

ORIGINAL ARTICLE

Factors Associated with Re-excision after Breast-Conserving Surgery for Early-Stage Breast Cancer

Woohyun Jung^{1,2}, Eunyoung Kang¹, Sun Mi Kim³, Dongwon Kim¹, Yoonsun Hwang¹, Young Sun¹, Cha Kyong Yom¹, Sung-Won Kim^{1,2}

¹Department of Surgery, Seoul National University Bundang Hospital, Seongnam; ²Department of Surgery, Seoul National University College of Medicine, Seoul; ³Department of Radiology, Seoul National University Bundang Hospital, Seongnam, Korea

Purpose: Re-excisions after breast-conserving surgery (BCS) for breast cancer cause delays in the adjuvant treatment, increased morbidity, and leads to poor aesthetic results. Thus, efforts to reduce the re-excision rate are essential. This study aimed to conclusively determine the re-excision rate and the factors associated with re-excision after BCS. Methods: We retrospectively reviewed the medical records and pathological reports of 711 cases that underwent BCS for early-stage breast cancer. Univariate and multivariate analyses were performed. Results: Of the 711 cases of BCS, 71 (10.0%) required re-excision. Patients in the re-excision group were younger than those in the no re-excision group. Non-palpable lesions, the presence of non-mass-like enhancement at magnetic resonance imaging, multifocality, the presence of a ductal carcinoma in situ (DCIS) component, and an infiltrative tumor border were also significantly associated with re-excision. Multivariate analysis indicated that younger age, non-palpable lesions, multifocal lesions, and the presence of a DCIS component were factors which were independently associated with re-excision. Tumors located in the lower inner quadrant had a relatively high involved resection margin rate as well as a narrow resection margin width, especially at the superior and medial margins. Lateral margins showed a tendency toward a wider resection margin width. **Conclusion:** At our institution, the rate of re-excision was low despite the lack of an intraoperative frozen section. Patients with non-palpable or multifocal tumors, a DCIS component, or those who were younger than 50 years were more likely to require re-excision after BCS. These factors should be considered when planning surgical management of early-stage breast cancer. Positive resection margin rates and margin widths differed on a directional basis based on tumor location, and these differences were considerable.

Key Words: Breast neoplasms, Safety of margin, Segmental mastectomy

INTRODUCTION

Breast-conserving surgery (BCS) has become the standard treatment for early-stage breast cancer since randomized trials showed that BCS followed by adjuvant radiation therapy is the equivalent to a total mastectomy in terms of overall and disease-free survival among patients with early-stage breast cancer [1,2]. Because BCS provides a better cosmetic outcome, and generally, a better quality of life than mastectomy, the rate of BCS is increasing. In Korea, the rate of BCS increased from 18.7% in 1996 to 55.7% in 2010 [3]. According to the breast

Correspondence to: Sung-Won Kim

Department of Surgery, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 463-707, Korea Tel: +82-31-787-7094, Fax: +82-31-787-4055 E-mail: brcakorea@gmail.com

Received: July 2, 2012 Accepted: October 12, 2012

cancer database at our institution, BCS was performed for 413 (51.4%) of 764 cases of breast cancer between June 2003 and December 2007, and the rate of BCS has increased annually (39.4% in 2004, 47.2% in 2005, 60.4% in 2006, and 63.0% in 2007) [4]. However, BCS has been associated with a higher risk of local recurrence than mastectomy [1], and the most important factor associated with local recurrence after BCS is the presence of tumor cells at the surgical resection margin [5,6]. Successful BCS requires a clear pathological resection margin, while maintaining an acceptable cosmetic result, but a significant proportion of patients undergoing BCS have a positive resection margin that requires re-excision. Re-excision rates vary from 15% to 60% [7-10]. Although re-excision after BCS does not affect survival, it can cause delays in the administration of adjuvant chemotherapy and radiation therapy. Moreover, additional surgery increases morbidity, patient anxiety, wound infection rates, leads to poor cosmetic results,

and adds to the costs of care, and thus, efforts to reduce the reexcision rate are important. Several risk factors associated with positive margins have been evaluated in previous studies. Younger age, smaller breasts, large tumor size, multifocality, lobular histology, presence of lymphovascular invasion (LVI), presence of ductal carcinoma *in situ* (DCIS), nodal involvement, and microcalcification upon mammography (MMG) have all been reported to influence the risk of re-excision, but study results vary considerably [7-14].

In this study, we aimed to assess the re-excision rates after BCS for early-stage breast cancer, and to evaluate the factors associated with re-excisions after BCS. In addition, we performed resection margin analyses to evaluate differences in resection margin status based on tumor location.

