RESEARCH ARTICLE

Impact of Radiotherapy on Background Parenchymal Enhancement in Breast Magnetic Resonance Imaging

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Abstract

Background: While many studies have shown that hormones can influence background parenchymal enhancement (BPE) in breast magnetic resonance imaging (MRI), only few have directly address the effect of radiotherapy. The purpose of this study was to evaluate the impact of radiotherapy on BPE in breast MRI. Materials and Methods: A retrospective search identified 62 women with unilateral breast cancer who had a breast MRI both before and after radiotherapy following breast-conserving surgery. In our study, we assumed that systemic therapy affected both breasts equivalently. We rated the level of BPE of both breasts using a four-point categorical scale. A change in the level of BPE prior to and after treatment was compared in the diseased and contralateral breasts. Results: All patients received a 4256 to 6480 cGy dose of whole breast radiotherapy over 3-7 weeks. The mean timing of the follow-up study was 6.6 months after completion of radiotherapy. Although the BPE showed a decrease in both breasts after treatment, there was a significant reduction of BPE in the irradiated breast compared with the contralateral breast (1.18 versus 0.98 average reduction in BPE level, p=0.042). Conclusions: Radiotherapy is associated with decrease in BPE with MRI.

Keywords: Magnetic resonance imaging - breast neoplasm - radiotherapy - background parenchymal enhancement

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Introduction

Most breast cancer patients receive combination therapy after surgery. Among these therapies, radiotherapy (RT) is a mainstay of treatment after breast-conserving surgery (BCS), particularly in locoregional management. Radiation compromises the microvasculature, and such alterations can be visualized by breast magnetic resonance imaging (MRI) (Li et al., 2010).

Background parenchymal enhancement (BPE) in a breast MRI refers to the normal enhancement of the fibroglandular tissue seen in the contrast-enhanced image (Hambly et al., 2011). Although the precise biological mechanisms accounting for changes in BPE are not well understood, several studies have suggested some relevant factors that may affect the level of BPE in breast MRI (King et al., 2012a; 2012b; 2012c). As the breast is a hormonally dynamic organ, it is known that the vascularity and tissue composition of the breast are influenced by hormonal changes, such as aging, menopause, menstrual cycle, and hormone therapy. These changes can be seen on contrast-enhanced breast MRI and are manifested as differences in BPE and the amount of fibroglandular tissue. The effects of antihormonal treatments, including selective estrogen receptor modulators and aromatase inhibitors, on BPE have been studied (King et al., 2012b; Mousa et al., 2012). Because MRI reflects blood flow patterns and these patterns are partially related to the hormonal sensitivity of the breast and the hormonal status of the patient, both morphologic and functional changes in the breast are reflected by MRI (Li et al., 2010).

While many studies have focused on the influence of hormones on BPE, to the best of our knowledge few studies directly address the effect of RT on BPE. Knowledge of the effect of RT on breast MRI could improve our understanding of the effect of this treatment. Given that systemic treatments, such as chemotherapy and antihormonal therapy, may influence both breasts equivalently, we assumed that the parenchyma of the irradiated breast might show characteristic changes as a consequence of RT.

The purpose of this study was to evaluate the impact of RT on BPE in breast MRI.

Materials and Methods

Patients

A waiver of authorization and patient consent was granted by the institutional review board for this retrospective study.

A retrospective query of electronic medical records was used to identify breast cancer patients who underwent

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BCS between March 2009 and June 2012. Among them, patients who had bilateral breast MRI examinations both before and after surgery were found. Patients with the first follow-up MRI performed within 18 months after completion of RT were included in this study.

Patient inclusion was planned to show alterations in the conserved breast as a consequence of RT and to compare these changes with those in the contralateral breast. The criteria for patient inclusion in this study were as follows: complete therapy for breast cancer, including surgery and a full course of RT; no surgery or cancer diagnosis involving the contralateral breast; no neo-adjuvant chemotherapy; and no prior history of bilateral breast radiation.

The medical records of these patients were reviewed to identify the age of the patient at the time of diagnosis, the date of surgery, the duration and dose of RT, histopathologic diagnosis, tumor stage, the regimen of hormonal therapy or adjuvant chemotherapy, and menopausal status at the time of each MRI study.

