**Original Article** | Breast Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2019.0674
Korean J Radiol 2020;21(8):946-954



Korean Journal of Radiology
KJR

# Preoperative Magnetic Resonance Imaging Features Associated with Positive Resection Margins in Patients with Invasive Lobular Carcinoma

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**Objective:** To investigate preoperative magnetic resonance imaging (MRI) findings associated with resection margin status in patients with invasive lobular carcinoma (ILC) who underwent breast-conserving surgery.

**Materials and Methods:** One hundred and one patients with ILC who underwent preoperative MRI were included. MRI (tumor size, multifocality, type of enhancing lesion, distribution of non-mass enhancement [NME], and degree of background parenchymal enhancement) and clinicopathological features (age, pathologic tumor size, presence of ductal carcinoma *in situ* [DCIS] or lobular carcinoma *in situ*, presence of lymph node metastases, and estrogen receptor/progesterone receptor/human epidermal growth factor receptor type 2 status) were analyzed. A positive resection margin was defined as the presence of invasive cancer or DCIS at the inked surface. Logistic regression analysis was performed to determine pre- and postoperative variables associated with positive resection margins.

**Results:** Among the 101 patients, 21 (20.8%) showed positive resection margins. In the univariable analysis, NME, multifocality, axillary lymph node metastasis, and pathologic tumor size were associated with positive resection margins. With respect to preoperative MRI findings, multifocality (odds ratio [OR] = 3.977, $p = 0.009$) and NME (OR = 2.741, $p = 0.063$) were associated with positive resection margins in the multivariable analysis, although NME showed borderline significance.

**Conclusion:** In patients with ILC, multifocality and the presence of NME on preoperative breast MRI were associated with positive resection margins.

**Keywords:** *Breast; Carcinoma, lobular; Magnetic resonance imaging; Margins of excision*

## INTRODUCTION

Breast-conserving surgery (BCS) with radiation therapy is the standard treatment for early-stage invasive breast cancer, and there is no significant difference in survival outcome between patients who undergo mastectomy and those who undergo BCS after 20 years of follow-up (1, 2). However, positive resection margins after BCS still pose difficulties in patient management. Positive resection margins are associated with a two-fold increase in the risk of ipsilateral breast tumor recurrence compared with negative margins (3). Consequently, almost 25% of patients who undergo BCS require additional re-excisions (4, 5).

Magnetic resonance imaging (MRI) has been reported to be more sensitive than mammography in detecting invasive cancer or ductal carcinoma *in situ* (DCIS), and is known to be more accurate than mammography or ultrasonography (US) in determining tumor diameters and margins and detecting multifocal, multicentric, and synchronous contralateral

**Received:** September 6, 2019 **Revised:** March 2, 2020
**Accepted:** March 3, 2020
This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2017R1D1A1B03035995).

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breast cancers (6-8). Several studies have investigated preoperative MRI features associated with resection margin status in invasive breast cancer, and reported that non-mass enhancement (NME) and less convex margins are associated with positive resection margins (9, 10).

However, these results were based on study populations composed mostly of patients with invasive ductal carcinoma (IDC) (9, 10). Furthermore, the majority of malignant NME lesions depicted by MRI in previous studies were confirmed as DCIS, so the sensitivity advantage of MRI over conventional imaging in depicting local tumor extent was reported to increase as DCIS component size increased, which would be less frequently detected in invasive lobular carcinoma (ILC) (11, 12). Therefore, it is unclear whether similar MRI features are associated with resection margin status in this subgroup.

Although the association between preoperative MRI and surgical outcomes in patients with breast cancer is still under debate, multiple studies have shown that preoperative MRI can significantly reduce re-excision rates after initial surgery in patients with ILC (13-16). Such results have been incorporated into recommendations from the European Society of Breast Cancer Specialists working group and the U.S. National Comprehensive Cancer Network guidelines (17, 18), in which preoperative MRI is recommended for patients with ILC and several other subgroups of patients with breast cancer.