METHODS

Between June 2003 and February 2011, 986 patients with invasive breast cancer underwent BCS at Seoul National University Bundang Hospital. A total of 726 of these were pathologically confirmed with early-stage breast cancer (pathologic T stage I and II) after surgery. Patients who underwent neoadjuvant chemotherapy and those with distant metastasis were excluded. We thus retrospectively reviewed the medical records of 701 patients; 10 of these patients had bilateral breast cancer and underwent bilateral BCS, giving a total of 711 cases of BCS. This study was approved by the Seoul National University Bundang Hospital Institutional Review Board (IRB No. B-1203/148-112).

Age, body mass index (BMI), clinical T and N stage, and palpability were recorded and analyzed. Clinical stage was evaluated by physical examination and radiologic findings were obtained from electronic medical records. We classified mammographic findings into 4 categories: no visualization, mass, microcalcification, and mass with microcalcification. We identified the presence of daughter nodules by ultrasonography (USG) and non-mass-like enhancement (NMLE) by breast magnetic resonance imaging (MRI). From pathologic reports, we obtained the pathologic stage, histologic type and nuclear grade, pathologic multifocality, hormone receptor status, presence of DCIS and LVI, tumor border type, and resection margin width in 4 directions (superior, inferior, medial, and lateral). Breast cancer staging was based on the seventh staging system of the American Joint Committee on Cancer/ International Union against Cancer [15].

All operations were performed under general anesthesia by one specialized breast cancer surgeon. Palpable tumors were excised with the acceptable margin width of more than 1 cm by intraoperative palpation. Non-palpable tumors were marked by USG-guided or MMG-guided needle localization before surgery. In some cases with non-palpable tumors, specimen mammography was performed to confirm the adequate resection. The intraoperative frozen section for resection margin evaluation was not performed routinely. Re-excision was performed for patients with a positive or close resection margins (> 0 to ≤ 2 mm) microscopically. A positive surgical margin is defined as the presence of tumor cells at the inked surface of the resected specimen. The operation for reexcision was also performed under general anesthesia in most of cases. In many cases, wide excision of the involved margin was sufficient for re-excision. Total mastectomy was performed for re-excision in some patients who expected poor cosmetic result after secondary BCS, and who wanted surgery without the possibility of further re-excision.

Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, USA). Pearson's chi-square or Fisher's exact test for categorical variables, and Student's t-test for continuous variables were used to identify associations between each of the clinicopathological factors and re-excision after BCS. Multivariate analysis was performed using logistic regression of the variables that were found to be statistically significant through univariate analyses. One-way ANOVA was used for the analyses of resection margins.

RESULTS

Clinicopathological characteristics

The mean age of patients was 50.8 ± 11.3 years, and the mean BMI was 23.3 ± 3.2 kg/m². The characteristics of tumors are presented in Table 1. In total, 557 (78.3%) cases were clinically assessed as T1 and axillary lymph node metastasis was clinically suspected in 58 (8.2%). In comparison, 503 (70.7%) cases were reported as pathologic T1 and axillary lymph node metastasis was found in 183 (25.7%). A palpable lesion was present in 523 (73.6%). A total of 210 patients (29.5%) had no visible lesion on preoperative MMG due to dense breast parenchyma; mass lesions and microcalcification were identified in 432 (60.8%) and 194 (27.3%) patients, respectively. Daughter nodules were found in 100 (14.1%) patients upon preoperative breast USG, and NMLE was found in 35 (4.9%) patients upon breast MRI. One hundred twenty-eight (18.0%) patients had multiple lesions according to the pathologic reports. Five hundred ninety-eight (84.1%) had ductal type and 36 (5.1%) had lobular type carcinomas. Approximately 75% had a DCIS component, and LVI was found in 215 (30.2%).

