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Preoperative breast MRI features associated with positive or close margins in breast-conserving surgery

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Abstract

Purpose: To determine preoperative magnetic resonance imaging (MRI) features associated with positive or close margins in patients with breast cancer who underwent breast-conserving surgery (BCS).

Materials and methods: A retrospective review identified 249 patients with invasive ductal carcinoma (IDC) who underwent preoperative MRI and BCS as a primary procedure between 2008 and 2010. The MR images were reviewed for descriptions of findings with no new interpretations made. Margins were defined as positive (tumor touching the inked specimen margin), close (< 2 mm tumor-free margin), or negative (≥ 2 mm tumor-free margin). Multivariate logistic regression analysis was performed to evaluate imaging and clinical factors predictive of positive or close margins.

Results: Of the 249 patients, 83 (33.3%) had positive or close margins and 166 (66.7%) had negative margins on the initial BCS specimen. Multivariate analysis showed that multifocal disease (odds ratio, 4.8; 95% CI, 1.9–12.2; $p = 0.001$), nonmass enhancement lesion (odds ratio, 3.0; 95% CI, 1.5–6.2, $p = 0.003$), greater background parenchymal enhancement (odds ratio, 2.5;

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95% CI, 1.1–5.6; $p = 0.023$), larger lesion size (odds ratio, 1.3; 95% CI, 1.0–1.7, $p = 0.032$), and presence of ductal carcinoma in situ on needle biopsy (odds ratio, 2.4; 95% CI, 1.3–4.6; $p = 0.008$) were independent predictors of positive or close margins.

Conclusions: Multifocal disease, nonmass enhancement lesion, or greater background parenchymal enhancement on preoperative breast MRI were significantly associated with positive or close margins. Identifying these MRI features before surgery can be helpful to reduce the reoperation rate in BCS.

Keywords

preoperative MRI; breast cancer; breast-conserving surgery; resection margins

1. Introduction

Breast-conserving surgery (BCS) is the standard therapy for breast cancer and the preferred surgical approach for most patients with early breast cancer [1]. BCS requires complete removal of the tumor with histologically negative resection margins. In cases of positive or close resection margins, patients undergo additional surgery [2]. It has been shown that local recurrence is reduced by negative resection margins [3]. Although survival of BCS followed by radiotherapy is similar to that of mastectomy, patients with BCS have a higher risk of positive margins [1, 2, 4]. Approximately 17% to 27% of patients attempting BCS undergo a reexcision [5–8]. However, repeated excisions result in additional stress for the patient, poor cosmetic outcome, and increased costs.

Patient and tumor factors have been shown to influence the need for reoperation, and nomograms for predicting positive margins have been developed [6–10]. Factors related to reexcision surgery include younger age, larger tumor size, lobular histologic subtype, and positive estrogen receptor (ER) status [6–8]. Predictors of positive margins include mammographic microcalcifications, multifocality, presence of ductal carcinoma in situ (DCIS), and lobular histology [9, 10]. Preoperative prediction of the likelihood of positive margins may be important to decrease the number of reexcisions in BCS [6]. It has been shown that DCIS component associated with invasive breast cancer is a major influencing factor [11]. Breast MRI can improve depiction of DCIS components and MR-guided needle biopsy or MR-guided surgery may lead to improved surgical outcomes [12].

MRI is the most sensitive imaging modality and can detect additional sites of malignancy that are occult at mammography and ultrasound [13, 14]. A meta-analysis of 19 studies showed preoperative breast MRI detects multifocal or multicentric disease in 16% of patients with breast cancer [15]. Despite the high sensitivity of MRI, prior studies have shown conflicting results with respect to the effect of preoperative MRI on surgical outcomes. Several studies showed that the use of preoperative MRI reduces reexcision rates, whereas others reported no significant reduction [16–21]. We previously published a study that compared reexcision rates between the preoperative MRI and the matched control groups in patients with early-stage breast cancer [17]. In that study, we found that reexcision rates following BCS were significantly lower in the preoperative MRI group. However, we did not evaluate the MRI features associated with positive or close margins. There are only a

few studies reporting on preoperative MRI features associated with positive margins after BCS in patients with breast cancer. Furthermore, those prior studies focused on a single MRI finding such as background parenchymal enhancement (BPE) level or lesion type, and included variable tumor histologic types [22, 23]. The purpose of our study was to determine preoperative breast MRI features associated with positive or close margins in patients with invasive ductal cancer (IDC) who underwent BCS.

