Doctoral Thesis in Medicine

Feasibility of Intraoperative specimen mammography for margin assessment in breast conservation surgery

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Feasibility of Intraoperative specimen mammography for margin assessment in breast conservation surgery

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ABSTRACT

Feasibility of Intraoperative specimen mammography for margin assessment in breast conservation surgery

Purpose: Breast conserving surgery (BCS) requires the establishment of adequate margins to reduce local recurrence. The purpose of this study was to determine whether intraoperative specimen mammography is effective and efficient as margin assessment method in Asian women.

Method: A total of 182 patients who had breast cancer treated with BCS between October 2015 and September 2017 were evaluated. After wide excision, intraoperative specimen mammography was used to assess margin adequacy. Whenever the margins were close to the lesions, further resection was performed. And 4 direction frozen section analysis were done in 84 patients who were treated with BCS between January 2012 and December 2014. We compared two groups of different margin assessment methods. The margins were histologically assessed and correlated with the specimen mammographic findings.

Results: 61.6% patients have dense breasts (mammographic density > 50%) and 85.7% of dense breasts could margin assess by intraoperative specimen mammography. Incomplete intraoperative excision detected by specimen mammography led to immediate re-excision in 24 (13.2%) cases which were more than 13 (15.5%) cases in group of frozen section analysis (p = 0.47). Significant correlations were found between the radiological and histological margins (R^2 = 0.222, p < 0.05). The operation time of frozen section analysis group were statistically significant longer than specimen mammography group (mean 108.4 and 85.2 minutes, respectively). Conclusion: Our results show that breast lesions intraoperative specimen mammography for BCS is useful to identify margin clearance regardless of the mammographic density.

Key words: Breast neoplasms; Margins of Excision; Mammography

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ABBREVIATION

BCS: Breast conserving surgery

FSA: frozen section analysis

DCIS: ductal carcinoma in situ

IDC: invasive ductal carcinoma

LCIS: lobular carcinoma in situ

ILC: invasive ductal carcinoma

US: ultrasound sonography

RCTs: randomized controlled trials

RGS: radio-guided surgery

ROLL: radio-guided occult lesion localization

RSL: radioactive seed localization

I. INTRODUCTION

Breast cancer treatment with breast conserving surgery (BCS) requires the establishment of adequate margins to reduce local recurrence, which can be achieved through several methods. Intraoperative assessment of margin status is commonly performed using frozen section analysis (FSA). However, this technique lacks a standardized sampling method for relatively rounded breast specimens, which is not always practical in a busy unit. Intraoperative specimen mammography has been found useful to identify margin involvement, especially in cases with micro-calcification or non-palpable lesions. Although surgical margin analysis has been acknowledged as a critical component of BCS, the best assessment technique has yet to be determined [1]. Proponents of specimen mammography report that this radiologic procedure allows surgeons to assess excision adequacy and to reduce the number of metachronous re-excisions required to achieve margin-negative resection [2].

In dense breast patients, it is especially difficult to define breast lesions using mammography. Nevertheless, intraoperative specimen mammography may be useful to assess the margin status of visible or non-visible lesions on preoperative mammography. To date, no studies have looked into the effectiveness of specimen mammography in dense breasts. The proportion of dense breasts in Korean women is higher than in Western women [3].

In the present study, we evaluated the influence of preoperative mammography density in specimen mammography analysis. The value of intra-operative specimen mammography to determine the margin status of excised palpable or non-palpable breast lesions was evaluated. Additionally, the level of agreement between the radiologic and final pathologic interpretations of margin status was analyzed.