MR imaging examination

Diagnostic breast MRI examinations were performed at 3.0 T (Magnetom Verio; Siemens Medical Solutions, Erlangen, Germany) with the patient in the prone position by using a dedicated surface breast coil. The MRI images were acquired using the following sequences: axial, turbo spin-echo T2-weighted imaging sequence with a TR/TE of 4530/93, flip angle of 80°, 34 slices, FOV of 320 mm, matrix size of 576×403, 1 NEX, slice thickness of 4 mm, acquisition time of 2 minutes 28 seconds; pre- and post-contrast, axial T1-weighted flash three-dimensional, VIBE sequence with TR/TE of 4.4/1.7, flip angle of 10°, slice thickness of 1.2 mm, acquisition time of 7 minutes 7 seconds, obtained before and at 7, 67, 127, 187, 247 and 367 sec after an injection of 0.1 mmol/kg body weight of Gd-DPTA (Gadovist, Schering, Berlin, Germany). After the examination, the unenhanced images were subtracted from the postcontrast images. Maximum-intensity projection images were created from the early phase of subtraction images.

MR image interpretation

The pre-treatment MRI was defined as the MRI study performed before the surgery. The post-treatment studies were timed from the completion of radiation. If a patient had more than one follow-up MRI studies, the first follow-up MRI was evaluated. An additional assessment was performed for patients with the second follow-up MRI. Duration of the pre-treatment MRI to the follow-up MRI(s) was recorded.

A fellowship-trained breast imaging radiologist (8 years of experience in MR imaging) and a board-certified first-year breast radiology fellow reviewed all MR images together with results determined by consensus. The BPE of each breast was assessed visually using a combination of maximum-intensity projection and early subtraction imaging. BPE was categorized on the basis of the proposed Breast Imaging Reporting and Data System (BI-RADS) criteria as follows: minimal (≤25% enhancement of glandular tissue); mild (26-50% enhancement of glandular tissue); moderate (51-75% enhancement of glandular tissue); and marked (>75% enhancement of glandular tissue) (Morris, 2010). Multi-sequential MR images were used for post-treatment assessment to exclude normal enhancement at the lumpectomy site.

In addition to separately evaluating the MR studies before and after RT, a side-by-side visual comparison of the bilateral breasts from each patient was performed. In this comparison, the BPE of the diseased breast was compared to that of the contralateral breast and was determined to be similar, lesser, or greater. The purpose of the side-by-side comparison was to increase sensitivity by comparing images at the same time and also to detect changes in BPE that may not have resulted in a change in level.

Statistical analysis

The changes in the level of BPE of the diseased breast before and after treatment were compared with those of the contralateral breast. The Wilcoxon signed rank test was used to compare the changes in the rating levels in the two breasts. Statistics software (SPSS, version 21; IBM) was used for statistical analysis, and a p value of 0.05 was considered to be significant.

Results

Patient characteristics

According to the above criteria, 62 patients were enrolled in the study. Total 147 breast MR studies were reviewed: all patients underwent the pre-treatment MRI and the first follow-up MRI; and 22 patients (35.5%) had the second follow-up MRI.

The surgery was performed 1 to 36 days after the pre-treatment MRI (mean, 9.1 days). The first follow-up MRI was performed 6.6 months on average after completion of RT (range, 3 days-17.6 months). The mean duration of the pre-treatment MRI to the first follow-up MRI was 11.2 months (range, 3.0-23.1 months). Of the 22 patients who had a second follow-up MRI, the mean duration after the pre-treatment MRI was 24.0 months (range, 17.1-35.3 months).

The patients and their pathologic characteristics are summarized in Table 1. The mean age of the 62 women included in the study was 43.1 years (range, 25-69 years). The tumors were classified as invasive ductal carcinoma in 45 patients (72.6%), ductal carcinoma in situ in 8 patients (12.9%), mucinous carcinoma in 3 patients (4.8%), medullary carcinoma in 3 patients (4.8%), invasive lobular carcinoma in 1 patient (1.6%), papillary carcinoma in 1 patient (1.6%), and malignant phyllodes tumor in 1 patient (1.6%). The breast cancer stage groups were classified as 0 (carcinoma in situ) in 8 patients (12.9%), I in 25 patients (40.3%), II in 24 patients (38.7%), and III in 5 patients (8.1%). All patients received a 4256 to 6480 cGy dose of whole breast RT for 3 to 7 weeks: 54 patients (87.1%) received 5940 cGy for 6 weeks; 4 patients (6.5%) received 5040 cGy for 5 weeks; 2 patients (3.2%) received 4250 cGy for 3 weeks; and 2 patients (3.2%) received 6480 cGy for 7 weeks. Total of 38 patients (61.3%) received hormonal therapy. Of these, 36 patients received Tamoxifen, and 2 patients received aromatase inhibitors.