Re-excision rate after BCS

Of the 711 cases of BCS for early-stage breast cancer, 71

414 Woohyun Jung, et al.

Table 1. The characteristics of tumors

| Variable | No. (%) | Variable | No. (%) |
|---------------------------------|------------|-----------------------------------|------------|
| Side | | Histologic type (pathology) | |
| Right breast | 346 (48.7) | Ductal | 598 (84.1) |
| Left breast | 365 (51.3) | Lobular | 36 (5.1) |
| Clinical T stage | | Others | 77 (10.8) |
| cT1 | 557 (78.3) | Pathologic T stage | |
| cT2 | 154 (21.7) | pT1 | 503 (70.7) |
| Clinical axillary LN metastasis | | pT2 | 208 (29.3) |
| Negative | 653 (91.8) | Pathologic axillary LN metastasis | |
| Positive | 58 (8.2) | Negative | 528 (74.3) |
| MMG finding | | Positive | 183 (25.7) |
| No visualization | 210 (29.5) | Histologic grade | |
| Mass | 297 (41.8) | I | 202 (28.4) |
| Microcalcification | 59 (8.3) | II | 233 (32.8) |
| Mass with microcalcification | 135 (19.0) | III | 245 (34.5) |
| Unknown | 10 (1.4) | Unknown | 31 (4.4) |
| USG finding: daughter nodule | | Estrogen receptor | |
| Negative | 610 (85.8) | Negative | 176 (24.8) |
| Positive | 100 (14.1) | Positive | 533 (75.0) |
| Unknown | 1 (0.1) | Unknown | 2 (0.3) |
| MRI finding: NMLE | | Progesterone receptor | |
| Negative | 627 (88.2) | Negative | 220 (30.9) |
| Positive | 35 (4.9) | Positive | 489 (68.8) |
| Unknown | 49 (6.9) | Unknown | 2 (0.3) |
| Location | | HER2 receptor* | |
| UOQ | 320 (45.0) | Negative | 618 (86.9) |
| LOQ | 106 (14.9) | Positive | 91 (12.8) |
| UIQ | 172 (24.2) | Unknown | 2 (0.3) |
| LIQ | 36 (5.1) | DCIS component | |
| Central | 71 (10.0) | Negative | 172 (24.2) |
| >1 quadrant | 6 (0.8) | Positive | 539 (75.8) |
| Palpable lesion | | Lymphovascular invasion | |
| Yes | 523 (73.6) | Negative | 484 (68.1) |
| No | 178 (25.0) | Positive | 215 (30.2) |
| Unknown | 10 (1.4) | Unknown | 12 (1.7) |
| Multiple lesion (pathology) | | Tumor border | |
| No | 583 (82.0) | Infiltrative | 508 (71.4) |
| Yes | 128 (18.0) | Pushing | 191 (26.9) |
| | | Unknown | 12 (1.7) |

LN=lymph node; MMG=mammography; USG=ultrasonography; MRI=magnetic resonance imaging; NMLE=non-mass-like enhancement; UOQ=upper outer quadrant; LOQ=lower outer quadrant; UIQ=upper inner quadrant; LIQ=lower inner quadrant; DCIS=ductal carcinoma *in situ*.

*HER2 receptor was classified by immunohistochemistry as follows: 0, 1+ or 2+ was negative, and 3+ was positive.

(10.0%) required re-excision due to a positive or close resection margin. Among these 71 cases, the resection margins of 57 were involved with invasive breast cancer (n=20) or DCIS (n=37) and the remaining 14 had a close resection margin (≤ 2 mm) with invasive breast cancer (n=8) or DCIS (n=6). A second BCS was performed in 51, and a total mastectomy (TM) in 18. A 37-year-old woman scheduled for TM was lost to follow-up before re-excision, and a 40-year-old woman who had a positive resection margin refused re-excision, and only attended regular follow-up sessions. Of the 51 patients who underwent a second BCS, 12 (23.5%) required a second

re-excision; a third BCS was performed in 4 patients and a TM in 8. No patients required a third re-excision. Thus, of the 711 cases of early-stage breast cancer for which BCS was planned, 685 (96.3%) were successfully managed without mastectomy.

Factors affecting re-excision

Upon univariate analysis (Table 2), the mean age of the no re-excision group was found to be higher than that of the re-excision group (51.2 years vs. 47.1 years; p = 0.002); in addition, the under 35-year-old subgroup had significantly higher

