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FULL PAPER

Does background parenchymal enhancement on MRI affect the rate of positive resection margin in breast cancer patients?

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Objective: The purpose of our study was to evaluate whether strong background parenchymal enhancement (BPE) would be a significant independent factor associated with positive resection margin in patients treated initially with breast-conserving surgery (BCS).
Methods: Retrospective evaluation of breast MRI examinations of 314 patients with breast cancer was carried out. Breast cancer was histologically confirmed in all patients who underwent BCS from January 2008 to December 2010. BPE was dichotomized into weak (minimal or mild) and strong (moderate or marked) enhancement for statistical analysis. Histopathological features of attained specimens were evaluated by an experienced pathologist and were also dichotomized for statistical analysis.
Results: On univariate analysis, positive extensive intraductal component ($p < 0.001$), strong BPE ($p = 0.001$) and human epidermal growth factor receptor 2 (HER2) positivity ($p = 0.08$) had significant association with positive surgical margin. Tumour size, axillary lymph node metastasis, nuclear grade, histological grade, lymphovascular invasion, oestrogen receptor and progesterone receptor did not show significant correlation with positive surgical margin. On multivariate analysis, the significant independent predictors were extensive intraductal component [odds ratio, 5.68; 95% confidence interval (CI), 2.72–11.82] and strong BPE (odds ratio, 2.39; 95% CI, 1.20–4.78).
Conclusion: Strong BPE is a significant independent factor for positive resection margin along with positive extensive intraductal component, and performing MRI during the period of lower parenchymal enhancement is needed in patients with strong BPE.
Advances in knowledge: As far as we know, this is the first study to reveal that BPE is a significant independent factor associated with positive resection margin.

Overall survival after breast-conserving surgery (BCS) followed by adjuvant radiation therapy has been shown to be equivalent to that after mastectomy for early stage breast cancer.[1–4] Nowadays, BCS has become the standard treatment for early stage breast cancer. However, the rate of local recurrence is higher in patients with BCS than in those with mastectomy,[2] and the most important predictor of local recurrence is margin status.[5] In a meta-analysis reporting local recurrence relative to margin status, odds ratio for local recurrence was 2.42 ($p < 0.001$) with a positive margin.[6] There are many known risk factors associated with positive resection margin, including younger age, less than 45 years of age, mammographic density of Category 4, larger tumour size, positive lymph nodes, tumour multifocality, the presence of microcalcification in mammography, lobular histology, higher grade, the presence of extensive intraductal component and the presence of lymphovascular invasion.[7–11]

Accurate pre-operative assessment of tumour extent is essential for surgical planning and for reducing positive surgical margin. Breast MRI has been widely used for pre-operative evaluation of tumour extent and could substantially decrease the rate of positive resection margins and reoperations in patients with breast cancer who underwent BCS.[12] However, the common problem in MRI interpretation is that there are some difficulties in lesion detection and cancer extent evaluation owing to strong background parenchymal enhancement (BPE) in pre-menopausal patients. Breast tissue is well known to be hormonally sensitive, especially to oestrogen, which is believed to cause increased vascularization of breast parenchyma during actively secreting phase. There are many studies reporting that BPE in pre-menopausal females is higher than that of postmenopausal females, which is thought to be associated with differences in hormone level.[13,14]

Our hypothesis was that additional cancer foci around the index cancer could be masked by strong BPE, and therefore, positive resection margin would be more frequent in patients who had strong BPE on pre-operative MRI than in patients with weak BPE. The purpose of our study was to evaluate whether the strong BPE would be a significant independent factor associated with positive resection margin.