Total of 43 patients (69.4%) received chemotherapy. The number of postmenopausal women was 16 (25.8%) on pre-treatment MRI and 52 (83.9%) on the first follow-up MRI. Of the 22 patients who had a second follow-up MRI, 21 women (95.5%) were postmenopausal.

Background parenchymal enhancement (BPE) on MRI

Prior to RT, of the 62 diseased breasts, 16 (25.8%), 17 (27.4%), 10 (16.1%), and 19 (30.6%) had minimal, mild, moderate, or marked BPE, respectively. After RT, 48 (77.4%), 10 (16.1%), 1 (1.6%), and 3 (4.8%), had minimal, mild, moderate, or marked BPE, respectively (Figure 1). The BPE was classified as the lowest assessment level (minimal BPE) in 48 (77.4%) diseased breasts and 42 (67.7%) contralateral breasts in the post-treatment period.

After treatment, the average level of BPE decreased from 2.5 to 1.3 in the irradiated breasts, compared with 2.4 to 1.5 in the contralateral breasts. The average reduction in BPE level was 1.2 in the diseased breasts, compared with 1.0 in the contralateral breasts. This difference was statistically significant (p=0.042). The number of irradiated breasts in which the BPE was stable, decreased, or increased is shown in Table 2. After RT, the BPE decreased by at least one level in the majority of the irradiated breasts (62.9%, 39/62) and by two or more levels in 38.7% of the irradiated breasts (24/62) (Figure 2). Twenty one breasts (33.9%) showed stable BPE, and 2 (3.2%) showed an increase in BPE. Of the 62 contralateral breasts, 40 (64.5%) showed a decrease in BPE, while 18 (29.0%) showed stable BPE and 4 (6.5%) showed an increase in BPE.

In the side-by-side visual comparison, 12 (19.4%) diseased breasts showed lower BPE than that of the contralateral breasts after RT, while only 3 (4.8%) showed lower BPE before RT (Figure 3).

For the 22 patients who had the second follow-up MRI study, an additional assessment was performed (Figure 4). The changes in BPE between the two follow-up MRI studies were smaller compared to the changes

Table 1. Patient and Pathologic Characteristics

Characteristics		No. of patients
Pathology	Invasive ductal carcinoma	45 (72.6)
	Ductal carcinoma in situ	8 (12.9)
	Others	9 (14.5)
AJCC Stage	0	8 (12.9)
	I	25 (40.3)
	II	24 (38.7)
	III	5 (8.1)
Hormone therapy	Tamoxifen	36 (58.1)
	Aromatase inhibitor	2 (3.2)
	Aromatase inhibitor	24 (38.7)
Chemotherapy	Received	43 (69.4)
	Not received	19 (30.6)

*Note-The numbers in parentheses are percentages, AJCC=American Joint Committee on Cancer

Table 2. Changes in the Level of Background Parenchymal Enhancement After Breast-Conserving Surgery and Radiotherapy

	Diseased breast	Contralateral breast
Average level of BPE		
Before RT	2.5	2.4
After RT	1.3	1.5
Average reduction in level*	1.2	1.0
Changes in level of BPE		
Stable	21 (33.9)	18 (29.0)
Any decrease	39 (62.9)	40 (64.5)
1 level	15 (24.2)	21 (33.9)
2 levels	11 (17.7)	12 (19.4)
3 levels	13 (21.0)	7 (11.3)
Any increase	2 (3.2)	4 (6.5)

*Significant difference in average reduction in BPE between disease breasts and contralateral breasts (p=0.042). Note- Except for level of BPE, the data shown represent the number of patients, with the percentages in parentheses

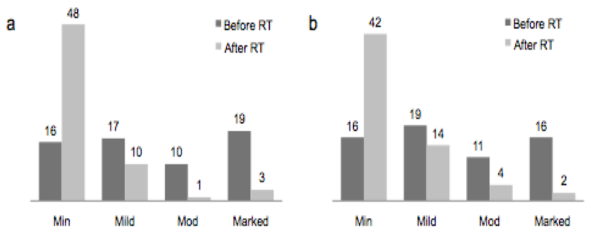

Figure 1. Number of Diseased (A) and Contralateral (B) Breasts With Minimal, Mild, Moderate, and Marked Background Parenchymal Enhancement Before and After Radiotherapy