2. Materials and Methods

2.1. Patient population

In this retrospective institutional review board-approved study, 631 women with IDC who underwent preoperative breast MRI between January 2008 and December 2010 were identified. Of these, 206 patients were excluded for the following reasons: neoadjuvant chemotherapy ($n = 100$), excisional biopsy ($n = 52$), prior history of breast cancer ($n = 33$), unavailable surgical pathology report ($n = 11$), occult primary breast cancer ($n = 6$), and bilateral cancer ($n = 4$). Of the remaining 425 patients, 249 (58.6%) initially underwent BCS. Therefore, our study population constituted 249 patients who underwent preoperative MRI and BCS as a primary procedure.

2.2. Breast MRI technique

MRI examinations were performed with the patient prone on a 1.5- or 3.0-T commercially available system (Signa or Signa HDX; GE Medical Systems, Waukesha, WI, USA) using a dedicated eight surface breast coil. The imaging sequence included a localizing sequence followed by a sagittal non-fat-suppressed T1-weighted sequence and a sagittal fat-suppressed T2-weighted sequence (repetition time [TR, msec]]/echo time [TE, msec], 4,000/85; in-plane resolution, 1.1 × 1.4 mm^2 to 1.3 × 1.6 mm^2). A T1-weighted 3D fat-suppressed fast spoiled gradient-echo sequence was performed before and three times after a rapid bolus injection of gadopentetate dimeglumine (Magnevist; Berlex Laboratories/Bayer Health Care Pharmaceuticals, Montville, NJ) administered IV (0.1 mml/L [milimole per liter] per kilogram of body weight), at a rate of 2 ml/sec with an automatic injector (Medrad, Pittsburgh, PA, USA) followed by a 20-mL saline flush and a 20-second scan delay. After contrast injection and saline bolus injection, sagittal images were obtained using the following parameters at 1.5T: TR/TE, 7.4/4.2; flip angle, 10°; acquisition matrix, 256 × 192; slice thickness, 3 mm with no gap; and temporal resolution, ~90 seconds. The parameters at 3.0T were the same except for the TR/TE, 5.9/2.2. For the fat-suppression technique, SPECIAL (spectral inversion at lipid) was used in T1-weighted imaging and IDEAL (iterative decomposition of water and fat with echo asymmetry and least-squares estimation) was used in T2-weighted imaging. In addition, subtraction and maximum intensity projection images were generated.

2.3. Data collection

One radiologist (with 7 years of experience in breast imaging) reviewed the breast MR images and reports for descriptions of BPE level (minimal, mild, moderate, or marked), amount of fibroglandular tissue (FGT; almost entirely fat, scattered areas of FGT, heterogeneous FGT, or extreme FGT), lesion type (mass or nonmass enhancement [NME]),

and multifocal disease. All MRI findings were based on the MR report with no new interpretations made. Because only IDC was included in this study, there were no index tumors presenting as enhancing foci. Multifocal disease was defined as findings within the same breast quadrant or less than 4 cm away from the index lesion [13, 14]. All suspicious findings underwent either percutaneous or surgical biopsy and were correlated with the pathologic reports. Lesion size was determined on the basis of the largest dimension provided in the MR report. In all cases, mammogram reports were reviewed to classify index cancers according to the Breast Imaging and Reporting Data System lexicon [24].