Table 1. Patients' characteristics

Characteristic	Minimal or mild enhancement ($n = 216$), n (%)	Moderate or marked enhancement ($n = 98$), n (%)	p-value
Age (years), mean ± SD	50.3 ± 10.4	43.4 ± 6.4	<0.001
pT staging			0.696
T0	15 (7)	10 (10)	
T1	113 (52)	47 (48)	
T2	81 (38)	37 (38)	
T3	7 (3)	4 (4)	
pN staging			0.746
N0	147 (74)	63 (71)	
N1	32 (16)	18 (20)	
N2	19 (10)	8 (9)	
N3	2 (1)	0 (0)	
Oestrogen receptor			0.572
Positive	149 (69)	71 (72)	
Negative	66 (31)	27 (28)	
Progesterone receptor			0.025
Positive	142 (66)	77 (79)	
Negative	73 (34)	21 (21)	
HER2-neu			0.261
Positive	42 (20)	14 (14)	
Negative	173 (80)	84 (86)	
Histologic type			0.957
Ductal NOS	186 (86)	86 (88)	
Lobular	7 (3)	3 (3)	
Other (mucinous, papillary etc.)	23 (11)	9 (9)	
Lymphovascular invasion			0.082
Positive	61 (33)	37 (44)	
Negative	126 (67)	48 (56)	
Histological grade			0.386
1	30 (14)	11 (11)	
2	65 (30)	37 (38)	
3	119 (56)	49 (51)	
Nuclear grade			0.999
1	103 (48)	47 (48)	
2	97 (46)	44 (45)	
3	13 (6)	6 (6)	

HER2, human epidermal growth factor receptor 2; NOS, not otherwise specified.

Table 2. Univariate analysis of associations with positive resection margin

Characteristics	Positive resection margin ($n = 44$), n (%)	Negative resection margin, ($n = 270$) n (%)	p-value
Tumour size			0.702
≥2 cm	15 (41.7)	114 (45.1)	
<2 cm	21 (58.3)	139 (54.9)	
Axillary LN metastasis			0.8
Positive	11 (28.9)	68 (27.0)	
Negative	27 (71.1)	184 (73.0)	
EIC			<0.001[a]
Positive (≥25%)	32 (72.7)	78 (28.9)	
Negative (<25%)	12 (27.3)	192 (71.1)	
Background parenchymal enhancement			0.001[a]
Strong	23 (52.3)	75 (27.8)	
Weak	21 (47.7)	195 (72.2)	
Nuclear grade			0.378
High	24 (54.5)	126 (47.4)	
Low	20 (45.5)	140 (52.6)	
Histological grade			0.291
High	27 (61.4)	141 (52.8)	
Low	17 (38.6)	126 (47.2)	
Lymphovascular invasion			0.439
Positive	15 (41.7)	83 (35.0)	
Negative	21 (58.3)	154 (65.0)	
Oestrogen receptor			0.147
Positive	35 (79.5)	185 (68.8)	
Negative	9 (20.5)	84 (31.2)	
Progesterone receptor			0.135
Positive	35 (79.5)	184 (68.4)	
Negative	9 (20.5)	85 (31.6)	
HER2			0.08
Positive	12 (27.3)	44 (16.4)	
Negative	32 (72.7)	225 (83.6)	

EIC, extensive introductal component; HER2, human epidermal growth factor receptor 2; LN, lymph node.
[a]Statistically significant.

METHODS AND MATERIALS

Patients

Institutional review board of Ajou University Medical Center, Suwon, Republic of Korea, approved this retrospective study. From January 2008 until December 2010, 351 patients who had known breast cancer underwent pre-operative MRI and BCS. We excluded 37 patients who received neoadjuvant chemotherapy, and finally, 314 patients (mean age, 48 years; age range, 25–80 years) were included in this study. Of 314 patients, 216 (69%) had minimal or mild BPE and 98 (31%) had moderate or marked BPE. Mean age was significantly different between the two groups (50.3 ± 10.4 *vs* 43.4 ± 6.4 years; $p < 0.001$). Histopathological tumour type was ducal non-specified type in 272 patients, mucinous carcinoma in 12, invasive lobular carcinoma in 10, invasive micropapillary carcinoma in 7, metaplastic carcinoma in 5, papillary carcinoma in 4, medullary carcinoma in 3 and apocrine carcinoma in 1 patient. Baseline characteristics of the patients are summarized in Table 1.

Imaging protocols

MR images were acquired on a 1.5-T scanner (Signa® HDxt; GE Healthcare, Milwaukee, WI) or 3-T system (Achieva; Philips Healthcare, Best, Netherlands) with the use of a dedicated breast

Table 3. Association of background parenchymal enhancement (BPE) and extensive intraductal component with surgical resection margin

Prescence of EIC and degree of BPE	Positive resection margin ($n = 44$)	Negative resection margin ($n = 270$)	Total ($n = 314$)
Strong BPE with positive EIC	17 (38%)	28 (62%)	45 (100%)
Strong BPE with negative EIC	6 (11%)	47 (89%)	53 (100%)
Total of strong BPE	23 (23%)	75 (77%)	98 (100%)
Weak BPE with positive EIC	15 (23%)	49 (77%)	64 (100%)
Weak BPE with negative EIC	6 (4%)	146 (96%)	152 (100%)
Total of weak BPE	21 (10%)	195 (90%)	216 (100%)