Table 2. Univariate analysis of associations with re-excision

| | No re-excision (n=640) No. (%) | Re-excision (n=71) No. (%) | <i>p</i> -value | | No re-excision (n=640) No. (%) | Re-excision (n=71) No. (%) | <i>p</i> -value |
|------------------------------|--------------------------------------|----------------------------------|-----------------|-----------------------------------|--------------------------------------|----------------------------------|-----------------|
| BMI* | 23.4 ± 3.3 | 22.9±3.0 | 0.194 | Pathologic T stage | | | 0.950 |
| Age (yr) | | | 0.005 | pT1 | 453 (90.1) | 50 (9.9) | |
| ≤35 | 38 (80.9) | 9 (19.1) | | pT2 | 187 (89.9) | 21 (10.1) | |
| 36-50 | 298 (87.9) | 41 (12.1) | | Pathologic axillary LN metastasis | | | 0.176 |
| >50 | 304 (93.5) | 21 (6.5) | | Negative | 480 (90.9) | 48 (9.1) | |
| Clinical T stage | | | 0.850 | Positive | 160 (87.4) | 23 (12.6) | |
| cT1 | 502 (90.1) | 55 (9.9) | | Histological grade | | | 0.643 |
| cT2 | 138 (89.6) | 16 (10.4) | | I | 171 (90.5) | 18 (9.5) | |
| Clinical LN metastasis | | | 0.202 | II | 195 (88.2) | 26 (11.8) | |
| Negative | 585 (89.6) | 68 (10.4) | | III | 214 (90.7) | 22 (9.3) | |
| Positive | 55 (94.8) | 3 (5.2) | | Histological type | | | 0.318 |
| Tumor location | | | 0.814 | Ductal | 542 (90.6) | 56 (9.4) | |
| UOQ | 286 (89.4) | 34 (10.6) | | Lobular | 30 (83.3) | 6 (16.7) | |
| LOQ | 96 (90.6) | 10 (9.4) | | Others | 68 (88.3) | 9 (11.7) | |
| UIQ | 156 (90.7) | 16 (9.3) | | Estrogen receptor | | | 0.325 |
| LIQ | 31 (86.1) | 5 (13.9) | | Negative | 162 (92.0) | 14 (8.0) | |
| Central | 66 (93.0) | 5 (7.0) | | Positive | 477 (89.5) | 56 (10.5) | |
| MMG finding | | | 0.054 | Progesterone receptor | | | 0.409 |
| No visualization | 185 (88.1) | 25 (11.9) | | Negative | 201 (91.4) | 19 (8.6) | |
| Mass | 277 (93.3) | 20 (6.7) | | Positive | 438 (89.6) | 51 (10.4) | |
| Microcalcification | 49 (83.1) | 10 (16.9) | | HER2 receptor [†] | | | 0.448 |
| Mass with microcalcification | 121 (89.6) | 14 (10.4) | | Negative | 559 (90.5) | 59 (9.5) | |
| USG finding | | | 0.072 | Positive | 80 (87.9) | 11 (12.1) | |
| No daughter nodule | 554 (90.8) | 56 (9.2) | | DCIS component | | | 0.036 |
| Daughter nodule | 85 (85.0) | 15 (15.0) | | Negative | 162 (94.2) | 10 (5.8) | |
| MRI finding | | | 0.030 | Positive | 478 (88.7) | 61 (11.3) | |
| No NMLE | 571 (91.1) | 56 (8.9) | | Lymphovascular invasion | | | 0.200 |
| NMLE | 28 (80.0) | 7 (20.0) | | Negative | 433 (89.5) | 51 (10.5) | |
| Palpability | | | 0.022 | Positive | 199 (92.0) | 16 (7.4) | |
| No | 152 (85.4) | 26 (14.6) | | Tumor border | • | • | 0.041 |
| Yes | 478 (91.4) | 45 (8.6) | | Infiltrative | 453 (89.2) | 55 (10.8) | |
| Multifocality (pathologic) | | | 0.001 | Pushing | 180 (94.2) | 11 (5.8) | |
| No | 535 (91.8) | 48 (8.2) | | - | • | • | |
| Yes | 105 (82.0) | 23 (18.0) | | | | | |

BMI=body mass index; LN=lymph node; UOQ=upper outer quadrant; LOQ=lower outer quadrant; UIQ=upper inner quadrant; LIQ=lower inner quadrant; MMG=mammography; USG=ultrasonography; MRI=magnetic resonance imaging; NMLE=non-mass-like enhancement; DCIS=ductal carcinoma in situ.

*Mean±SD; †HER2 receptor was classified by immunohistochemistry as follows: 0, 1+ or 2+ was negative, and 3+ was positive.

Table 3. Multivariate analysis of associations with re-excision

| | OR (95% CI) | p-value |
|-------------------------------------|----------------------|---------|
| Age under 35 yr | 5.035 (1.802-14.067) | 0.005 |
| Age 36-50 yr | 2.119 (1.098-4.089) | 0.025 |
| No lesion at MMG | 1.090 (0.544-2.184) | 0.808 |
| Microcalcification at MMG | 0.927 (0.319-2.657) | 0.879 |
| Mass with microcalcification at MMG | 1.134 (0.515-2.496) | 0.756 |
| Daughter nodule in USG | 1.012 (0.468-2.186) | 0.976 |
| NMLE at MRI | 1.729 (0.624-4.794) | 0.293 |
| Non-palpable lesion | 1.889 (1.013-3.524) | 0.045 |
| Multifocal lesion (pathologic) | 2.031 (1.031-3.999) | 0.040 |
| Presence of DCIS | 2.613 (1.069-6.387) | 0.035 |
| Infiltrative border | 1.621 (0.762-3.450) | 0.210 |