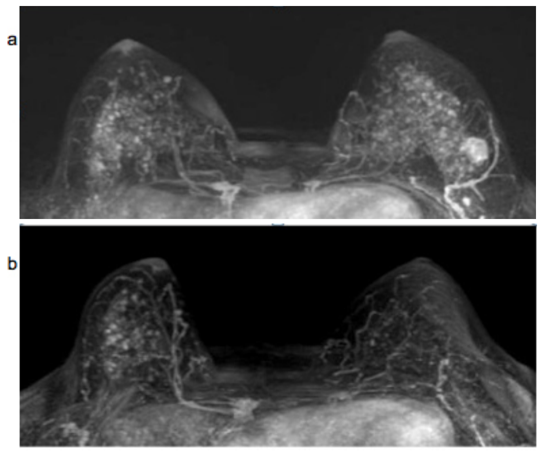

Figure 2. Contrast-Enhanced Subtraction Maximum Intensity Projection MR Images in a 43-Year-Old Woman with Breast Cancer. a) The baseline image before treatment shows marked BPE of both breasts, and **b)** the follow-up MR image 7 months after the completion of radiotherapy shows a reduction of BPE in both breasts. The irradiated left breast shows minimal BPE, while the contralateral breast shows moderate BPE. In the side-by-side visual comparison, the irradiated breast shows lower BPE than that of the contralateral breast. A malignant tumor was removed from the left breast by breast-conserving surgery

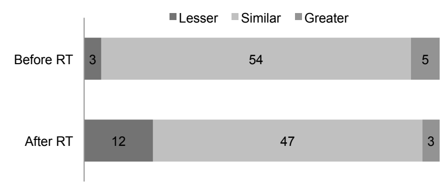

Figure 3. Side-by-side Comparison of the Background Parenchymal Enhancement of the Diseased Breast and the Contralateral Breast of an Individual

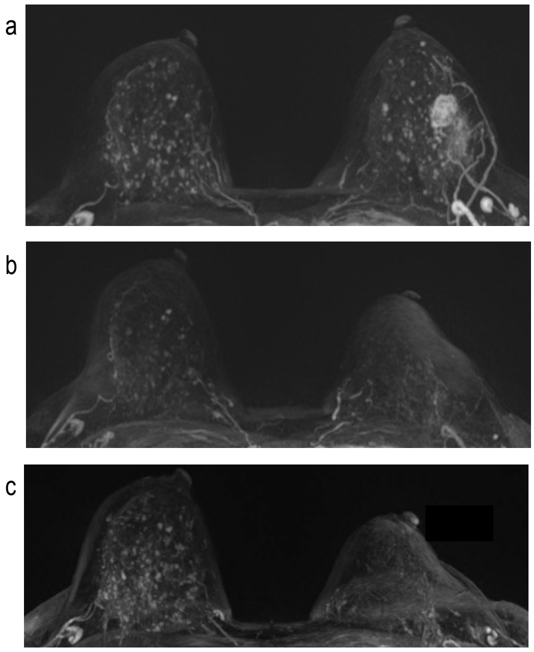

Figure 4. Contrast-Enhanced Subtraction Maximum Intensity Projection MR Images in a 40-year-old Woman with Breast Cancer. a) The baseline image before treatment shows moderate BPE of both breasts; **b)** the first follow-up MR image 13 months after the completion of radiotherapy shows a reduction of BPE in both breasts. The irradiated left breast shows minimal BPE, while the contralateral breast shows mild BPE. A malignant tumor was removed from the left breast by breast-conserving surgery and c) The second follow-up MRI 25 months after the completion of radiotherapy shows increased BPE in the contralateral breast. The irradiated left breast shows minimal BPE without interval change

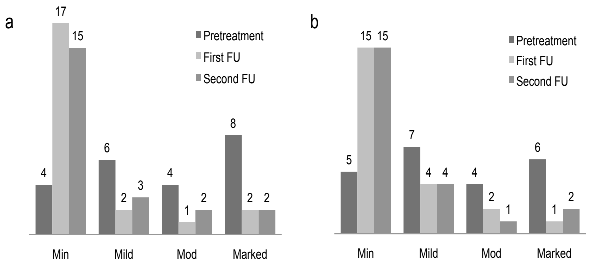

Figure 5. Number of Diseased (A) and Contralateral (B) Breasts with Minimal, Mild, Moderate, and Marked Background Parenchymal Enhancement at Pre-Treatment and Two Follow-Up Studies