Data collected included age at diagnosis, mode of detection (screening mammogram, screening ultrasound or MRI, or palpable symptom), biopsy method (stereotactic, US-guided, or MRI-guided), biopsy pathology, index tumor size (invasive component), histologic tumor type, tumor grade (histologic grade or if not available, nuclear grade), surgical margin status, axillary nodal status, ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status. In terms of biopsy method and pathology, index tumor biopsies were recorded. All biopsies were performed according to previously described techniques [25, 26]. Initial pathology reports were used to assess the surgical margin status, and the closest distance between tumor cells and the resection margin was recorded. According to the most recent guidelines, a distance of 2 mm or greater to the inked specimen margin was classified as a negative margin. A distance of less than 2 mm was considered close and lesions touching the inked specimen margin were considered positive [27]. For multifocal disease, all reported MR findings that were considered suspicious were correlated with pathologic reports from a percutaneous core-needle or surgical biopsy. ER and PR status was defined as positive if immunohistochemistry (IHC) staining results were greater than 1% [28]. HER2 status was defined as positive if IHC staining result was reported as 3+ or if fluorescent in situ hybridization result showed *HER2* gene amplification [29]. For molecular subtype classification, patients were classified into three subtypes: ER-positive/HER2-negative (PR may be positive or negative), HER2-positive (ER and PR may positive or negative), and triple-negative (ER negative, PR negative, and HER2 negative) [30, 31].

2.4. Statistical analysis

Close and positive margins were grouped to allow a binary outcome of margin status as either negative or close/positive. Univariate analysis was performed to compare clinical, pathologic, and imaging characteristics between the two groups. The chi-square or Fisher exact test was used for categorical variables, and the t-test or Wilcoxon rank-sum test was used to compare continuous variables. Multivariate logistic regression analysis with backward feature selection was performed to evaluate the independent factors associated with close/positive margins. Variables with $p < 0.1$ at univariate analysis were included in a final multivariate model. Categorical variables were treated as dichotomous variables. Area under the receiver operating characteristic curve (AUC) and its 95% confidence interval (CI) were reported to assess performance of the multivariate model. Optimal cutoff value to predict positive or close margins was identified from the highest Youden index. Positive predictive value (PPV) and negative predictive value (NPV) of the multivariate model were calculated. All statistical tests were two-sided, and $p < 0.05$ was considered statistically

significant. All analyses were performed using SAS software (v. 9.3, SAS Institute, Cary, NC).

3. Results

Of the 249 patients with IDC and preoperative MRI, 83 (33.3%) had positive ($n = 48$) or close ($n = 35$) margins and 166 (66.7%) had negative margins on the initial BCS specimen. Patients with close/positive margins were younger on average than those with negative margins (49.0 years vs 52.4 years, $p = 0.018$) (Table 1). The proportions of biopsy pathology between the two groups were statistically significant different ($p < 0.001$). Patients with close/positive margins were significantly more likely to have concurrent DCIS (coexistence with IDC and DCIS or underestimation of IDC) (73.5% vs 48.2%, $p < 0.001$). A stereotactic biopsy was used in 19 of 83 (22.9%) patients with close/positive margins compared with the use of a stereotactic biopsy in 17 of 166 (10.2%) patients with negative margins ($p = 0.011$). The proportions of the lesions by mode of detection were similar in both groups: screening mammogram (50.6% vs 47.6%), screening ultrasound or MRI (13.3% vs 15.7%), and palpable symptom (36.1% vs 36.7%) ($p = 0.850$). The mean pathologic tumor size was 1.4 cm (SD, 0.9 cm; range, 0.1–4.5 cm) for the close/positive margin group and the mean pathologic tumor size was 1.3 cm (SD, 0.8 cm; range, 0.1–4.0 cm) for the negative margin group ($p = 0.873$). There were no statistically significant differences between the two groups in histologic tumor type ($p = 0.756$), tumor grade ($p = 0.856$), axillary lymph node status ($p = 0.697$), and breast cancer molecular subtype ($p = 0.555$).