II. METHODS

A. Patients and Tumor characteristics

Between October 2015 and September 2017, we evaluated 182 patients of breast cancer performed intraoperative specimen mammography after BCS at the XXX University Hospital. Patients with bilateral breast cancer or distant metastasis or diffuse micro-calcifications were excluded. Additionally, a retrospective chart review was performed on 84 patients with FSA aiming to compare operation time, margin status, and frequency of a second operation for further resection. The mammogram reports were based on visual analysis by two radiologists. The mammographic findings of breast density were classified according to the following categories, based on the American College of Radiology, Breast Reporting and Data System: Category a : The breasts are almost entirely fatty ; Category b : The breasts present scattered areas of fibroglandular density ; Category c : The breasts are extremely dense, which may obscure small masses ; Category d : The breasts are extremely dense, which lowers the mammography sensitivity [4]. The lesions were pathologically confirmed as ductal carcinoma *in situ* (DCIS), invasive ductal carcinoma (IDC), lobular carcinoma in situ (LCIS), invasive lobular carcinoma (ILC), and other malignant neoplasms. Histologic margins were measured as the closest distance between the specimen's edge and the cancer cell location. This study was approved by the XXX University Hospital Institutional Review Board (IRB No. MED-OBS-11-361). For this type of study, informed consent from the patients was not required.

B. Surgical technique

All surgical procedure was performed by two specialized breast cancer surgeons. Prior to surgery, non-palpable lesions with micro-calcifications were marked by wire-guided localization, which was performed with a hooked wire through an 18-gauge spinal needle. Following wire insertion, medio-lateral oblique view mammography was performed to identify the wire location. The locations of palpable and non-palpable lesions were confirmed by ultrasound sonography (US) in the operating room. After excision, four directions (superior, inferior, medial, and lateral) margins were oriented using vicryl sutures. One metallic clip was placed for the superior surface, and two metallic clips were placed for

lateral margin. According to the histopathological results, obtained from the first surgery, a second operation was performed in patients exhibiting ink on the tumor surface.

C. Specimen mammography

Direction-oriented specimens were sent to the mammography unit. Single-image standard compression magnification radiographs were obtained (Figure 1). Specimen mammography was immediately identified, and if mass or calcifications were near the specimen's margins, further resection was performed upon the surgeons' decision.

For the evaluation of margin status, the closest distance from the cancer to the specimen edge was measured. A radiologist with 10 years of experience retrospectively measured the distance without knowing the patient's pathologic information.

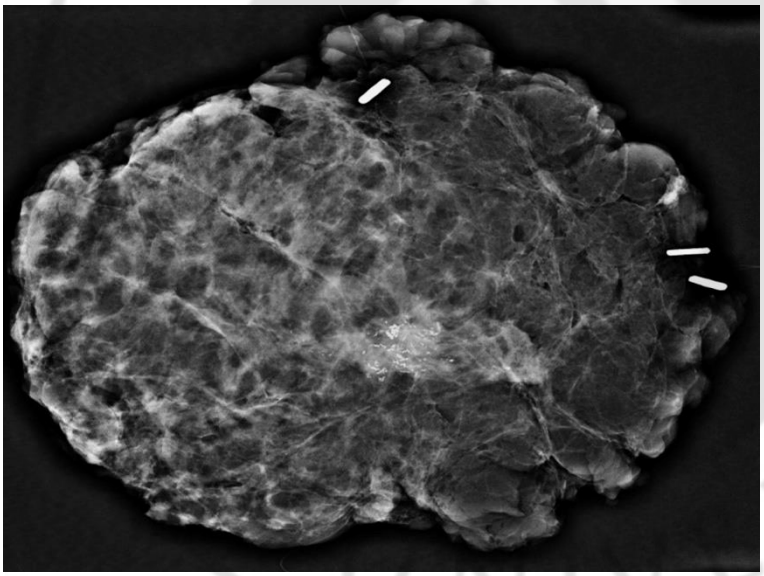

Fig. 1. Direction-oriented specimen were sent to the mammography unit and obtained standard compression magnification radiographs.

D. Frozen section analysis

After excision of the breast specimen, the four directions (superior, inferior, medial, and

lateral) were marked with sutures, while maintaining orientation. The embedding specimen was sent to the pathologist, and the suture site was thinly sliced. The pathologist returned the results after 30 minutes.

