually evaluating the degree of enhancement as severe (marked), intermediate (moderate), mild and absent (minimal) [6–8], or it can be measured quantitatively by manually placing a region of interest (ROI) on the most enhancing part of the normal tissue [7]. These two methods are subject to rater variations. Alternatively, BPE can be measured precisely based on segmented fibroglandular tissue in the breast, by averaging the enhancements from all pixels [9].

BPE may influence the diagnostic performance of breast MRI. It was noted that the degree of background tissue enhancement might affect the detection sensitivity of breast MRI [1,2,8,10], as well as the staging of cancer [11]. It was shown that for evaluating tumor extent, the accuracy of MRI with moderate/marked BPE was significantly lower than that with minimal/mild BPE [11,12]. Also, the detection of non-mass-like enhancements, such as ductal carcinoma in situ (DCIS), is more difficult in the presence of moderate/marked BPE [11].

A recent study examining the relationships between breast cancer and both amount and the enhancement of fibroglandular tissue at MRI has found that increased BPE is strongly predictive of breast cancer odds [13]. The breast cancer odds also increased with increasing amount of fibroglandular tissue, but the BPE remained significant after adjustment for the amount of fibroglandular tissue [13].

Neoadjuvant chemotherapy (NAC) has been increasingly used for treatment of breast cancer, and MRI is commonly used to monitor the tumor response during and after NAC. The value of BPE

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surrounding primary breast tumors in the diseased breast on MRI was noted to be associated with response to NAC [14]. Change of BPE in the contralateral normal breast following NAC has not been studied before. Since BPE may affect the detection of residual tumor or contralateral breast lesions, it may be clinically important to investigate how BPE changes following the administration of chemotherapeutic regimens. A previous study has found that the breast density (characterized by fibroglandular tissue volume and the percent density by normalizing fibroglandular tissue volume to the total breast volume) is decreased in patients receiving NAC [15], and that the density reduction was most likely mediated through the suppression of ovarian function due to chemotherapy [16,17]. It was noted that the likelihood of permanent chemotherapy-induced menopause is directly related to age [16]. Older age and the addition of taxane to doxorubicin and cyclophosphamide (AC) increased the risk of chemotherapy-induced amenorrhea (CIA) and the amenorrhea was more likely to be irreversible for women >40 [17].

In the present study we investigated the degree of BPE in the contralateral normal breast of patients undergoing NAC. The pretreatment baseline BPE was correlated with age, and compared between pre/peri-menopausal women (<55 years old) and postmenopausal women (≥55 years old). The BPE measured in baseline and follow-up MRI studies during the course of NAC treatment was compared to evaluate the impact of chemotherapy on BPE.

2. Materials and methods

2.1. Subjects

This retrospective study was approved by the institutional review board and was HIPAA compliant. All patients gave informed consent to participate in the breast MRI studies. Forty-five subjects (30–72 years old, mean 48 years old) were analyzed in this study. The patient cohort was recruited in a period of 3½ years (from March 2003 to August 2006) among 65 patients who elected to receive NAC either due to inoperable tumor or with clinically documented lymph node involvement. Each NAC patient received several MRI scans for response monitoring. In this study, only those patients who had the baseline (B/L) MRI prior to the NAC, the first follow-up (F/U-1) MRI after 2 cycles of doxorubicin (Adriamycin) and cyclophosphamide (AC), and the second follow-up (F/U-2) MRI after 4 cycles of AC or 2 cycles of AC plus 1 month of taxane regimen were included for data analysis. In total, 45 patients were studied. Twenty patients of the initial 65 patients were excluded from this study due to lack of baseline MRI ($n = 2$), lack of F/U-1 MRI ($n = 11$), and lack of F/U-2 MRI ($n = 7$). Of the 45 patients, 33 women were <55 years old, and 12 were ≥55 years of age. Thirty-nine women had pathology-proven invasive ductal cancers (IDC), 5 had infiltrating lobular cancers (ILC), and 1 had IDC mixed with ILC. The baseline tumor size ranged from 0.5 to 9.9 cm (mean ± STD = 4.1 ± 2.5 cm). According to the American Joint Committee on Cancer (AJCC) TNM system, 10 patients had stage I cancer and 35 patients had stage II cancer. Of the 45 women, 25 had estrogen receptor (ER)-positive cancers and 20 had ER-negative cancers. Twenty-four women had Her-2-positive cancers and 21 had Her-2-negative cancer. Five women had triple-negative cancers. Twenty-seven women had cancers in the left breast and 18 had cancers in the right breast. In the present study, only the contralateral normal breast was analyzed. Thirty-four of the 45 patients in this study had been investigated and reported before [15]. However, the purpose of these two studies was different. The previous paper was to investigate the reduction of breast density, and the current study was to measure background parenchymal enhancement.

