Possible Prognostic Value of Contralateral Normal Breast Enhancements in DCE-MRI of Breast Cancer Patients Undergoing Chemotherapy

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Purpose:

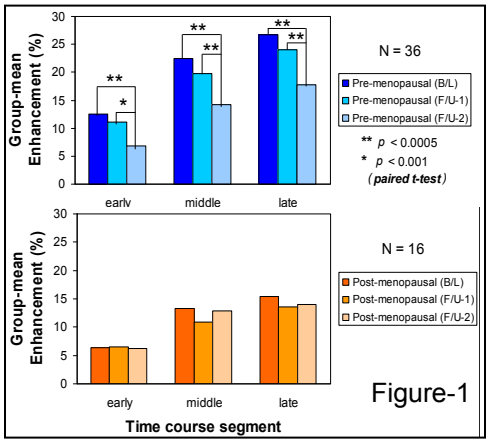
The perfusion in normal fibroglandular breast tissue of pre-menopausal women is altered by hormonal variations over the women's menstrual cycle, whose cyclic effects can be measured via dynamic contrast enhanced (DCE)-MRI [1, 2]. It is also suggested that chemotherapy-induced ovarian suppression has a positive prognostic impact for disease-free survival among pre-menopausal patients with breast cancer [3, 4]. This suggests then at least part of the beneficial effects of neoadjuvant chemotherapy (NAC) in pre-menopausal patients can be postulated to be derived from this side-effect of NAC rather than its direct cytotoxic effect on tumor cells. Although NAC has been increasingly used for treatment of breast cancer, the effect on the ovaries by commonly used classes of chemotherapeutic agents, anthracyclines and taxanes, is not still fully elucidated, other than that of alkylating agents, such as cyclophosphamide, which are known to be more associated with ovarian damage [5]. At our institute we have been performing longitudinal MRI studies for monitoring response in breast cancer patients. In the present study we retrospectively analyzed contrast enhancements from fibroglandular tissues in the normal contralateral breast as a measure of NAC-induced ovarian suppression effects, and evaluated the changes in longitudinal studies during the course of treatment. The patients were first separated into pre/peri menopausal (<55 years old) and post-menopausal groups (≥ 55 years old) and then further separated into 2 sub-groups for each based on their final pathological report: pathologic complete response (pCR) and residual disease present (RDP). To avoid the bias coming from the arbitrary ROI selection, we applied a computer-based segmentation algorithm to segment the entire fibroglandular tissues contained in the normal breast, and measured the mean enhancement time course. The enhancements at 3 time periods (1-3, 3-5, 5-7 min) after contrast injection were analyzed and compared between the groups.

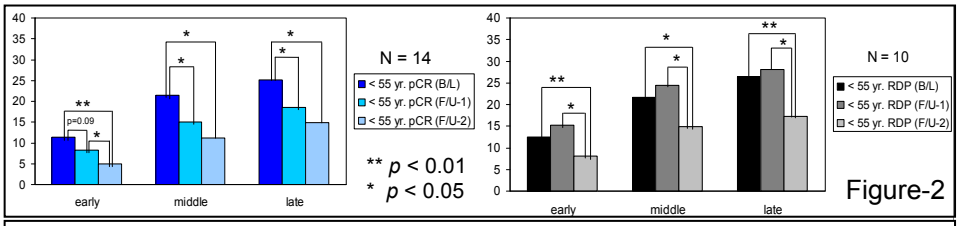
Methods:

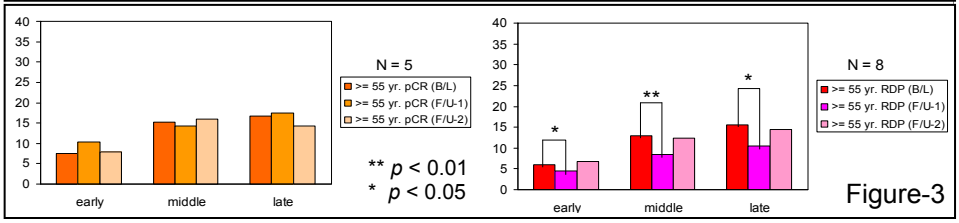
Out of a total of 52 subjects w/ at least 3 MRI studies (B/L: pre-treatment, F/U-1, and F/U-2) that were analyzed in this study (N=36 for <55 yo, and N=16 for ≥ 55 yo), the final pathological report was available for 37 patients (N=24 for <55 yo and N=13 for ≥55 yo) all of whom received 1 or 2 cycles (except for one 65 yr. old patient w/ 3) of adriamycin and cyclophosphamide (AC) prior to F/U-1 and followed by additional AC and/or second-line taxane-based regimen prior to F/U-2. The patient cohort was recruited from May 2002 to July 2006, who elected to receive neoadjuvant chemotherapy either due to inoperable tumor or with clinically documented lymph node involvement. All MRI was performed on a 1.5T Philips Eclipse MR scanner. Bilateral DCE-MRI was acquired using a 3D gradient echo pulse sequence, 32 axial partitions with 4-mm thickness. Sixteen frames (4 pre and 12 post) were prescribed, each of which took 42 sec to acquire. The contrast agent (Omniscan®, 1 cc/10 lbs) was injected in about 15 sec followed by a saline flush at start of the 5th frame acquisition. For analysis, first the normal contralateral breast was segmented, and then the entire fibroglandular tissues contained in all 32 imaging slices were obtained using the fuzzy C-means algorithm. Lastly a volume-averaged enhancement time course was generated for each study. The mean enhancement intensity in each of three time segments was calculated: 'early' (the first 4 post-contrast frames, approximately 1-3 min), 'middle' (the next 4 frames, 3-5 min), and 'late' (the last 4 dyn. frames, 5-7 min). Finally the enhancement between two age groups (< vs. ≥ 55 yo) as well as pCR vs. RDP sub-groups were compared.

Results:

Fig.1 shows the graphs of the percent enhancement values measured from the three time segments of the 2 age groups and compared among the B/L, F/U-1, and F/U-2 studies. The reduction in enhancement with respect to B/L was significant only in the pre-menopausal group. The mean enhancement values at all 3 time segments were also significantly higher in the pre-menopausal group compared to the counterparts of the post-menopausal at B/L and F/U-1 (results not shown). Fig.2 shows the graphs of the percent enhancement values measured from the three time segments of the pCR and RDP sub-groups in the younger age group, whereas those of the older age group are shown in Fig.3. Paired, two-tailed t-test was used to evaluate the statistical significance of changes observed over the course of treatment.







Discussion:

The cut-off age (55-yo) was chosen to ensure that women ≥ 55 yo were indeed post-menopausal. The results indicated that the reduction of enhancement values in the normal breast of pre-menopausal women over the course of NAC can be attributed to that of chemotherapy-induced ovarian suppression as indicated by the lack of such changes in enhancement values of the post-menopausal women. The reductions of enhancement observed at F/U-1 (post 1-2 cycles of AC) in the pCR sub-group of the younger women, which was not observed in the RDP sub-group of the same age group, suggest that the early onset of this side effect of chemotherapy during the course of NAC can potentially has a positive prognostic value in the pre-menopausal women. This early onset or lack thereof in these 2 sub-groups could not be explained by the differences in number AC-regimen cycles received by the patients (ave. AC-cycles: 1.3 and 1.5 for pCR and RDP, respectively). The difference in number of AC-cycles between the 2 sub-groups of the post-menopausal women was slightly higher than that of pre-menopausal (ave. AC-cycles: 1.4 and 1.8 for pCR and RDP, respectively). The apparent association of early reductions of enhancement observed at F/U-1 with the RDP sub-group of post-menopausal women can be perhaps explained by the notion of a reduced perfusion in fibroglandular breast tissue resulting in less effective delivery of chemotherapeutic agents to the tumor cells in the ipsilateral breast. Despite a relatively small number of subjects included in this study, the results demonstrate that the chemotherapy-induced effects observed in the normal breast may have a possible prognostic role in predicting treatment-outcome, which needs to be further investigated.

References: [1] Kuhl et al. Radiology 1997; 203:137-44. [2] Delille et al. Breast J. 2005; 11(4):236-41. [3] Goldhirsch et al. Annals of Oncology 1990; 1:183-8. [4] Pagani et al. Eur. J. Cancer 1998; 34(5):632-40. [5] Gradishar et al. Semin. Oncol. 1989; 16:425-36.

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