E. Statistical Analysis

Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, USA). Categorical variables were evaluated using the chi-square test. A level of $p < 0.05$ was considered statistically significant. Linear regression results are presented as the coefficient with confidence intervals and R^2 values. Univariate and multivariate analyses were preformed using logistic regression.

Ⅲ. RESULTS

The clinicopathologic characteristics of the 182 patients with specimen mammography and the 84 patients who had FSA after BCS are reported in Table 1. In specimen mammography group, histological findings of the lesions revealed that 116 (63.7%) cases were IDC, 38 (20.9%) were pure DCIS, and 24 (13.2%) were IDC based on DCIS. No histological differences in FSA group. After confirmation of margin status by two methods, there were no statistical difference of proportion of further resection (22.0% vs. 25.0%, p = 0.47).

A significant difference was found between the preoperative mammographic density and the possibility of margin assessment, regardless of lesion status. The relationship was shown in Table 2. Within the study population, Among the 182 patients with specimen mammography, 19(10.4%) patients showed in less than 25% mammographic density subgroup, 51(28.0%) patients showed in 25~50% mammographic density subgroup and a proportion of 112(61.6%) patients exhibited higher than 50% preoperative mammographic density. The mammographic margins were confirmed by specimen mammography in 164(90.1%). The patients' specimens with less than 25% density in the preoperative mammography allowed lesion identification totally. In the 25~50% density subgroup and 50~75% density subgroup was showed 49(96.1%) and 74(92.5%) respectively. Whereas, in the subgroup of more than 75% density, lesions were confirmed only 22(68.8%). The results indicated that the difficulty to determine margin status increased with breast density (p = 0.003). In order to detect the effectiveness of specimen mammography, comparing intra-operative margin assessment data between FSA group and specimen mammography group (Table 3). Two different intraoperative margin assessment methods were compared in terms of mean operation time, the narrowest margin from the lesion, and the second operation for further resection. The operation time was significantly shorter in specimen mammography group than that in FSA group (85.2min vs. 108.4min, p = 0.026). 12(14.3%) specimens were found to have very-close margin and 7(8.3%) specimens were reported positive margin in FSA group. In specimen mammography group, 39(21.4%) specimens were found to have very-close margin and 19(10.4%) specimens were reported positive margin. There were no significant differences between two groups regarding the incidence of very-close margins (<1 mm) (p = 0.421) and positive margins (p = 0.196). The second operation rate in FAS

group showed 8(9.5%) and specimen mammography group showed 16(8.8%) (p = 0.252). The correlation between radiological and histological margins is shown in Figure 2. A significant correlation was found between the intraoperative specimen mammography and the histological nearest distance from lesions ($p < 0.05$).

Table 1. Comparison of clinicopathological characteristics between patients with specimen mammography versus frozen section analysis.

Characteristics	Specimen mammography (n=182) No. (%)	Frozen section analysis (n=84) No. (%)	*p*-value
Mean age (years, range)	48.9 (29-81)	44.5 (32-79)	0.41
Menopausal status			
Pre-menopause	106 (58.2)	55 (65.5)	0.37
Post-menopause	76 (41.8)	29 (34.5)	
Histologic findings			
IDC	116 (63.7)	55 (65.5)	
IDC + DCIS	24 (13.2)	19 (22.6)	
DCIS	38 (20.9)	4 (4.8)	0.02
ILC	1 (0.5)	6 (7.1)	
ILC + LCIS	1 (0.5)	0 (0)	
Others	2 (1.2)	0 (0)	
T stage			
Tis	38 (20.9)	4 (4.8)	
T1	119 (65.4)	59 (70.2)	0.21
≥T2	25 (13.7)	21 (25.0)	
Axillary LN metastasis			
Yes	36 (19.8)	31 (36.9)	<0.05
No	146 (80.2)	53 (63.1)	
Further resection			
Intra-operative	24 (13.2)	13 (15.5)	0.47
2nd operation	16 (8.8)	8 (9.5)	

IDC=invasive ductal carcinoma; DCIS=ductal carcinoma *in situ*; ILC=invasive lobular carcinoma; LCIS=lobular carcinoma *in situ*; LN=lymph node.