However, to the best of our knowledge, no studies have reviewed specific preoperative MRI features related to surgical outcomes in patients with ILC. Despite the improved accuracy of MRI in demonstrating tumor extent, the increasing incidence of BCS is less clear in patients with ILC compared with those with IDC (19). Further identification of imaging features related to resection margin status would aid in patient management by enhancing confidence in performing BCS for ILC patients at low risk for positive margins, and identifying patients at high risk for re-excision who may require more aggressive surgery.

Therefore, the purpose of this study was to investigate preoperative MRI findings associated with resection margin status in patients with ILC.

## MATERIALS AND METHODS

### Patients

Our Institutional Review Board approved this retrospective study and waived the requirement to obtain informed consent. We conducted a retrospective chart review and identified 197 consecutive patients with newly diagnosed ILC who underwent preoperative MRI and surgery from May 2012 to August 2017. Patients who underwent vacuum-assisted biopsy (n = 4), surgical excisional biopsy (n = 2), or neoadjuvant chemotherapy before MRI (n = 17) were excluded. Among the remaining 174 patients, 73 patients who underwent total mastectomy were excluded. Finally, 101 patients (mean age, 52.1 years; range, 34–76 years) who underwent BCS were included in this study (Fig. 1).

### Histopathologic Analysis

Pathologic data including pathologic tumor size, histologic grade, estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor type 2 (HER2) status, and presence of metastasis in surgically resected axillary lymph nodes were obtained from the final pathologic reports. A tumor was considered ER/PR-positive when 10% of tumor cells in the testing sample had positively stained nuclei (20). The immunohistochemical staining results for HER2 were scored as 0, 1+, 2+, or 3+ according to the number of cells with positively stained membranes. Tumors with a score of 0 or 1+ were classified as HER2-negative, whereas tumors with a score of 3+ were classified as HER2-positive. In tumors with a score of 2+, additional gene amplification using silver *in situ* hybridization was performed to determine HER2 status. HER2 positivity was defined as a HER2/chromosome 17 ratio greater than 2.0 (21).

### Lesion Localization and Assessment of the Resection Margin

Preoperative wire localization of non-palpable lesions was performed with mammogram or US guidance. In all cases, intraoperative margin excision and frozen section analysis were performed. According to the Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline (22), a "positive resection margin" was defined as the presence of invasive cancer or DCIS at the inked surface of the resected specimen, in either the frozen section or permanent specimen. The presence of lobular carcinoma *in situ* (LCIS) at the inked surface was considered to indicate a negative resection margin.

### MRI Technique

Breast MRI examinations were performed using one of two 3T MRI systems: Discover 750 (GE Healthcare,

 https://doi.org/10.3348/kjr.2019.0674 

Milwaukee, WI, USA) or Ingenia (Philips Healthcare, Best, The Netherlands). Patients lay in the prone position, and imaging was performed with a dedicated phased array breast coil (8-channel [GE Healthcare] or 16-channel [Philips Healthcare]). Before the contrast agent was injected, a three-plane localizing sequence, axial T2-weighted fast spin echo and T2-stimulated inversion recovery sequence, and axial T1-weighted sequence with/without fat suppression were obtained. A bolus injection of a gadolinium-based contrast agent (Dotarem [gadoterate meglumine], Guerbet, Paris, France; Magnevist [gadopentetate dimeglumine], Berlex Laboratories, Wayne, NJ, USA; or Gadovist [gadobutrol], Bayer AG, Berlin, Germany) at a dose of 0.2 mmol/kg was administered at a rate of 2 mL/s, followed by a 20 mL saline flush. After the contrast agent was injected, T1-weighted three-dimensional (3D) dynamic contrast-enhanced images were acquired in the axial plane. This included one pre-contrast acquisition and six post-contrast bilateral axial acquisitions. Post-contrast images were obtained immediately after the contrast material was injected with no time delay. The length of each dynamic series was 63 (Discover 750) or 64 seconds (Ingenia). T1-weighted 3D delayed post-contrast images were later obtained in the sagittal plane. Image subtraction was performed after the dynamic series, including subtraction of the pre-contrast images from the 1st, 2nd, and 6th post-contrast images.