The lesion size on MRI was significantly larger in patients with close/positive margins compared to those with negative margins (mean, 2.3 cm; range, 0.6–6.3 cm vs mean, 1.6 cm; range, 0.3–6.4 cm, respectively; $p = 0.002$) (Table 2). Multifocal disease was reported significantly more frequently in patients with close/positive margins (19.3% vs 6.0%, $p = 0.001$). NME lesions were significantly more commonly reported in patients with close/positive margins (44.6% vs 15.1%, $p < 0.001$). There was no significant difference in the distribution of BPE level ($p = 0.130$) or FGT amount ($p = 0.645$). At mammography, calcifications or masses with associated calcifications were more frequently observed in patients with close/positive margins (32.5% vs 17.5%; $p = 0.007$).

Multivariate logistic regression analysis confirmed that multifocal disease (odds ratio [OR], 4.8; 95% CI, 1.9–12.2; $p = 0.001$), NME lesion (OR, 3.0; 95% CI, 1.5–6.2; $p = 0.003$), higher BPE level (OR, 2.5; 95% CI, 1.1–5.6; $p = 0.023$), larger size on MRI (OR, 1.3; 95% CI, 1.0–1.7; $p = 0.032$), and the presence of DCIS on needle biopsy (OR, 2.4; 95% CI, 1.3–4.6; $p = 0.008$) were significant predictors of close/positive margins (Table 3). The AUC value for the multivariate model was 0.75 (95% CI, 0.69–0.82) (Fig. 1). The NPV and PPV were 81.3% (135 of 166) and 62.7% (52 of 83), respectively. Representative images of positive and negative margins are shown in Figs. 2 and 3.

4. Discussion

This study demonstrates that several MRI features such as multifocal disease, NME lesion, greater BPE, and larger lesion size have a higher association with positive or close margins

in patients with IDC undergoing BCS. The presence of DCIS on needle biopsy was also significantly associated with positive or close margins. Our findings are consistent with the results from previous studies that showed multifocal disease, large tumor size, and the presence of DCIS component as preoperative risk factors for positive margins [6, 10, 32]. Pleijhuis et al. [10] developed a nomogram for predicting positive margins based on multicenter data, and included the absence of preoperative breast MRI as one of predictive variables. In a nomogram reported by Shin et al. [9], variables predicting for positive margins included microcalcifications on mammography, high breast density, 0.5 cm difference in tumor size between MRI and ultrasound, presence of DCIS, and lobular histology. However, those prior studies did not evaluate preoperative MRI features associated with positive margins in BCS.

Breast MRI detects additional unsuspected multifocal or multicentric disease in the preoperative setting. However, detection of additional disease at preoperative breast MRI may not translate into improved clinical outcomes. Sung et al. [17] reported that reexcision rates among patients with early breast cancer undergoing conservation were lower among women who underwent MRI, but preoperative MRI did not affect rates of local or regional recurrence or disease-free survival. Preoperative MRI could theoretically have helped to avoid positive margins, although conflicting results regarding the effect of MRI on the reexcision rate have been reported [16–21]. Reexcision rates for BCS have shown a wide variation from 0% to 60%, because there have been mixed definitions of the acceptable margin width [5, 33, 34]. In a recent study using the National Cancer Data Base, the rate of repeat surgeries after initial BCS varied by patient, tumor, and facility factors in patients with stage 0 to II breast cancer [5]. This suggests that the use of preoperative MRI may not be the only factor that influences the reexcision rate. Additionally, multifocal and multicentric disease is more frequently found on MRI in HER2-positve breast cancer [30, 35]. A randomized prospective multicenter trial, the Alliance A011104/American College of Radiology Imaging Network 6694, is underway to assess the effect of preoperative MRI on surgical outcomes in patients eligible for BCS [36]. This study will focus on patients with HER2-positive or triple-negative breast cancer. Thus, the targeted use of preoperative MRI and adoption of guidelines for surgical margins would help reduce reexcision rates [34].