2.2. Neoadjuvant chemotherapy

Biweekly AC was administered as the first-line regimen. After 2 cycles of AC, the patients continued to receive 2 additional cycles of AC or were switched to a taxane-based regimen based on the oncologist's evaluation. The second-line taxane-based regimen comprised paclitaxel or Nab-paclitaxel (Abraxane, albumin-bound nanoparticle of paclitaxel), combined with carboplatin. All Her-2-positive patients also received trastuzumab. Her-2-negative patients also received bevacizumab.

2.3. MRI studies

The breast MRI study was performed on a 1.5 T MR scanner (Philips Medical Systems, Cleveland, OH) with a dedicated four-channel breast coil. The imaging protocol included sagittal view pre-contrast T_1-weighted imaging, and axial view bilateral dynamic contrast-enhanced MR imaging using a 3D Spoiled Gradient Recalled (SPGR) pulse sequence with 16 frames, including 4 pre-contrast and 12 post-contrast sets. The parameters were TR = 8.1 ms, TE = 4.0 ms, flip angle = 20°, 32 axial partitions with slice thickness = 4 mm, matrix size = 256 × 128, and field of view = 32–38 cm. Gadodiamide (Omniscan, GE Healthcare) contrast agent was injected 0.1 mmol/kg in about 15 s at the beginning of the fifth acquisition followed by 10 cc saline for flushing. The scan time was 42 s per acquisition.

2.4. Breast and fibroglandular tissue segmentation

For each case, the side of contralateral normal breast was identified. The fibroglandular tissues on all imaging slices were segmented by an experienced operator (H.Y., a medical physicist with 5 years of experience in segmenting breast MRI) by using a computer-assisted algorithm [18]. This method has small measurement errors, with the intra-operator variation of 2.8% and inter-operator variation of 3.8% [18]. The measurement variation caused by body position is in the range of 3%–4% [18].

To ensure consistency, the operator had to go through training process using test data sets and demonstrated that the measurements done on two occasions could reach <5% measurement variation. The superior (the beginning slice) and inferior (the ending slice) boundaries of the breast were determined by comparing the thickness of breast fat with the body fat. Non-breast subcutaneous fat on the chest typically displays homogenous thickness across the chest wall, whose fat–air boundary is closely parallel with the chest wall–fat boundary [19].

The procedures for the breast and fibroglandular tissue segmentation consisted of the following: (a) determining the posterior boundary of the breast by performing an initial V-shaped cutting at

Table 1
Background parenchymal enhancement (mean ± standard deviation, %) in the group women <55 and ≥55 years old.

		Baseline MRI	F/U-1 MRI	F/U-2 MRI
<55 years old	Entire DCE period	20.1 ± 7.4	18.8 ± 6.9	13.3 ± 5.7*,†
	Early (1 ~ 3 min)	12.1 ± 9.5	11.4 ± 10.5	7.1 ± 5.6*,†
	Middle (3 ~ 5 min)	22.0 ± 14.9	20.5 ± 15.8	14.6 ± 10.1 *,†
	Late (5 ~ 7 min)	26.2 ± 15.9	24.7 ± 16.5	18.1 ± 11.4 *,†
≥55 years old	Entire DCE period	12.1 ± 5.1	11.0 ±3.8	11.8 ± 4.8
	Early (1 ~ 3 min)	6.5 ± 4.3	7.0 ± 5.4	6.6 ± 4.0
	Middle (3 ~ 5 min)	13.8 ± 7.1	11.5 ± 6.8	13.9 ± 9.7
	Late (5 ~ 7 min)	16.1 ± 8.9	14.5 ± 7.9	14.8 ± 8.3

* Significantly lower compared to the baseline value.
† Significantly lower compared to the F/U-1 value.