### Image Analysis

One board certified, breast-dedicated radiologist with 5 years of subspecialty experience in breast imaging reviewed the breast MR images according to the American College of Radiology Breast Imaging-Reporting and Data System (23). Tumor size was defined as the maximal diameter of the enhancing tumor on the early post-contrast subtraction images, which were obtained by subtracting the pre-contrast images from the 2nd post-contrast images acquired approximately 2 minutes after contrast material injection. Multifocal disease was defined as findings suspicious of additional sites of malignancy within the same quadrant as the index cancer. Enhancing lesions were divided into masses or NME. We further categorized the 101 cases into masses without NME and NME with or without a mass. In patients with NME, we analyzed NME distribution (focal, linear, or segmental). Background parenchymal enhancement (BPE) was categorized as minimal, mild, moderate, or marked based on a combination of pre-contrast, 2nd post-contrast T1-weighted images and subtraction images (23). After categorization, we dichotomized BPE into weak (minimal or mild) and strong (moderate or marked).

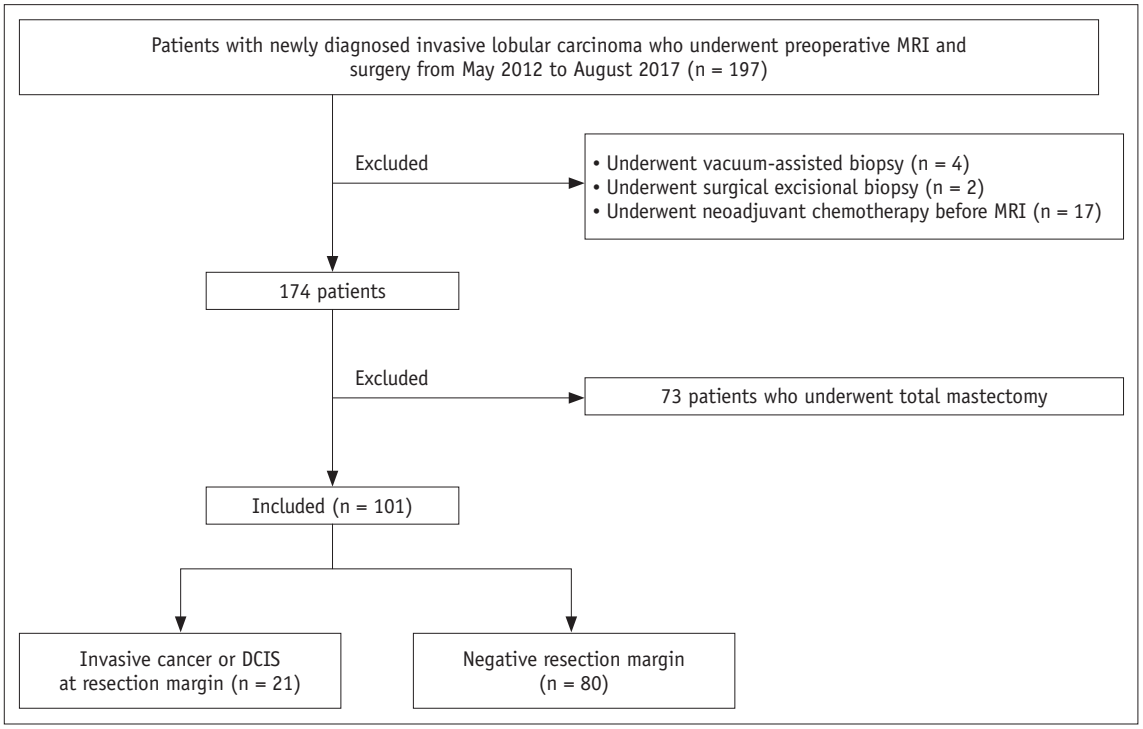


**Fig. 1. Patient selection diagram.** DCIS = ductal carcinoma *in situ*, MRI = magnetic resonance imaging


https://doi.org/10.3348/kjr.2019.0674

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### Statistical Analysis

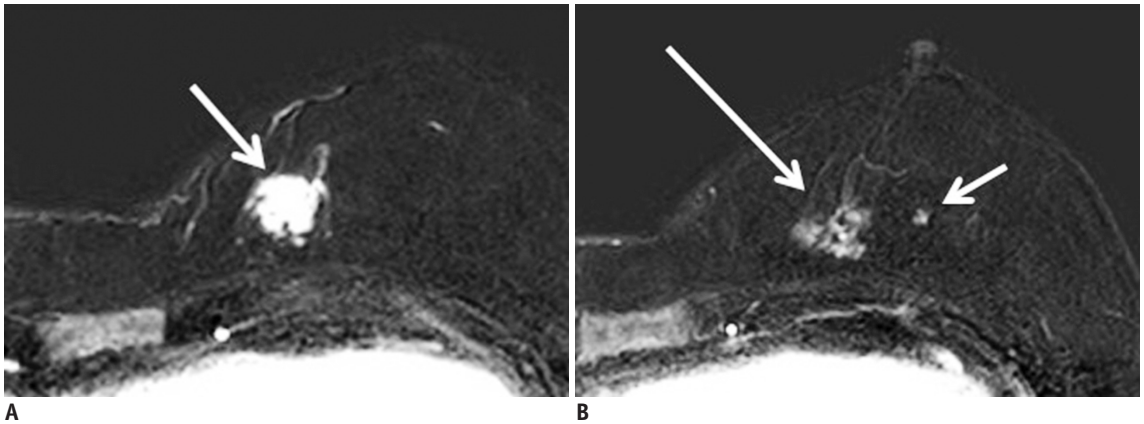
The patients were divided into two groups according to resection margin status. Clinicopathological variables and imaging features were compared between the groups using the chi-square test or Fisher's exact test for categorical variables and the independent *t* test for continuous variables. Univariable logistic regression analysis was used to identify variables associated with positive resection margins. Multivariable logistic regression analysis was used to identify preoperative variables significantly associated with positive resection margins, using only preoperative variables that showed a significant association ($p < 0.05$) in the univariate analysis. Additional multivariable logistic regression analysis was performed using preoperative and postoperative variables that showed a significant association ($p < 0.05$) in the univariate analysis. All statistical analyses were performed using SPSS version 23.0.0 (IBM Corp., Armonk, NY, USA), and a $p$ value < 0.05 was considered statistically significant.