We found that lesions presenting as NME and greater BPE were significantly more likely to show positive or close margins. Our finding is supported by a previously published study in which NME lesions or masses with associated NME showed a higher rate of reexcision [22]. In fact, one prior study showed that moderate or marked BPE and the presence of an extensive intraductal component were independent factors for positive margins [23]. In that prior study, the authors attempted to evaluate whether qualitative assessment of BPE would be associated with positive margins. Our multivariate model, however, included multiple MRI and mammography findings as well as clinicopathologic features. Furthermore, only patients with IDC were included in the study. Therefore, our study provides more conclusive evidence that multifocal disease, NME lesion, and higher BPE are preoperative MRI features associated with positive or close margins in patients with IDC. The rate of positive margins may be decreased in breast cancer surgery with MRI-guided localization and bracketing [12, 37]. If preoperative MRI shows multifocal disease and/or associated NME,

MRI-guided surgery can potentially help reduce the rate of positive margin and reexcision in patients with invasive breast cancer.

The association of DCIS on needle biopsy with positive margins after BCS has been previously reported [6, 9, 33, 38]. Similar to prior studies, we found that presence of DCIS on biopsy was a significant predictor of positive or close margins in multivariate analysis. DCIS could be diagnosed with needle biopsy when IDC is present adjacent to a relatively large area of DCIS [38]. It is possible that DCIS in the biopsy specimen that is more likely to exhibit NME lesions or calcifications may be a risk factor of positive margins in patients with IDC.

Our study had several limitations. This was a single-institution retrospective study over a limited time period. However, our surgeons had access to all images and were able to review any imaging findings at their discretion. All imaging reports provide detailed descriptions of any findings as well as the corresponding image numbers. We could not control for potential selection bias for women undergoing preoperative MRI vs those not undergoing BCS. Our study included only IDC patients with or without DCIS and therefore our findings cannot be applied to other tumor histologies. We also did not prove whether the use of preoperative MRI reduces the reexcision rate. However, this is beyond the scope of the current study.

In summary, we have identified preoperative MRI features associated with a positive or close margin following BCS in patients with IDC: multifocal disease, NME lesion, larger size, and higher BPE. The presence of DCIS on needle biopsy increased the odds of a positive or close margin. These factors can be helpful in predicting the possibility of reexcision. Further prospective studies are needed to confirm our results.

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Highlights

- Breast MRI findings before surgery are associated with positive resection margins.
- It is important to detect nonmass enhancement or multifocality in invasive cancer.
- Use of preoperative MRI can help reduce the rate of positive margins and reexcisions.

