Translational Oncology
www.transonc.com

Volume 10 Number 5 October 2017 pp. 786–792 786

Association Between Background Parenchymal Enhancement and Pathologic Complete Remission Throughout the Neoadjuvant Chemotherapy in Breast Cancer Patients

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Abstract

PURPOSE: To retrospectively investigate the quantitative background parenchymal enhancement (BPE) of the contralateral normal breast in patients with unilateral invasive breast cancer throughout multiple monitoring points of neoadjuvant chemotherapy (NAC) and to further determine whether BPE is associated with tumor response, especially at the early stage of NAC. *MATERIALS AND METHODS:* A total of 90 patients with unilateral breast cancer who then received six or eight cycles of NAC before surgery were analyzed retrospectively. BPE was measured in dynamic contrast-enhanced MRI at baseline and after 2nd, 4th, and 6th NAC, respectively. Correlation between BPE and tumor size was analyzed, and the association between pathologic complete remission (pCR) and BPE was also analyzed. *RESULTS:* The BPE of contralateral normal breast showed a constant reduction throughout NAC therapy regardless of the menopausal status ($P < .001$ in all). Both the BPEs and the changes of BPE in each of the three monitoring points were significantly correlated with those in tumor size ($P < .05$ in all), and the reduction of BPE after 2nd NAC had the largest diagnostic value for pCR (AUC = 0.726, $P < .001$), particularly in hormonal receptor (HR)-negative patients (OR = 0.243, 95%CI = 0.083 to 0.706, $P = .009$). *CONCLUSION:* The BPE of contralateral normal breast had a constant decreased tendency similar to the change of tumor size in NAC. Reduction of BPE at the early stage of NAC was positively associated with pCR, especially in HR-negative status.

Translational Oncology (2017) 10, 786–792

Introduction

Breast background parenchymal enhancement (BPE) is referred to as normal fibroglandular breast tissue enhancement on the MR mammography (MRM) after injecting contrast agents, which is known to be evaluated qualitatively according to the BI-RADS lexicon or measured quantitatively by a fully automated computerized

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Received 10 July 2017; Revised 20 July 2017; Accepted 24 July 2017

1936-5233/17
http://dx.doi.org/10.1016/j.tranon.2017.07.005

scheme [1,2]. Since BPE is thought to coincide with the amount of blood flow in the fibroglandular tissue and may reflect breast activity, there are many studies that demonstrated that BPE was associated with fibroglandular tissue (FGT), patient's age, menopausal status, and menstrual phase [3–6].

Previous studies have investigated the influence of BPE on the affected breast harboring breast cancer. It was proposed that increased levels of BPE are an important risk factor for breast cancer [3,7,8]. It was revealed that moderate or marked BPE surrounding breast tumors may affect the accuracy of the tumor size estimation, leading to a positive resection margin after breast conservation surgery [9].

In addition, higher BPE around the tumor at preoperative MR imaging could be an independent factor associated with worse recurrence-free survival in patients with ductal carcinoma in suit (DCIS) [10,11]. Besides surgery treatment, it was also previously demonstrated that other well established treatments, such as radiation, chemotherapy and antihormonal medications were also associated with BPE [7,12–14]. The reductions of BPE may have been caused by any other therapies or by their combination.

A few of studies recently have focused on the association between BPE and tumor outcome to neoadjuvant chemotherapy (NAC). Preibsch et al. demonstrated that the decreased BPE after NAC seemed to correlate with tumor response by using qualitative analysis [15]. Given the typical symmetry between left and right breast, Chen et al. and van der Velden et al., respectively, investigated the alternation of BPE in the contralateral normal breast by using fully automated computerized method [16,17]. Chen et al. found that a reduction of BPE was associated with pathologic complete remission (pCR) to NAC in estrogen receptor (ER)*negative patients, while van der Velden et al. revealed that the association between BPE and long-term outcome was significant particularly in patients with ER-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancers. Although these studies confirmed that the alternation of BPE can predict tumor outcome in NAC, they have not reached an agreement on different subtypes according to immunohistochemistry (IHC). Additionally, some of the published studies ignored the fact to unify the observation point of BPE after NAC, and some of them aimed for a change of BPE before the surgery just after completing NAC. None of them focused on the change of BPE at every time point throughout NAC in breast patients.