OR=odds ratio; MMG=mammography; USG=ultrasonography; NMLE=non-mass-like enhancement; MRI=magnetic resonance imaging; DCIS=ductal carcinoma *in situ*.

re-excision rates than the other age groups of 36 to 50 and over 50 (19.1% vs. 12.1% and 6.5%, respectively; p = 0.005). Non-palpability (14.6% vs. 8.6%; p = 0.022) was also associated with a high re-excision rate. BMI, tumor location, and clinical stage were not associated with re-excision. The presence of NMLE upon MRI was associated with re-excision, and the lack of a visible lesion and microcalcification during MMG and daughter nodules upon USG showed a relative association with re-excision upon univariate analysis. Pathologic multifocality (18.0% vs. 8.2%; p = 0.001), the presence of a DCIS component (11.3% vs. 5.8%; p = 0.036), and an infiltrative tumor border (10.8% vs. 5.8%; p = 0.041) were found to be significantly associated with re-excision upon univariate analysis. Pathologic stage, histologic type, and LVI were not

416 Woohyun Jung, et al.

found to be associated with re-excision.

Multivariate logistic regression analysis was performed with the variables associated with re-excision through univariate analysis (variables with p < 0.1). The results are shown in Table 3. Younger age, non-palpable lesions, multifocality, and the presence of a DCIS component were identified as being independently associated with re-excision after BCS. Of these factors, age, MMG, USG, and MRI findings, and palpability can be measured preoperatively.

Resection margin analyses

We analyzed the positive resection margin rate and the resection margin width in 4 directions – superior, inferior, medial, and lateral - among 5 subgroups categorized by tumor location, namely the upper outer quadrant (UOQ), lower outer quadrant (LOQ), upper inner quadrant (UIQ), lower inner quadrant (LIQ), and the central region. In this analysis, 6 cases were excluded for ambiguous tumor location, and finally, 705 cases (2,820 resection margins) were evaluated. The rate of resection margin involvement across all directions was 2.6%. The positive margin rate was highest at the medial margin and was lowest at the lateral margin, but this difference was not significant (3.3% vs. 2.0%, p = 0.517). The mean resection margin width across all 4 directions was 2.0 cm, and the lateral margin width was relatively wider than that of the other directions. Among the 5 subgroups, the LIQ subgroup had the highest rate of positive resection margins (4.2%), especially with respect to the superior and medial margins (5.6%). The LIQ subgroup also had the narrowest mean resection margin width as the superior, medial, and lateral resection margin widths were all narrowest in the LIQ subgroup. In the UOQ, UIQ, and central subgroups, the mean resection margin width was found to be significantly different in different directions. This was because the lateral resection margin width was found to be relatively wider than the width of the other margins. For detailed results relating to the positive resection margin rate see Table 4; results pertaining to resection margin width are shown in Table 5.

DISCUSSION

We aimed to evaluate the re-excision rate after BCS and to identify factors associated with re-excision. The re-excision rate at our institution was 10.0%. Univariate analysis indicated that younger age, the presence of NMLE at MRI, a non-palpable lesion, multifocal lesions noted in pathologic reports, the presence of a DCIS component, and an infiltrative tumor border were significantly associated with re-excision, and no visible lesion, microcalcification upon MMG, and a daughter nodule upon breast USG tended to be associated with a higher rate of re-excision. However, multivariate analysis revealed that only the factors of younger age, non-palpable lesions, multifocal lesions, and the presence of a DCIS component were independently associated with re-excision after BCS.

Reported re-excision rates vary widely [7-10]. The 10% re-excision rate at our institution is comparable with the rates reported previously, despite an intraoperative frozen section for resection margin not being performed at our institution. Studies that involved an assessment of intraoperative frozen sections have reported re-excision rates ranging from 11.3% to 20% [16,17]. Of the 51 patients who underwent a second BCS for the first re-excision, 12 (23.5%) required a second re-excision. This is a very high rate compared with the first re-ex-

Table 5. Resection margin width by tumor location

| | | Margin width (cm) | | | | | | |
|---------|----------|-------------------|--------|---------|-----------------|--|--|--|
| | Superior | Inferior | Medial | Lateral | <i>p</i> -value | | | |
| UOQ | 1.74 | 1.93 | 2.05 | 2.39 | < 0.001 | | | |
| LOQ | 1.96 | 1.73 | 1.99 | 2.10 | 0.154 | | | |
| UIQ | 1.80 | 1.82 | 1.82 | 2.39 | < 0.001 | | | |
| LIQ | 1.51 | 1.81 | 1.48 | 1.94 | 0.151 | | | |
| Central | 2.28 | 1.88 | 2.38 | 2.28 | 0.033 | | | |
| Total | 1.83 | 1.86 | 1.99 | 2.31 | | | | |

UOQ=upper outer quadrant; LOQ=lower outer quadrant; UIQ=upper inner quadrant; LIQ=lower inner quadrant.