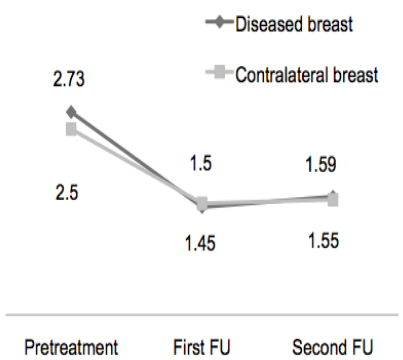

Figure 6. Changes in the Average Level of the Background Parenchymal Enhancement on Serial Follow-Up Mri Studies

demonstrated on the first follow-up MRI (Figure 5). The average BPE level of the irradiated breasts increased from 1.45 to 1.59 in the second follow-up studies (Figure 6). The average BPE level of the contralateral breasts also increased slightly from 1.5 to 1.55.

Discussion

In patients with breast cancer, RT is of critical importance after BCS. While many studies have focused on the effects of hormones on BPE, few studies directly address the effect of RT on BPE. We planned to evaluate the impact of RT on BPE in breast MRI. Our results demonstrated that the irradiated breast showed visible decrease in BPE in the majority of patients with breast cancer (62.9%). Although BPE was reduced in both breasts, the average reduction in BPE level was greater in the irradiated breast (1.2) than in the contralateral breast (1.0, p=0.042). There were many factors influencing BPE, including systemic treatments and menopausal status or menstrual cycle. However, given that these factors may influence both breasts equivalently, the difference is thought to be partly due to RT.

According to a recent study examining the relationships between breast cancer and the level of BPE, higher levels of BPE in MRI have been associated with greater risks for breast cancer. Compared with the odds ratio for a normal control, the odds ratio for breast cancer increased significantly with increasing BPE (King et al., 2011). If it can be clearly established that RT is associated with a decrease in BPE, then BPE can potentially serve as an indicator for RT response in breast cancer patients. Further studies are warranted to demonstrate relationship between the cancer recurrence rate and the level of BPE.

Because the detection of malignancy by MRI relies on the differential enhancement between the neoplastic tissue and the normal breast parenchyma, it has been postulated that benign enhancement may obscure the detection of small malignancies by masking this difference. Therefore, the reduction of BPE might increase the detection rate of a small malignancy. In a study demonstrating the effect of BPE on short-interval follow-up, mild, moderate, and marked BPE were shown to be associated with a significantly lower rate of BI-RADS category 1 and 2 assessments and a significantly higher rate of category 3 assessments compared with minimal BPE (Hambly et al., 2011). The improved sensitivity is even more meaningful in the monitoring of locoregional recurrence in breast cancer patients.

Our results are consistent with the results of a recent study on the usual findings in routine follow-up MRI in women after BCS (Li et al., 2010). The study reported that BPE decreased bilaterally after the completion of surgery and radiation. The reduction of BPE was slightly greater in the treated breast than in the contralateral breast. The mean levels of BPE were 1.57 in the treated side and 1.73 in the contralateral side on early post-treatment MRI and 1.19 in the treated side and 1.21 in the contralateral side on late post-treatment MRI. Although there was no significant difference observed in the early post-treatment MRI, the late post-treatment MRI showed significant differences between the two breasts.

In the present study, the additional evaluation of patients with a serial follow-up MRI demonstrated increased average levels of BPE in both breasts on the second follow-up studies. It is possible that some of the temporarily compromised parenchymal tissues had recovered over time.

The first limitation of our study is that it was retrospective. As such, there were variabilities in the dose and duration of RT and the interval between MRIs. In addition, the patients received a wide range of combination therapies. Some information, such as last menstrual period and menopausal status, were not reliably recorded and hence could not be used for analysis. Although we cannot exclude the possible effects of these confounding factors, it is unlikely that they would matter in the comparison of the two breasts because they would affect both breasts equivalently.

A second limitation is that we used qualitative, rather than quantitative, measures to assess BPE. The BPE was qualitatively rated on the basis of proposed BI-RADS criteria. Although some quantitative methods for measuring overall BPE on breast MRI have been suggested, they have not been validated at this time. In addition, because MRI shows normal enhancement at the lumpectomy site during the recent postoperative period, this will influence the grading of BPE.

In conclusion, our results showed that RT is associated with decreases in BPE. This study provided preliminary evidence for the usefulness of MRI for predicting of RT response. Additional prospective studies on this topic are warranted to validate its clinical utility.

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