Thus, the purpose of this retrospective study was to quantify BPE in breast cancer patients throughout different time points during NAC and further to determine whether quantitative MR imaging assessments of BPE in the contralateral normal breast are associated with tumor response, especially at the early stage of NAC.

Materials and Methods

Patient Enrollment

The institutional review board granted a waiver of authorization and patient consent for our retrospective study, which was in compliance with the Health Insurance Portability and Accountability Act (HIPAA). Between August 2014 and April 2016, 116 patients diagnosed with breast cancers were confirmed by core needle biopsy, and received six or eight cycles of neoadjuvant chemotherapy (NAC). Diagnosis of suspicious axillary lymph node was confirmed by ultrasound-guided fine-needle aspiration. Altogether, 26 patients were excluded — among them 10 did not receive surgery after NAC, 5 had bilateral breast cancers, and 11 had insufficient MRI data. Finally, 90 patients (mean age ± SD, 49.84 ± 10.04 years; age range, 28–69 years) with unilateral breast cancer (72 invasive ductal carcinomas, 5 ductal carcinoma in suit, 2 invasive lobular carcinoma and 11 tumor classification unclear) were included in our study. Menopausal status was recorded in medical history, then patients were separated into pre-menopausal (mean age ± SD, 40.88 ± 6.55 years, N = 50) and post-menopausal groups ((mean age ± SD, 57.02 ± 5.55, N = 40). Among them, all patients underwent contrast-enhanced breast MRI before and after NAC.

NAC Protocol

The NAC regimens included CEF (cyclophosphamide 600 mg/m^2 on day 1, epirubicin 60 mg/m^2 on day 1 and 5-fluorouracil 600 mg/m^2 on day 1 every 3 weeks), PC (paclitaxel 80 mg/m^2 and carboplatin AUC 2 mg min/ml on days 1, 8, and 15 of a 28-day cycle) and PE (paclitaxel, 80 mg/m^2 on Days 1, 8, and 15, epirubicin 60 mg/m^2 on day 1 every 3 weeks) for a median of 4 cycles (range 1 to 6 cycles). TEC (Taxotere 75 mg/m^2, epirubicin 60 mg/m^2 cyclophosphamide 600 mg/m^2 on day 1 of a 21-day cycle). For HER-2 positive patients, Trastuzumab was administered as 4 mg/kg loading dose followed by 2 mg/kg weekly combined with chemotherapy (PCH). Breast surgery with axillary dissection was performed within 4 weeks at the last chemotherapy dose for all the patients. In total, 5 patients received CEF, 20 patients received PC, 2 cases underwent PE, 29 cases underwent TEC and 39 patients received PCH.

MRI Study Protocol

MRI was performed with 1.5-T Dedicated spiral breast MRI Systems (Aurora Imaging Technology, Aurora Systems, Inc., Canada) with breast coil. The patient was prone, and images were acquired in the axial planes with the following sequences: a T2-weighted fat-suppressed sequence (TR 6680 ms, TE 29 ms, thickness 3 mm), and axial T1-weighted fat suppressed (TE/TR 4.8/29 ms, thickness 1.1 mm, FOV 360 mm, matrix 360 × 360 × 128) before and four times after a bolus injection of gadopentetate dimeglumine at 2 ml/s with an injector and followed by 20 ml normal saline flush. Postcontrast images were obtained at 90, 180, 270, and 360 seconds after injection. The same acquisition parameters were used throughout NAC studies. The baseline MRI scans were scheduled prior to initiation of NAC, at least 10 days after biopsy. The follow-up MRI scans were usually scheduled after the 2nd, 4th, 6th, and 8th cycle of NAC just before commencing the next cycle, respectively. Only 12 patients received eight cycles of NAC; therefore, the data of 8th follow-up MRI were excluded in this study.

Histopathological Analysis

Prior to NAC, biopsy of the primary tumor was taken for histological analysis. Pathologic tumor response was assessed by the Miller and Payne grading [18]. pCR in the breast was defined as the absence of invasive carcinoma (residual ductal carcinoma in situ allowed) by pathologic examination.

Image Processing

We developed a fully automated scheme for the quantitative analysis of BPE in DCE-MRI. It has been used in our previous study [19]. Our fully automated method consists of three steps, segmentation of the whole breast, fibroglandular tissues, and enhanced fibroglandular tissues. Based on the volume of interest