Table 4. Involved resection margin rate by tumor location

| | Positive resection margin rate, No. (%) | | | | | | | | | | |
|---------|-----------------------------------------|----------|----------|----------|--------|----------|---------|----------|-------|----------|-----------------|
| | Superior | | Inferior | | Medial | | Lateral | | Total | | <i>p</i> -value |
| | Neg | Pos | Neg | Pos | Neg | Pos | Neg | Pos | Neg | Pos | |
| UOQ | 311 | 9 (2.8) | 313 | 7 (2.2) | 308 | 12 (3.8) | 312 | 8 (2.5) | 1,244 | 36 (2.8) | 0.659 |
| LOQ | 105 | 1 (0.9) | 103 | 3 (2.8) | 102 | 4 (3.8) | 105 | 1 (0.9) | 415 | 9 (2.1) | 0.382 |
| UIQ | 167 | 5 (2.9) | 164 | 8 (4.7) | 168 | 4 (2.3) | 168 | 4 (2.3) | 667 | 21 (3.1) | 0.549 |
| LIQ | 34 | 2 (5.6) | 35 | 1 (2.8) | 34 | 2 (5.6) | 35 | 1 (2.8) | 138 | 6 (4.2) | 0.874 |
| Central | 70 | 1 (1.4) | 71 | 0 (0.0) | 70 | 1 (1.4) | 71 | 0 (0.0) | 282 | 2 (0.7) | 0.569 |
| Total | 687 | 18 (2.6) | 686 | 19 (2.7) | 682 | 23 (3.3) | 691 | 14 (2.0) | 2,746 | 74 (2.6) | 0.517 |

Neg = negative; Pos = positive; UOQ = upper outer quadrant; LOQ = lower outer quadrant; UIQ = upper inner quadrant; LIQ = lower inner quadrant.

cision rate. This tendency was also found in a previous study of multiple re-excisions after BCS [18]. Given this finding, the performance of a second BCS for re-excision requires more careful consideration than the performance of the first BCS. Especially when planning a second BCS for re-excision, the patient should be informed of the possibility that the risk of a further re-excision is higher than that associated with the first re-excision. On the other hand, 96.3% of cases for which BCS was initially planned achieved breast conservation in this study, and previous studies have reported that multiple re-excisions do not affect local recurrence or systemic failure [18,19]. Overall, when breast surgeons are planning a re-excision surgery, they must consider the possibility of a second re-excision, the patient's general condition, the desired cosmetic result, the patient's preference, and cost effectiveness.

Univariate analysis identified several risk factors for re-excision. Most of these factors have been studied previously; our findings are both consistent and different from those reported in other studies. Aziz et al. [10] reported that younger age, the presence of a DCIS, larger tumor size, and LVI were significantly associated with a positive resection margin upon univariate analysis, but age was the only factor found to be significant upon multivariate analysis. Cabioglu et al. [13] found, through multivariate analysis, that multifocality was a risk factor for a positive margin, whereas Kurniawan et al. [9] reported that microcalcification upon MMG, multifocal disease, and a larger tumor size were associated with a positive margin upon multivariate analysis. Ramanah et al. [20] identified multifocality, the presence of a DCIS, and the absence of a preoperative positive histologic diagnosis as factors predicting re-excision. Miller et al. [11] also reported the presence of a DCIS as a predictor of a positive margin. Lovrics et al. [21] reported that palpability, the absence of multifocality and LVI, a preoperatively confirmed diagnosis, a small tumor, ductal histology, cavity margin dissection, and larger volumes of excision were predictors of negative margins. NMLE upon MRI was found to be a significant factor associated with reexcision in the univariate analysis performed in the present study. In previous studies, DCIS, invasive lobular carcinoma, focal adenosis, and fibrocystic changes can appear as a NMLE upon MRI, and estrogen receptor-negative invasive ductal carcinoma can also be seen as a NMLE in less than 20% of cases [22,23]. NMLE has also been reported to have various positive predictive values for malignancy based on enhancement patterns [24] and has been reported as the major cause of false-positive breast findings [25]. More definitive and specific studies of NMLE, as viewed by MRI and resection margins, are needed. Daughter nodules upon USG and microcalcification with no visible lesion upon MMG showed a tendency to be associated with re-excision. These preoperative radiologic findings were not found to be significantly associated with re-excision in multivariate analysis. NMLE observed by MRI and daughter nodules seen by USG were significantly associated with pathologic multifocal disease in the present study, and no visible lesion and microcalcification upon MMG were associated with non-palpability. These factors must thus be considered together when planning BCS. A pathologic infiltrative tumor border was also identified as significant in univariate analyses, but was not significant in multivariate analysis. Large tumor size, LVI, and lobular histology have been reported to be significant in several previous studies [8,9,13,14,21], but no significant association between these factors and re-excision was found in the present study.

