

Alteration of Fibroglandular Tissue Volume and Contrast Enhancements Measured by MRI in the Normal Breast of Patients Receiving Neoadjuvant Chemotherapy

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Background and Purpose:

For women who have been diagnosed with breast cancer, their cancer risk in the contralateral breast is increased. And the cumulative incidence at 20 years is 15.4%. After the initial diagnosis most patients will receive chemotherapy; while only a small portion with very early stage cancer will not. Other than the targeted agents (such as trastuzumab for HER-2), most commonly used chemotherapeutic agents will also reach normal breast tissues and very likely to cause tissue damage. Unfortunately, the change in the normal breast tissues exposed to the therapy has rarely been studied. We have studied a cohort of patients undergoing neoadjuvant chemotherapy using serial MRI studies to investigate the effect on normal tissues. Such an investigation provides a good database for studying the alterations in the fibroglandular tissue volume and the contrast enhancements in the normal breasts of these patients. An MRI-based analysis method, developed by us, was used to measure the fibroglandular tissue volume and the percent density by normalizing to the whole breast volume. Since the entire fibroglandular tissues are known, one can use it as a single ROI to measure the contrast enhancement, not subjected to the arbitrary placement of ROI. The changes in the fibroglandular tissue volume and contrast enhancements during the therapy period were analyzed.

Materials and Methods:

74 breast cancer patients (age 30-79, mean 50 y/o) receiving NAC were studied. Out of these 47 subjects were further analyzed for their kinetic enhancement at baseline, F/U-1 and F/U-2 MRI. Patients were further divided into two groups with patients above 55 years old (post-menopausal) and patients under 55. All patients started with bi-weekly Adriamycin and Cyclophosphamide (AC) followed by the second-line taxane-based regimen. HER-2-positive patients also received trastuzumab (Herceptin®) with taxane. Some HER-2-negative patients received bevacizumab (Avastin®) with taxane. All patients had several breast MRI exams, including a pre-treatment baseline MRI, and several follow-up studies during and after the course of therapy. The MRI study was performed using a 1.5 T MR scanner. Non-contrast 3D SPGR (RF-FAST) T1 weighted images without fat suppression (TR= 8.1 ms, TE= 4.0 ms, flip angle=20°, slice thickness = 3-4 mm) were used for calculation of the breast density in the contra-lateral breast not harboring tumor. Computer-assisted algorithms were used to segment the breast volume and the fibroglandular tissue volume. The adaptive FCM was applied for segmentation of the fibroglandular tissue from the surrounding fatty tissue. The volume of fibroglandular tissue is calculated, and the percent density is obtained by normalizing to the total breast volume. The change of percent breast density (slope) before and after NAC was calculated. For kinetic enhancement, the whole segmented fibroglandular tissue was measured and a mean enhancement was obtained. ANOVA test was used to correlate the breast density change during NAC with age and baseline (B/L, pre-treatment) percent breast density. All variables (age, slope, B/L percentage density) were transformed to normally distributed before performing the ANOVA test.

Results:

The median durations of the study interval from the first MRI (baseline) to the second, third, fourth, and fifth MRI (follow-up) were 42 days, 86 days, 135 days, 166 days, and 192 days respectively. The measured breast density in the baseline MRI showed significant difference between the two age groups ($15.2 \pm 9.4\%$ for < 55 y/o vs. $8.0 \pm 5.4\%$ for > 55 y/o, $P < 0.0005$), which is a well-known fact that density reduces with age. When the last MRI of each subject was compared to her own baseline, 66% of patients (49/74) showed decreased breast density (Fig. 1 and 2 show 2 case examples). To minimize the error coming from fluctuations, for each patient the density measured in the baseline and all follow-up studies were fitted to obtain the slope to indicate the mean change. Using ANOVA test, it was found that the change (slope) was not significantly associated with age (Fig. 3), but showed a higher reduction in patients with a higher B/L density ($p=0.017$) (Fig. 4). After controlling for age, the significant association remains ($p=0.034$). For kinetic enhancement analysis, premenopausal women showed stronger enhancements and larger fluctuations than post-menopausal subjects ($P < 0.05$) and a trend of enhancement reduction from B/L to F/U-2 in the pre-menopausal patients, but not in the postmenopausal patients (Fig. 5).

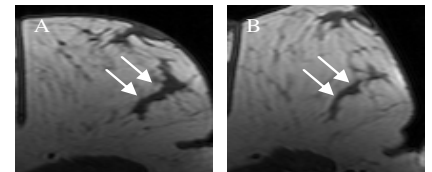


Fig. 1. A 34 y/o patient with invasive ductal cancer. Compared to the baseline MRI (A), the third MRI (B), performed 89 days after the beginning of the NAC, showed a 59% reduction of the fibroglandular tissue (arrows).

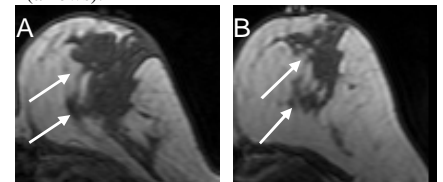


Fig. 2. A 41 y/o woman with IDC. Compared with baseline MRI (A), the fourth MRI (B), performed 124 days after the beginning of the NAC, showed a 39% reduction of the fibroglandular tissue (arrows).

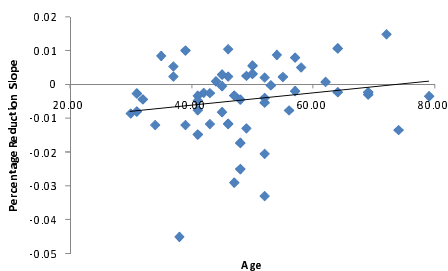


Figure 3. Change of breast density vs. age

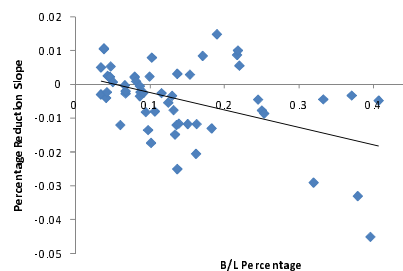


Figure 4. Change of density vs. B/L density

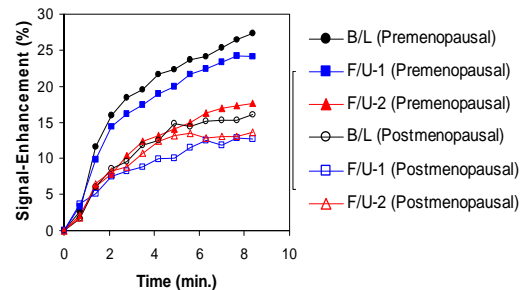


Figure 5. Mean signal enhancement of fibroglandular tissue in 32 pre-menopausal and 15 post-menopausal women.

Discussion:

Our results showed that following NAC, patients with higher baseline percent breast density were more likely to show a higher reduction of breast density. The mechanism of tissue damage is not known, but it may be possible that the higher vascular supply associated with the higher density may allow more delivery of therapeutic agents to the normal tissue, and causes more damage and a higher reduction in the fibroglandular tissue volume. The reason for the reduced contrast enhancement in follow-up MRI studies after therapy in the premenopausal women was not clear, but it may be also associated with damaged vessels thus lower vascular supply and contrast enhancements. In the future it will be interesting to correlate the change of normal breast tissues with the risk of developing contralateral breast cancer in these patients.

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