EIC, extensive intraductal component.

coil. Patients underwent imaging in the prone position with the breasts immobilized. Contrast material was injected into an antecubital vein by an automatic injector [0.1 mmol kg^{-1} gadopentetate dimeglumine (Magnevist®; Bayer Schering Pharma AG, Berlin, Germany)] and followed by a 20-ml saline flush at a rate of 2 ml s^{-1}. The imaging protocol of a 1.5-T scanner consisted of fat suppressed axial fast spin-echo T_2 weighted images [repetition time (TR)/echo time (TE), 4000/74 ms; slice thickness, 3 mm] and dynamic unenhanced and contrast-enhanced fat-saturated three-dimensional (3D) gradient-echo T_1 weighted imaging (5.1/2.4; flip angle, 10°; image matrix, 300 × 300 pixels; field of view, 300 × 300 mm; section thickness, 1.5 mm; and section gap, 0 mm). The imaging protocol of a 3-T scanner consisted of fat-suppressed axial fast spin-echo T_2 weighted images (TR/TE, 7562/70 ms; slice thickness, 3 mm) and dynamic unenhanced and contrast-enhanced fat saturated 3D gradient-echo T_1 weighted imaging (7.6/3.9; flip angle, 10°; slice thickness, 3 mm). Sagittal and coronal reformatted images were obtained using raw data. Standard subtraction images were obtained by subtracting the pre-contrast images from the early peak post-contrast image (obtained at 80 s after contrast injection) on a pixel-by-pixel basis. In addition, maximum intensity projection (MIP) reconstructions were applied to the subtraction images.

Image analysis

All images were reviewed retrospectively in consensus by two breast radiologists with 5 and 10 years' experience. Breast parenchymal enhancement of the entire normal breast was visually assessed by using a combination of post-contrast fat-suppressed T_1 weighted image, subtraction and MIP images. Breast parenchymal enhancement was categorized based on proposed breast imaging reporting and data system criteria as minimal, mild, moderate or marked,[15] and then dichotomized into weak (minimal or mild) or strong (moderate or marked) enhancement for statistical analysis.

Histopathological evaluation

The surgical specimens were cut into 5-mm slices, fixed in 10% neutral buffered formalin and processed for histological examination. Each paraffin block was sliced and stained with haematoxylin and eosin for evaluation. All specimens were reviewed by an experienced pathologist.

A positive surgical margin is defined as the presence of tumour cells at the inked surface of the resected specimen. The margin is negative if there is no ink on any cancer cell.

The specimens were evaluated according to the following histopathological features: histological type of carcinoma, Black nuclear grade (nuclear grade 1, poorly differentiated; grade 2, moderately differentiated; and grade 3, well differentiated), modified Bloom–Richardson histological grade (histological grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated), presence of oestrogen receptor (ER) and progesterone receptor (PR), and expression of the C-ERBB2 oncogene. For evaluation of the expression of ER, PR and C-ERBB2, the corresponding paraffin block was immunostained with commercially available rabbit monoclonal antibodies to ER (clone SP1; Spring Bioscience, Pleasanton, CA), PR (clone SP2; Spring Bioscience) and C-ERBB2 (clone SP3; Spring Bioscience). The Allred scoring system was used for evaluation of the hormone receptors. Sentinel node biopsy or axillary nodal dissections were performed, and the N stage was recorded.

For statistical comparison, variables were dichotomized according to tumour size (≤2 *vs* >2 cm), axillary lymph node metastasis (negative *vs* positive groups), nuclear grade [high (grade 1) *vs* non-high (grades 2 and 3)], histological grade [non-high (grades 1 and 2) *vs* high (grade 3)], expression of ER and PR (negative *vs* positive) and expression of C-ERBB2 (negative *vs* positive).

Statistical analysis

Pearson's χ^2 or Fisher's exact test were used to identify associations between each of the clinicopathological factors and the rate of positive resection margin. Multivariate analysis was performed using logistical regression of the variables that were found to be statistically significant on univariate analyses. Statistical analyses were performed using SPSS® v. 18.0 (SPSS Inc., Chicago, IL) with a value of $p < 0.05$ considered to be significant.