Multivariate analysis indicated that 4 factors were significantly associated with re-excision. In younger patients, the re-excision rate was high. Many previous studies have reported similar results [7,9,10,13,14]. Because the cosmetic result is thought to be more important in young patients, the extent of excision might be minimized for cosmetic reasons in such patients [26]. Non-palpable tumors were also identified as a risk factor for re-excision in multivariate analysis. Some previous studies have reported a high re-excision rate with nonpalpable tumors due to potential technical difficulties [21,27]. Many methods of reducing the positive resection margin rate of non-palpable tumors have been proposed. Needle localization is the most popular and traditional method. A study of needle localization reported the same positive resection margin rate for palpable tumors and needle-localized non-palpable tumors, but the rate remained high (38%) [28]. USG-guided resection has also been suggested for reducing the resection margin positive rate [29]. Radio-guided occult lesion localization and radioactive seed localization have also been performed at some institutions. These radio-guided techniques reportedly have better resection margin outcomes [30]. Multifocal tumors were also identified as a risk factor for re-excision. Although multifocality was identified based on pathological reports in our study, the number of preoperatively suspected multifocal tumors was not very different from the number observed. If a multifocal tumor is suspected, careful planning and performance of BCS are always required. The presence of a DCIS component was identified as an independently associated risk factor in the present study, supporting the findings of a number of previous studies [9-11,20].

At our institution, tumor involvement of the resection margin relative to the total resection margin was 2.6%. As can be seen in Table 4, the positive resection margin rate was highest in LIQ tumors. In particular, the superior and medial margin of LIQ tumors showed a tendency toward a higher involved

418 Woohyun Jung, et al.

resection margin rate. The width of the resection margin was relatively narrow in LIQ tumors, especially the width of the superior and medial margins. This finding was due to the relatively small volume of the LIQ. Given these findings, ensuring a wider resection margin at the superior and medial sides of LIQ tumors is worth considering, but this could cause poor cosmetic results. Oncoplastic surgery, such as the use of a partial flap and the insertion of a prosthesis, could be an option for obtaining both a clear resection margin and a better cosmetic result.

This study had several limitations. First, as it was a retrospective study it may be subjected to selectional bias. Second, some of the identified risk factors, such as the presence of a DCIS component and pathologic multifocality, were only noted postoperatively and cannot be considered when planning surgery.

In conclusion, the re-excision rate at our institution was low, even though intraoperative frozen section was not performed. When we plan a BCS for early-stage breast cancer, non-palpable tumors, multifocal tumors, the presence of a DCIS component, and the age of the patient should be considered to ensure proper surgical management and to lower the re-excision rate. We also identified a tendency for the positive resection margin rate and width to differ based on tumor location; for example, a high positive resection margin rate and a relatively narrow width of the superior and medial margins were observed for LIQ tumors, and these factors could have a great impact on surgical planning.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

- Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-41.
- Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-32.
- Ahn SH, Yoo KY; Korean Breast Cancer Society. Chronological changes of clinical characteristics in 31,115 new breast cancer patients among Koreans during 1996-2004. Breast Cancer Res Treat 2006;99:209-14.
- Kang E, Han SA, Kim S, Kim SM, Jang M, Lee HE, et al. Five-years of breast cancer management in a new hospital: analysis using clinical data warehouse. J Breast Cancer 2010;13:96-103.
- 5. Singletary SE. Surgical margins in patients with early-stage breast can-