## RESULTS

The mean pathologic tumor size was 15.2 mm (standard deviation, 8.9 mm; range, 3–43 mm). Among the 101 patients, 11 (10.8%) had combined DCIS and 62 (61.4%) had combined LCIS. Negative resection margins were achieved in all of the patients with combined DCIS. Of the 101 patients, 15 (14.9%) had axillary lymph node metastasis.

Among the 101 patients, 21 (20.8%) showed positive resection margins. Among the 21 patients with positive resection margins, 9 (42.9%) were converted to mastectomy at the time of the initial operation, 11 (52.4%) underwent additional local excision at the time of the initial operation, and 1 (4.8%) underwent re-excision later. Of the 11 patients who underwent immediate additional local excision, 3 (27.3%) later underwent mastectomy due to a positive margin on the re-excision specimen. Therefore, 12 (57.1%) of the 21 patients with positive resection margins were eventually converted to mastectomy (Figs. 2, 3).

**Fig. 3. 48 year-old female with invasive lobular carcinoma at right upper outer breast.** Preoperative axial early contrast-enhanced T1-weighted subtraction MR image show suspicious non-mass enhancement at right upper outer breast (arrow). At breast-conserving surgery, positive resection margin was confirmed by intraoperative frozen sectional analysis and additional local excision was performed immediately.



**A** **B**

**Fig. 2. 71-year-old female with invasive lobular carcinoma at left upper breast.**
**A, B.** Preoperative axial early contrast-enhanced T1-weighted subtraction MR images show malignant mass at left upper medial breast (arrow in **A**) with adjacent suspicious non-mass enhancement (long arrow in **B**) and additionally detected suspicious focus at left subareolar breast (short arrow in **B**). At breast-conserving surgery, positive resection margin was confirmed on intraoperative frozen sectional analysis and additional local excision was performed immediately.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When comparing MRI features between the positive and negative resection margin groups, the presence of NME (NME with/without mass) showed significant difference between the two groups (47.6% vs. 21.3%, $p = 0.015$). The incidence of multifocality on preoperative breast MRI also showed significant difference between the two groups (57.1% vs. 22.5%, $p = 0.002$). The mean pathologic tumor size was significantly larger in the positive resection margin group (22.3 ± 10.5 mm vs. 13.4 ± 7.5 mm, $p < 0.001$), and patients with positive resection margins had a higher rate of pathologic lymph node metastasis (38.1% vs. 8.8%, $p = 0.003$) (Table 1).