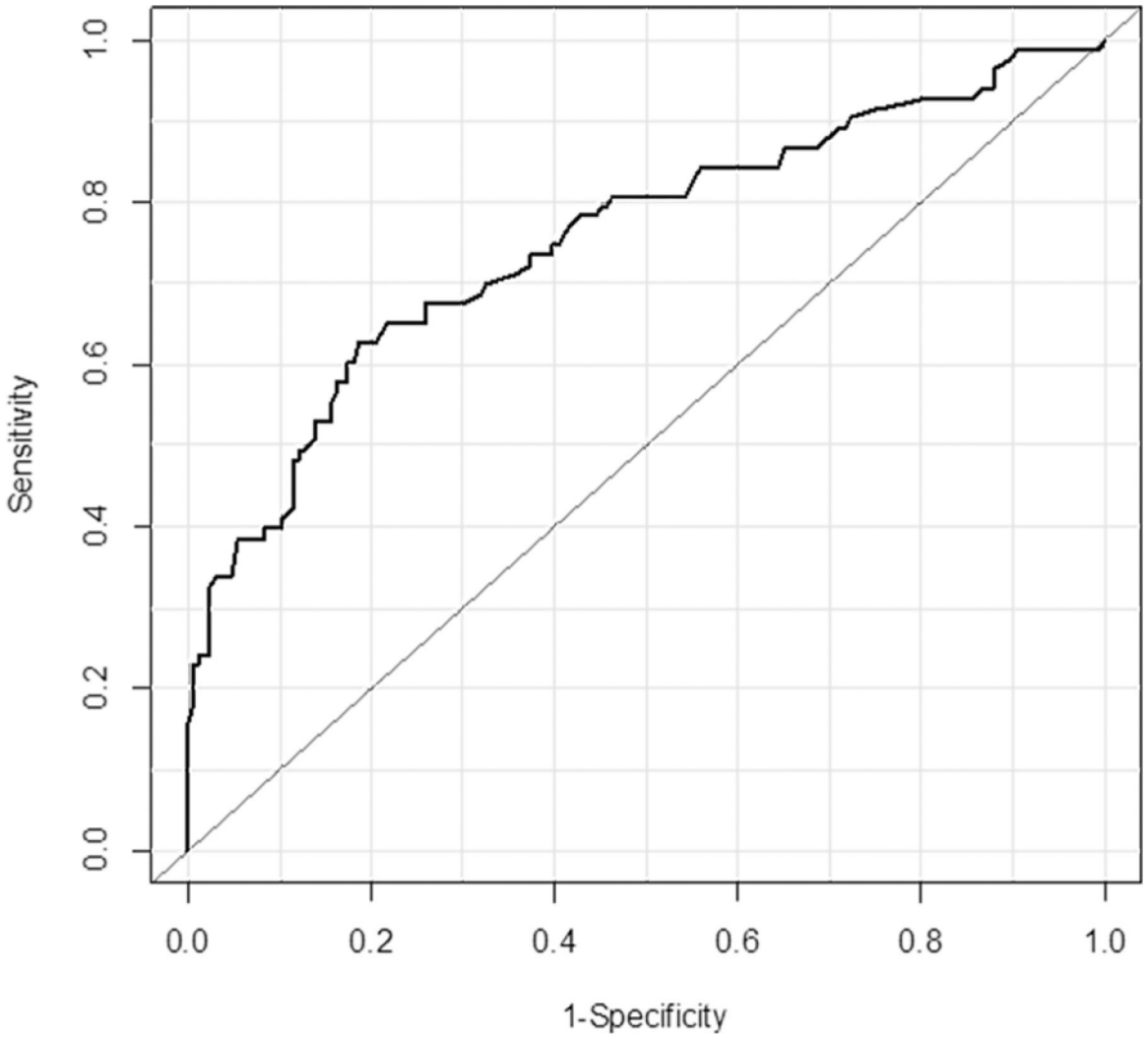

Fig. 1.
Graph shows the receiver operating characteristic curve for the multivariate model.

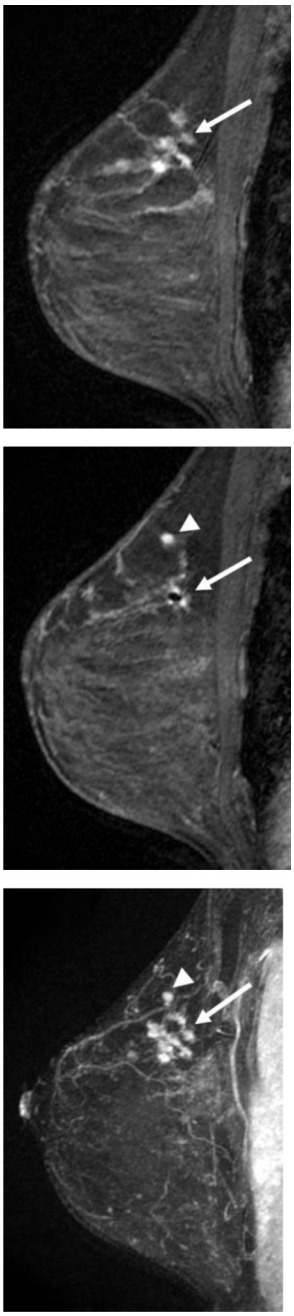

Fig. 2.