Table 2. Relationship of preoperative mammographic density and possibility of mammographic margin assessment of specimen mammography

Preoperative mammography density	Cases (n=182) No. (%)	Mammographic margin assessment (n=164) No. (%)	*p*-value
<25%	19/182 (10.4)	19/19 (100)	0.003
25~50%	51/182 (28.0)	49/51 (96.1)	
50~75%	80/182 (44.0)	74/80 (92.5)	
>75%	32/182 (17.6)	22/32 (68.8)	

Table 3. Retrospective analysis of operation time and re-operation rate according to intra-operative margin assessment

Variables	Frozen section analysis	Specimen mammography	*p*-value
Operation time (min, range)	108.4 (45-215)	85.2 (20-175)	0.026
Very-close margin*/Total (%)	12/84 (14.3)	39/182 (21.4)	0.421
Positive margin†/Total (%)	7/84 (8.3)	19/182 (10.4)	0.196
2nd operation/Total (%)	8/84 (9.5)	16/182 (8.8)	0.252

† Ink on tumor surface
* Histological nearest distance from lesion <1mm

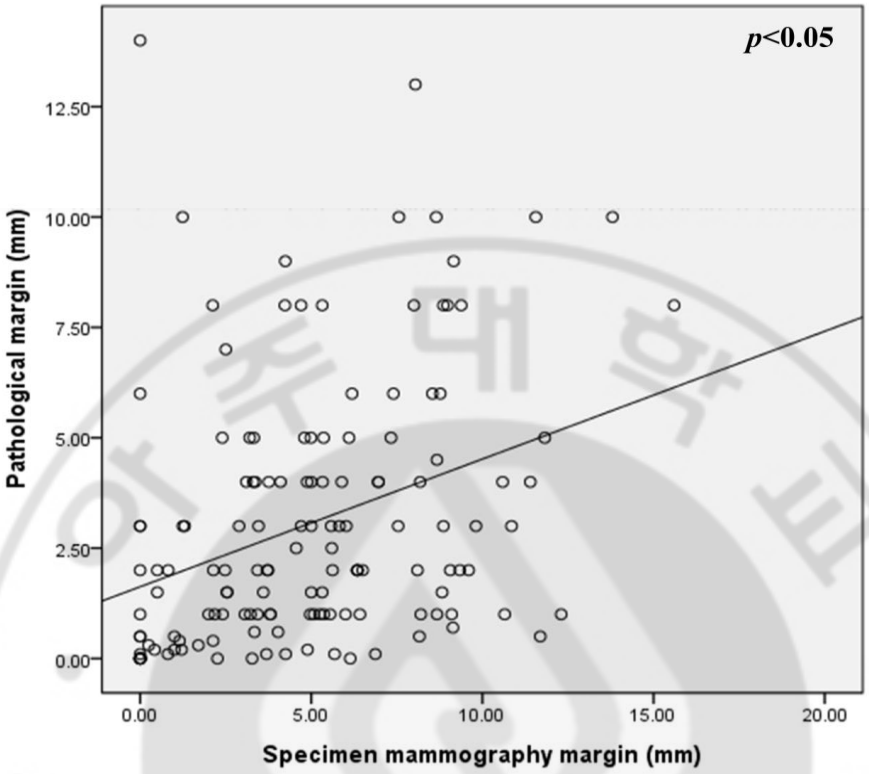

Fig. 2. Correlation between the intraoperative specimen radiological margins and the histological margins nearest distance lesion. (R^2 = 0.222, p < 0.05).

Ⅳ. DISCUSSION

As the use of BCS in oncoplastic surgery, expands worldwide, greater efforts are needed to achieve cancer-free margins, which are associated with local recurrence of breast cancer. The reported rates of margin positivity at the initial BCS range between 10% and 27% [5-8]. Furthermore, in the second operation after oncoplastic surgery, it is difficult to find margins with the remaining cancer cells, which led several studies to try to establish the most effective method for intraoperative surgical margin assessment.