In the univariable logistic regression analysis, NME on preoperative breast MRI (odds ratio [OR] = 3.369; 95% confidence interval [CI] = 1.227–9.251; $p = 0.018$), multifocality on preoperative breast MRI (OR = 4.593; 95% CI = 1.671–12.623; $p = 0.003$), pathologic tumor size (OR = 1.117; 95% CI = 1.052–1.186; $p < 0.001$), and

**Table 1. Comparison of Variables according to Status of Resection Margin**

| Characteristics | Positive Resection Margin (n = 21) | Negative Resection Margin (n = 80) | *P* |
|---|---|---|---|
| Age (years) | 49.6 ± 8.9 | 52.8 ± 10.0 | 0.193 |
| Pathologic tumor size (mm) | 22.3 ± 10.5 | 13.4 ± 7.5 | < 0.001 |
| DCIS present | | | 0.114 |
| Yes | 0 (0.0) | 11 (13.8) | |
| No | 21 (100.0) | 69 (86.3) | |
| LCIS present | | | 0.288 |
| Yes | 15 (71.4) | 47 (58.8) | |
| No | 6 (28.6) | 33 (41.3) | |
| Lymph node metastases | | | 0.003 |
| Yes | 8 (38.1) | 7 (8.8) | |
| No | 13 (61.9) | 73 (91.3) | |
| Estrogen receptor | | | > 0.999 |
| Positive | 20 (95.2) | 75 (93.8) | |
| Negative | 1 (4.8) | 5 (6.3) | |
| Progesterone receptor | | | > 0.999 |
| Positive | 17 (81.0) | 64 (80.0) | |
| Negative | 4 (19.0) | 16 (20.0) | |
| HER2 | | | 0.635 |
| Positive | 2 (9.5) | 5 (6.3) | |
| Negative | 19 (90.5) | 75 (93.8) | |
| Wire localization | | | > 0.999 |
| Yes | 17 (81.0) | 64 (80.0) | |
| No | 4 (19.0) | 16 (20.0) | |
| Size on MRI (mm) | 20.1 ± 9.4 | 17.6 ± 8.5 | 0.234 |
| BPE | | | 0.368 |
| Weak | 15 (71.4) | 65 (81.3) | |
| Strong | 6 (28.6) | 15 (18.8) | |
| Presence of NME | | | 0.015 |
| Yes | 10 (47.6) | 17 (21.3) | |
| No | 11 (52.4) | 63 (78.8) | |
| Distribution of NME | | | 0.290 |
| Focal | 5 (50.0) | 12 (70.6) | |
| Linear/segmental | 5 (50.0) | 5 (29.4) | |
| Multifocality | | | 0.002 |
| Yes | 12 (57.1) | 18 (22.5) | |
| No | 9 (42.9) | 62 (77.5) | |

Unless otherwise indicated, data in parentheses are percentages. BPE = background parenchymal enhancement, DCIS = ductal carcinoma *in situ*, HER2 = human epidermal growth factor receptor type 2, LCIS = lobular carcinoma *in situ*, MRI = magnetic resonance imaging, NME = non-mass enhancement


https://doi.org/10.3348/kjr.2019.0674

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axillary lymph node metastasis (OR = 6.418; 95% CI = 1.985–20.750; $p$ = 0.002) were significantly associated with positive resection margins (Table 2).

In the multivariable logistic regression analysis of preoperative variables, multifocality on preoperative breast MRI was independently associated with positive resection margins (OR = 3.977; 95% CI = 1.408–11.231; $p$ = 0.009). NME on preoperative breast MRI tended to be associated with positive resection margins but showed borderline significance (OR = 2.741; 95% CI = 0.948–7.925; $p$ = 0.063) (Table 3).