45-year-old woman with breast cancer and positive surgical margins. Sagittal T1-weighted fat-suppressed postcontrast (A and B) and sagittal subtraction maximum intensity projection (C) MR images of left breast show 3 cm clumped nonmass enhancement containing the signal void artifact from a biopsy clip (arrows) and multifocal disease (arrowheads) in the upper outer quadrant. Invasive ductal carcinoma (IDC) and ductal carcinoma in situ (DCIS) were diagnosed in the biopsy specimen. Patient underwent MR-guided needle localization. Surgical margins were focally positive for IDC and DCIS. Pathology revealed three foci of IDC.

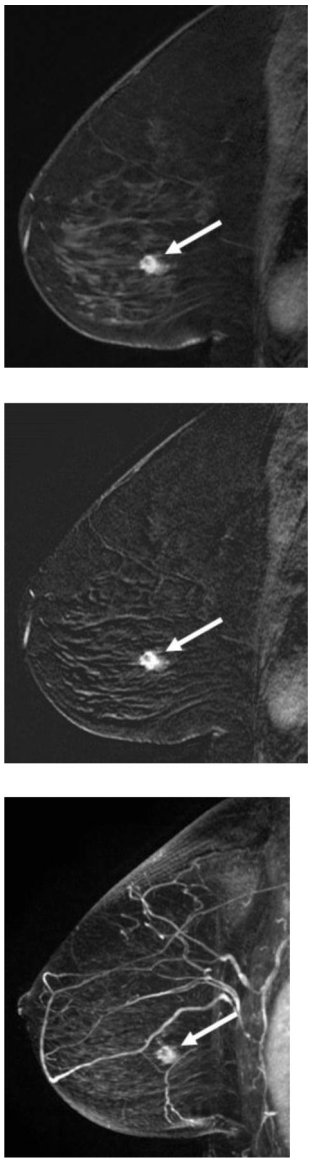

Fig. 3.

58-year-old woman with breast cancer and negative surgical margins. Sagittal T1-weighted fat-suppressed postcontrast (A), sagittal postcontrast subtraction (B), and sagittal subtraction maximum intensity projection (C) MR images of left breast show 1.5 cm irregular enhancing mass (arrows) in the lower outer quadrant. There is no evidence of multifocal disease. Absence of ductal carcinoma in situ was noted in the biopsy specimen. Pathology revealed unifocal invasive ductal carcinoma with negative surgical margins.

Table 1.

Patient and tumor characteristics.

Characteristic	All (*n* = 249)	Close/Positive margins (*n* = 83)	Negative margins (*n* = 166)	*P*
Age (years)*				
Mean ± SD	51.2 ± 10.8	49.0 ± 10.5	52.4 ± 10.9	0.018
Range	21–84	25–78	21–84	
Mode of detection				0.850
Screening mammogram	121 (48.6)	42 (50.6)	79 (47.6)	
Screening US or MRI	37 (14.9)	11 (13.3)	26 (15.7)	
Palpable symptom	91 (36.5)	30 (36.1)	61 (36.7)	
Biopsy method				.
Stereotactic	36 (14.5)	19 (22.9)	17 (10.2)	0.011
US	203 (81.5)	63 (75.9)	140 (84.3)	
MRI	10 (4.0)	1 (1.2)	9 (5.4)	
Biopsy pathology				< 0.001
DCIS only	20 (8.0)	15 (18.1)	5 (3.0)	
Invasive only	108 (43.4)	22 (26.5)	86 (51.8)	
Invasive and DCIS	121 (48.6)	46 (55.4)	75 (45.2)	
Presence of DCIS on biopsy				< 0.001
Yes	141 (56.6)	61 (73.5)	80 (48.2)	
No	108 (43.4)	22 (26.5)	86 (51.8)	
Size of invasive cancer (cm)				0.873
Mean ± SD	1.3 ± 0.8	1.4 ± 0.9	1.3 ± 0.8	
Range	0.1–4.5	0.1–4.5	0.1–4.0	
Histologic type				0.756
Ductal	237 (95.2)	80 (96.4)	157 (94.6)	
Ductal and lobular	12 (4.8)	3 (3.6)	9 (5.4)	
Tumor grade				0.856
Low or intermediate	106 (42.6)	36 (43.4)	70 (42.2)	
High	143 (57.4)	47 (56.6)	96 (57.8)	
Axillary lymph node status				0.697
Negative	173 (69.5)	59 (71.1)	114 (68.7)	
Positive	76 (30.5)	24 (28.9)	52 (31.3)	
Breast cancer subtype				0.555
ER+/HER2-	186 (74.7)	64 (77.1)	122 (73.5)	
HER2+	29 (11.6)	11 (13.3)	18 (10.8)	
TN	31 (12.5)	8 (9.6)	23 (13.9)	
Unknown	3 (1.2)	0 (0)	3 (1.8)	