- cer treated with breast conservation therapy. Am J Surg 2002;184:383-93.
- Borger J, Kemperman H, Hart A, Peterse H, van Dongen J, Bartelink H. Risk factors in breast-conservation therapy. J Clin Oncol 1994;12:653-60.
- Schiller DE, Le LW, Cho BC, Youngson BJ, McCready DR. Factors associated with negative margins of lumpectomy specimen: potential use in selecting patients for intraoperative radiotherapy. Ann Surg Oncol 2008;15:833-42.
- Waljee JF, Hu ES, Newman LA, Alderman AK. Predictors of re-excision among women undergoing breast-conserving surgery for cancer. Ann Surg Oncol 2008;15:1297-303.
- Kurniawan ED, Wong MH, Windle I, Rose A, Mou A, Buchanan M, et al. Predictors of surgical margin status in breast-conserving surgery within a breast screening program. Ann Surg Oncol 2008;15:2542-9.
- Aziz D, Rawlinson E, Narod SA, Sun P, Lickley HL, McCready DR, et al. The role of reexcision for positive margins in optimizing local disease control after breast-conserving surgery for cancer. Breast J 2006;12:331-7.
- 11. Miller AR, Brandao G, Prihoda TJ, Hill C, Cruz AB Jr, Yeh IT. Positive margins following surgical resection of breast carcinoma: analysis of pathologic correlates. J Surg Oncol 2004;86:134-40.
- 12. Chagpar AB, Martin RC 2nd, Hagendoorn LJ, Chao C, McMasters KM. Lumpectomy margins are affected by tumor size and histologic subtype but not by biopsy technique. Am J Surg 2004;188:399-402.
- Cabioglu N, Hunt KK, Sahin AA, Kuerer HM, Babiera GV, Singletary SE, et al. Role for intraoperative margin assessment in patients undergoing breast-conserving surgery. Ann Surg Oncol 2007;14:1458-71.
- Dillon MF, Hill AD, Quinn CM, McDermott EW, O'Higgins N. A pathologic assessment of adequate margin status in breast-conserving therapy. Ann Surg Oncol 2006;13:333-9.
- Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010. p.347-77.
- 16. Weber WP, Engelberger S, Viehl CT, Zanetti-Dallenbach R, Kuster S, Dirnhofer S, et al. Accuracy of frozen section analysis versus specimen radiography during breast-conserving surgery for nonpalpable lesions. World J Surg 2008;32:2599-606.
- Olson TP, Harter J, Muñoz A, Mahvi DM, Breslin T. Frozen section analysis for intraoperative margin assessment during breast-conserving surgery results in low rates of re-excision and local recurrence. Ann Surg Oncol 2007;14:2953-60.
- Coopey S, Smith BL, Hanson S, Buckley J, Hughes KS, Gadd M, et al. The safety of multiple re-excisions after lumpectomy for breast cancer. Ann Surg Oncol 2011;18:3797-801.
- O'Sullivan MJ, Li T, Freedman G, Morrow M. The effect of multiple reexcisions on the risk of local recurrence after breast conserving surgery. Ann Surg Oncol 2007;14:3133-40.
- Ramanah R, Pivot X, Sautiere JL, Maillet R, Riethmuller D. Predictors of re-excision for positive or close margins in breast-conservation therapy for pT1 tumors. Am J Surg 2008;195:770-4.
- Lovrics PJ, Cornacchi SD, Farrokhyar F, Garnett A, Chen V, Franic S, et al. The relationship between surgical factors and margin status after breast-conservation surgery for early stage breast cancer. Am J Surg 2009; 197:740-6.
- 22. Kuhl C. The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical

- practice. Radiology 2007;244:356-78.
- Agrawal G, Su MY, Nalcioglu O, Feig SA, Chen JH. Significance of breast lesion descriptors in the ACR BI-RADS MRI lexicon. Cancer 2009;115:1363-80.
- 24. Mahoney MC, Gatsonis C, Hanna L, DeMartini WB, Lehman C. Positive predictive value of BI-RADS MR imaging. Radiology 2012;264:51-8.
- Baltzer PA, Benndorf M, Dietzel M, Gajda M, Runnebaum IB, Kaiser WA. False-positive findings at contrast-enhanced breast MRI: a BI-RADS descriptor study. AJR Am J Roentgenol 2010;194:1658-63.
- 26. Vicini FA, Kestin LL, Goldstein NS, Chen PY, Pettinga J, Frazier RC, et al. Impact of young age on outcome in patients with ductal carcinomain-situ treated with breast-conserving therapy. J Clin Oncol 2000;18: 296-306.
- Lovrics PJ, Cornacchi SD, Farrokhyar F, Garnett A, Chen V, Franic S, et al. Technical factors, surgeon case volume and positive margin rates after breast conservation surgery for early-stage breast cancer. Can J Surg 2010;53:305-12.
- 28. Atkins J, Al Mushawah F, Appleton CM, Cyr AE, Gillanders WE, Aft RL, et al. Positive margin rates following breast-conserving surgery for stage I-III breast cancer: palpable versus nonpalpable tumors. J Surg Res 2012:177:109-15.
- Krekel NM, Zonderhuis BM, Stockmann HB, Schreurs WH, van der Veen H, de Lange de Klerk ES, et al. A comparison of three methods for nonpalpable breast cancer excision. Eur J Surg Oncol 2011;37:109-15.
- Dua SM, Gray RJ, Keshtgar M. Strategies for localisation of impalpable breast lesions. Breast 2011;20:246-53.