**Table 2. Univariate Logistic Regression Analysis of Variables for Predicting Positive Resection Margins**

| Variables | OR | 95% CI | *P* |
|---|---|---|---|
| Pathologic tumor size (mm) | 1.117 | 1.052–1.186 | < 0.001 |
| DCIS present | | | |
| Yes | 0.000 | 0.000–0.000 | 0.999 |
| No | Ref | | |
| LCIS present | | | |
| Yes | 1.755 | 0.617–4.997 | 0.292 |
| No | Ref | | |
| Lymph node metastases | | | |
| Yes | 6.418 | 1.985–20.750 | 0.002 |
| No | Ref | | |
| Estrogen receptor | | | |
| Positive | 1.333 | 0.147–12.069 | 0.798 |
| Negative | Ref | | |
| Progesterone receptor | | | |
| Positive | 1.062 | 0.314–3.596 | 0.922 |
| Negative | Ref | | |
| HER2 | | | |
| Positive | 1.558 | 0.280–8.661 | 0.613 |
| Negative | Ref | | |
| Wire localization | | | |
| Yes | 1.062 | 0.314–3.596 | 0.922 |
| No | Ref | | |
| Size on MRI (mm) | 1.033 | 0.979–1.089 | 0.234 |
| BPE | | | |
| Weak | Ref | | |
| Strong | 1.733 | 0.577–5.211 | 0.327 |
| Presence of NME | | | |
| Yes | 3.369 | 1.227–9.251 | 0.018 |
| No | Ref | | |
| Distribution of NME | | | 0.290 |
| Focal | Ref | | |
| Linear/segmental | 2.400 | 0.475–12.130 | |
| Multifocality | | | |
| Yes | 4.593 | 1.671–12.623 | 0.003 |
| No | Ref | | |

CI = confidence interval, OR = odds ratio, Ref = reference

In the multivariable logistic regression analysis of pre- and postoperative variables, only multifocality on preoperative breast MRI (OR = 3.263; 95% CI = 1.034–10.304; $p$ = 0.044) and pathologic tumor size (OR = 1.092; 95% CI = 1.023–1.166; $p$ = 0.008) were independently associated with positive resection margins (Table 3).

## DISCUSSION

In our study, we found that multifocality on preoperative breast MRI was independently associated with positive resection margins in patients with ILC, whereas NME showed borderline significance. The rate of positive resection margins in our study was 20.8% (21/101), which was within the previously reported range of 20–70% (24, 25). As preoperative MRI is recommended for patients with ILC (17, 18), our study results could provide assurance in cases which are unlikely to yield positive margins at BCS, help identify high-risk cases in which the extent of resection should be increased, and allow patients to be warned about the higher likelihood of additional procedures being needed to attain negative margins.

Although ILC is the second most common histological subtype of breast cancer, it is more challenging clinically and radiologically to detect than IDC (26). Due to its infiltrative nature, both mammography and US show lower sensitivity in depicting ILC, and MRI has been shown to be particularly useful in the assessment of tumor extent in this subgroup (26). However, surgeons may still prefer to adopt a more aggressive local approach for these patients, mainly due to the higher risk of incomplete resection with BCS (19). In the past five years, several studies have reported that preoperative MRI can reduce re-excision rates in patients with ILC, but none has reviewed the MRI features of ILC related to surgical outcomes (13-16).

In past studies with study populations composed mostly of patients with IDC, NME on preoperative MRI, tumor size exceeding 5 cm, and multifocal lesions were factors associated with positive resection margins after BCS (9, 27, 28). As DCIS lesions commonly appear as NME on MRI (29, 30), previous studies suggested an association between DCIS components and positive resection margins (12). In one study, 55% (22/40) of the NME lesions around index cancer masses were malignant, with 81.8% (18/22) confirmed as DCIS (11). In addition, as DCIS commonly presents as microcalcifications on mammography (31), previous studies