RESULTS

Of 314 patients, 44 patients had positive resection margin and 270 patients had negative resection margin. On univariate analysis, positive extensive intraductal component (EIC) and strong BPE were significantly associated with positive resection margin ($p < 0.001$ and

$p = 0.001$, respectively). The positivity of HER2 tended to be associated with positive resection margin ($p = 0.08$). Tumour size, axillary lymph node metastasis, nuclear grade, histological grade, lymphovascular invasion, ER and PR were not found to be associated with positive resection margin. The result of the univariate analysis is summarized in Table 2.

Of 216 patients with weak BPE, 195 (90%) patients had negative resection margin. Furthermore, of 152 patients with both weak BPE and negative EIC, 146 (96%) had negative margin and only 6 (4%) had positive resection margin (Table 3). Of 98 patients with strong BPE, 23 (23%) had positive resection margin (Figure 1), and of 45 patients with both strong BPE and positive EIC, 17 (38%) patients had positive resection margin. Comparing between BPE status and EIC status, 15 (23%) of 64 patients with weak BPE but positive EIC had positive resection margins compared with 6 (11%) of 53 patients with strong BPE but negative EIC.

Multivariate logistic regression analysis was performed with the variables associated with positive resection margin through univariate analysis. Positive EIC [odds ratio, 5.68; 95% confidence interval (CI), 2.72–11.82] and strong BPE (odds ratio, 2.39; 95% CI, 1.2–4.78) were identified as being independently associated with positive resection margin after BCS (Table 4). HER2 was not a significant independent factor for positive resection margin (odds ratio, 5.68; 95% CI, 2.72–11.82).

DISCUSSION

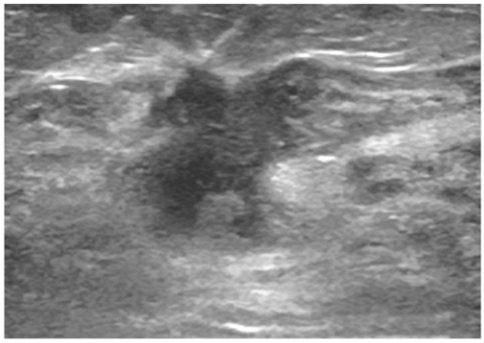
Until now, many risk factors for positive resection margin have been identified, including younger age, larger tumour size, multifocal lesions, lobular carcinoma, the presence of lymphovascular invasion, the presence of ductal carcinoma *in situ* (DCIS) and nodal metastasis.[7–11,16,17] As far as we know, this is the first study to reveal that BPE is a significant independent factor associated with positive resection margin.

There are many studies investigating the association of menstrual cycle and BPE on MRI reporting various results. BPE was lowest in the second week of menstrual cycle and highest in the first and fourth weeks.[18] In another study, breast parenchymal enhancement was lowest in the second and third week of menstrual cycle.[19] In a recent study, fatty breasts showed the highest parenchymal enhancement in the fourth week and the lowest enhancement in the second week, while dense breasts showed the highest parenchymal enhancement in the third week and the lowest enhancement in the fourth week of the menstrual cycle in pre-menopausal patients.[13] There are several studies reporting the clinical influence of BPE in daily practice. Strong BPE could cause many false-positive or false-negative interpretations.[20] Moderate or marked BPE was associated with abnormal interpretation rate compared with minimal or mild BPE; however, it was not associated with biopsy rate, positive predictive value, sensitivity or specificity of MRI.[21,22]

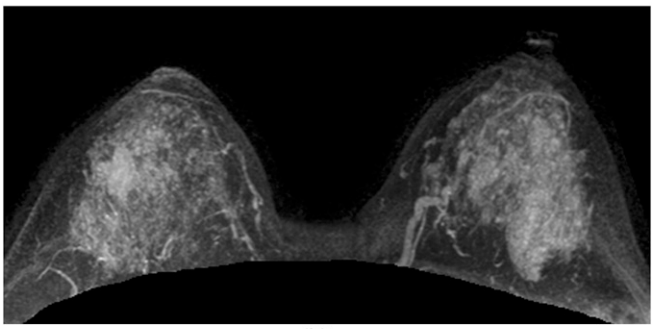
There are some controversies about the advantage of pre-operative MRI for reducing positive resection margin. In the study of Mann et al,[23] pre-operative breast MRI was useful for reducing re-excision rate without increasing the mastectomy rate in patients with invasive lobular carcinoma. By contrast, Pengel et al[24] revealed that the rate of incomplete tumour excision was not significantly different between patients with pre-operative MRI *vs* those without MRI. However, in cases of histologic type of invasive ductal carcinoma (IDC), pre-operative MRI was significantly associated with lower rate of incomplete excision. In a recent randomized controlled trial,[25] addition of breast MRI was not significantly associated with reduced re-operation rate.