Several studies have reported intraoperative methods for pathological evaluation, such as FSA, touch smear, and imprint cytology. The re-excision rate of FSA ranges between 3% and 10%, whereas, that of imprint cytology ranges from 0% to 33%. Both are significantly lower than that achieved without intraoperative pathological assessment [9,10]. However, FSA has several limitations, such as loss of tissue for permanent pathology, technical difficulties caused by a large amount of adipose tissue, significantly longer operation time, and lower accuracy for non-palpable lesions and/or those containing micro-calcifications [11,12]. Intraoperative ultrasonography allows the guidance of lesion distance, which can be visualized with ultrasound. Therefore, it should be performed in selective lesions without multifocality, with numerous calcifications. According to two randomized controlled trials (RCTs) [13,14], the positive margin rates of palpable and non-palpable tumors with intraoperative ultrasonography were 3% and 11%, respectively. Several other radio-guided surgery (RGS) techniques have been proposed to improve margin clearance, including radio-guided occult lesion localization (ROLL) and radioactive seed localization (RSL). ROLL involves an intra-tumoral injection of a radioactive tracer under ultrasound or stereotactic guidance. The surgical excision range can be detected with a hand-held gamma probe. RSL uses a small titanium seed containing ^{125}I, which can be detected in the mammography. A recent meta-analysis of seven RCTs demonstrated that RGS reduces operation time but increases the excised volume. Moreover, no significant differences were found between RGS and wire-guided localization in terms of positive margin and re-operation rate [15].

Intraoperative specimen radiography can be used for both non-palpable lesions with calcifications and palpable lesions visible on mammograms. However, few data are available in the literature concerning the accuracy, sensitivity and specificity of specimen

mammography. Several previous RCTs reported a 15.7% positive margin rate and a 5.7% re-operation rate [16 – 18].

The present study, compared two methods of intraoperative margin assessment, revealing a significantly longer operation time in the FSA group. On the other hand, for very-close margins, with less than 1 mm distance between the lesion and the resection margin and rate of re-operation, no differences were observed between two groups. Therefore, in cases where it is difficult to measure the margins, specimen mammography could be helpful to reduce operation time.

The present study found a significant correlation between the radiological and histological margins. However, there are several limitations regarding the data about radiological and histological margins. First, the radiological margins measured the closet distance between the resection borders on the 2-dimensional mammography, whereas, the histological margin microscopically measured the closest distance from the six-direction surface of the specimen, Therefore, a mismatch might have occurred between the radiological and histological margin status. Second, after specimen compression in the mammography unit, the direction and margin might have been distorted. A previous retrospective study revealed a significant association between specimen radiographs and histological results [19].

Several factors may affect mammographic breast density, such as age, body mass index, parity, menstrual status and race [20 – 22]. In fact, a significant difference was found between Korean and Western women, regarding breast density [3]. The Korean government encourages women over 40 years of age to undergo a mammography every two years for early detection of breast cancer. However, among Korean women, the mammographic sensitivity to breast masses rather than calcification is lower than in Western women due to a high frequency of dense breasts. No studies have been published about the relationship between breast density and specimen mammography. Therefore, we evaluated the possibility to identify the lesion on specimen mammography regardless of the initial mammographic density (Table 2). Among the 182 patients, the margin status in 106 (58.2%) could be

identified by micro-calcifications, whereas, others presented micro-calcification-free masses. According to our results, margin status was confirmed in 97.1% of the lesions with less than 50% mammographic density and in 85.7% lesions of other lesions. Therefore, mammographic density was found to affect margin status identification on specimen mammography.

Ⅴ. CONCLUSION

In conclusion, this study suggests that specimen mammography can be useful to assess margin status, especially in Asian breast cancer patients who have denser breast than Western's. Moreover, preoperative mammographic density can affect margin assessment on specimen mammography. Further RCTs with larger sample sizes are needed to confirm the significant advantage compared with other methods of intraoperative margin assessment.

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