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**Table 3. Multivariate Analysis of Pre/Postoperative Variables for Predicting Positive Resection Margins**

| Preoperative Variables | | | | Pre/Postoperative Variables | | | |
|---|---|---|---|---|---|---|---|
| Variables | OR | 95% CI | *P* | Variables | OR | 95% CI | *P* |
| Presence of NME | | | | Presence of NME | | | |
| Yes | 2.741 | 0.948–7.925 | 0.063 | Yes | 1.805 | 0.543–6.000 | 0.335 |
| No | Ref | | | No | Ref | | |
| Multifocality | | | | Multifocality | | | |
| Yes | 3.977 | 1.408–11.231 | 0.009 | Yes | 3.263 | 1.034–10.304 | 0.044 |
| No | Ref | | | No | Ref | | |
| | | | | Pathologic tumor size (mm) | 1.092 | 1.023–1.166 | 0.008 |
| | | | | Lymph node metastases | | | |
| | | | | Yes | 2.735 | 0.676–11.065 | 0.158 |
| | | | | No | Ref | | |

have reported that the presence of microcalcifications on mammography and presence of DCIS were both associated with resection margin status in patient populations composed mostly of patients with IDC (32).

In this study, we questioned whether similar MRI features were also associated with resection margin status in patients with ILC. Of the 101 patients included in our study, 11 (10.8%) had combined DCIS, but negative resection margins were achieved in all of these patients. However, our study results showed that multifocality and NME on preoperative MRI were associated with positive resection margins in ILC patients, although NME showed borderline significance. Tumors with higher cellularity usually present as masses, whereas scattered tumor cells and tumors with lower cellularity present as NME, which may underlie the association between NME and resection margin status (33). Among the enhancing patterns of ILC on MRI, NME has been correlated with malignant cells streaming in a single-file fashion in the breast stroma or small tumor aggregates separated by normal tissue, which would likely cause underestimation of tumor extent (34, 35). Our results are also consistent with previous studies, which have reported that NME lesions show higher discordance than mass lesions in estimating tumor size (36).

In addition, the lack of MRI-guided lesion localization may have also attributed to the higher positive resection margin rate in NME lesions. Although previous trials investigating the benefit of breast MRI for treatment planning in women with invasive breast cancer have failed to demonstrate a positive effect on surgical outcome, one recent study that utilized MRI-guided biopsy and MRI-guided lesion bracketing demonstrated a low overall positive margin rate of 3.7% (12). Therefore, we can infer that in real-world clinical practice where the use of MRI-guided lesion localization is often lacking, the improved assessment of tumor extent by MRI may not be fully applicable to surgery. This would be especially related to NME, which is often less discernible on conventional imaging (37).

ILC has been associated with higher rates of positive resection margins after BCS compared to IDC (38, 39). In a previous study that focused on the associations between clinicopathologic variables and positive resection margins, tumor size exceeding 2 cm and lymph node involvement were associated with positive resection margins in ILC (40). Our study showed similar results, with multifocality at MRI and tumor size being independently associated with positive resection margins. Axillary lymph node metastasis was also associated with positive resection margins, although this was not statistically significant in the multivariable analysis. Our study results imply that multifocality on MRI and tumor size are most strongly associated with positive margins in patients with ILC, for whom more aggressive surgery such as resection of shave margins, wide excision, or mastectomy should be considered. Patients with none of these risk factors and without NME on MRI have a lower risk of positive margins and may more confidently receive BCS.

There are several limitations of this study. First, this was a retrospective study and patients were recruited from a single tertiary referral center, so selection bias was inevitable. Second, one breast-dedicated radiologist reviewed the breast MR images. Although a high agreement rate among readers has been reported when differentiating NME from mass lesions, interobserver variability would be present if another radiologist were to review the same images (41). Third, our study had a small number of events


https://doi.org/10.3348/kjr.2019.0674

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(21 cases with positive resection margins), which may have caused overfitting of the model. An event per variable ≥ 10 would be preferable, and larger studies are required to confirm our results (42).

In conclusion, in patients with ILC, multifocality and NME on preoperative breast MRI were associated with positive resection margins. These findings may aid in determining the extent of resection required prior to BCS.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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