However, the accuracy of extent measurement is strongly influenced by the degree of BPE. Focally, asymmetrically or

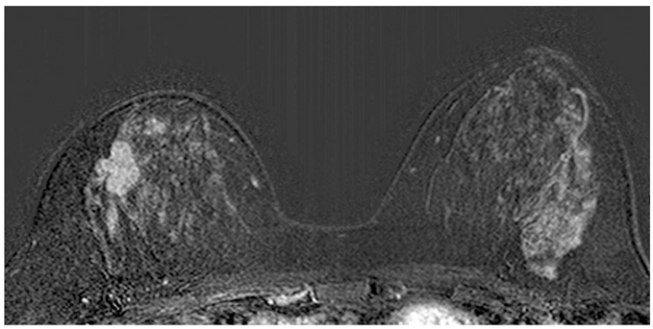
Figure 1. Invasive ductal carcinoma in a 35-year-old female with marked background parenchymal enhancement (BPE). (a) Ultrasound examination shows a 1.7-cm irregular hypoechoic mass at 10 h direction of the right breast. Maximum-intensity projection (b) and axial subtraction image (c) show a mass with irregular shape and margin in the right breast with moderate BPE. Patient underwent breast-conserving surgery and, histopathologically, the medial margin was positive. Intraductal component was about 5%.



(a)



(b)



(c)

Table 4. Logistic regression analysis for variables associated with margin status

Variables	β	Standard error	Odds ratio	95% confidence interval
EIC	1.736	0.374	5.675	2.724–11.821
Background parenchymal enhancement	0.872	0.354	2.391	1.195–4.783
HER2	0.395	0.412	1.484	0.661–3.329

EIC, extensive intraductal component; HER2, human epidermal growth factor receptor 2.

regionally distributed BPE could cause false-positive interpretation, and by contrast, additional malignant foci around the index cancer could be masked by adjacent parenchymal enhancement causing false-negative interpretation.[26,27] The accuracy was significantly lower in patients with moderate or marked BPE causing underestimation or overestimation of lesion extent.[28,29] Our results revealed that of 216 patients with weak BPE, only 21 (10%) patients had positive resection margin, and of 98 patients with strong BPE, 23 (23%) had positive resection margin. Positive EIC and strong BPE were two independent factors significantly associated with positive resection margin in both univariate and multivariate analyses. Positive EIC showed more significant association with positive resection margin than did strong BPE, with higher odds ratio. Our result is consistent with previous studies reporting that EIC was significantly associated with positive resection margin.[7,9,10]

In our univariate analysis, known risk factors, including larger tumour size, higher nuclear and histological grade and the presence of lymphovascular invasions were not significantly associated with positive resection margin. Instead, HER2 tended to be associated with positive resection margin ($p = 0.08$). One retrospective study by Miller et al[16] suggested increased risk of positive resection margin associated with HER2 positivity. Similarly, Atalay and Irkkan[30] reported increased risk of having residual disease on re-excision specimen with initial positive margin associated with HER2 positivity. In addition, a recent study reported that the extent of tumour was more accurately measured in patients with HER2-negative tumour than in patients with HER2-positive tumour.[29] We assume that HER2 overexpression is more frequent in DCIS than IDC,[31,32] and therefore, it can cause inaccurate measurement of lesion extent and positive resection margin.

There are several limitations in our study. First, it was a retrospective study and comprised patients who had pathologically proven breast cancers. It could cause a selection bias. Second, MR scanners and protocols were not uniform. We evaluated BPE using a combination of post-contrast fat-suppressed T_1 weighted image, subtraction and MIP images. Different MR scanners and protocols could cause some bias.

In conclusion, strong BPE is a significant independent factor for positive resection margin along with positive EIC. Therefore, we should pay attention to patients who have strong BPE on MRI and try to perform MRI during the period of lowest parenchymal enhancement.

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