Note—Unless otherwise indicated, data are numbers of patients, and data in parentheses are percentages. SD = standard deviation, US = ultrasound, DCIS = ductal carcinoma in situ, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, TN = triple negative

Table 2.

Comparison of imaging characteristics between patients with positive or close margins and those with negative margins.

Characteristic	Close/Positive margins (*n* = 83)	Negative margins (*n* = 166)	*P*
Lesion size on MRI (cm)			0.002
Mean ± SD	2.3 ± 1.5	1.6 ± 0.9	
Range	0.6–6.3	0.3–6.4	
Lesion type			< 0.001
Mass	46 (55.4)	141 (84.9)	
NME	37 (44.6)	25 (15.1)	
Multifocal disease			0.001
Absent	67 (80.7)	156 (94.0)	
Present	16 (19.3)	10 (6.0)	
BPE			0.130
Minimal	12 (14.5)	42 (25.3)	
Mild	31 (37.3)	62 (37.4)	
Moderate	26 (31.3)	46 (27.7)	
Marked	14 (16.9)	16 (9.6)	
BPE (dichotomous)			0.050
Minimal	12 (14.5)	42 (25.3)	
Mild, moderate, or marked	71 (85.5)	124 (74.7)	
FGT			0.645
Almost entirely fatty	1 (1.2)	5 (3.0)	
Scattered	13 (15.7)	29 (17.5)	
Heterogeneous	55 (66.3)	112 (67.5)	
Extreme	14 (16.9)	20 (12.0)	
FGT (dichotomous)			0.496
Almost entirely fatty or scattered	14 (16.9)	34 (20.5)	
Heterogeneous or extreme	69 (83.1)	132 (79.5)	
Mammographic findings			0.003
Mass	26 (31.3)	84 (50.6)	
Calcification	21 (25.3)	16 (9.6)	
Mass with associated calcifications	6 (7.2)	13 (7.8)	
Other[a]	30 (36.1)	53 (31.9)	
Mammographic calcifications[b]			0.007
Present	27 (32.5)	29 (17.5)	
Absent	56 (67.5)	137 (82.5)	

Note—Unless otherwise indicated, data are numbers of patients, and data in parentheses are percentages. SD = standard deviation, NME = nonmass enhancement, BPE = background parenchymal enhancement, FGT = fibroglandular tissue

[a]Other includes focal asymmetry, architectural distortion, and mammographically occult lesion

[b]Calcification or mass with associated calcifications

Table 3.

Multivariate logistic regression analysis for factors associated with positive or close margins.

Variable	OR	95% CI	*P*
Lesion size on MRI (cm)	1.3	1.0–1.7	0.032
Multifocal disease	4.8	1.9–12.2	0.001
Lesion type on MRI (mass vs NME)	3.0	1.5–6.2	0.003
BPE (minimal vs mild, moderate, or marked)	2.5	1.1–5.6	0.023
Presence of DCIS on needle biopsy	2.4	1.3–4.6	0.008

Note—OR = odds ratio, NME = nonmass enhancement, BPE = background parenchymal enhancement, DCIS = ductal carcinoma in situ, MRI = magnetic resonance imaging