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Macroscopic Intraoperative Margin Assessment and Risk Factors of Margin Involvement in Breast Cancer Conserving Surgery

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Abstract

Background: Surgical margin status after Breast-Conserving Surgery (BCS) is an important prognostic factor in breast cancer treatment.

Objective: To assess whether the protocol applied for intraoperative evaluation of the surgical specimen could affect the rate of margin involvement and to analyze other risk factors influencing margin status.

Methods: We identified patients treated with BCS between 2004 and 2015 at a breast cancer referral center. Invasive lesions underwent an intraoperative macroscopic pathologic evaluation, using "ink on tumor" as margin definition. Multivariate logistic regression methods identified the risk factors for surgical margin involvement.

Results: Of 1,054 patients receiving BCS, intraoperative margin assessment was performed in 78.3%. Failure to accomplish an intraoperative evaluation of margins was strongly associated with the rate of positive margins: 27.5% compared to 6.1% in the group whose margins were assessed. The overall definitive rate of inadequate margins was 10.7%. The multivariate study identified the following variables as independent predictors of margin involvement: Absence of intraoperative pathologic assessment of the margin, younger age, personal history of benign breast pathology, lack of preoperative diagnosis, intraductal histology and tumor size.

Conclusion: These clinicopathologic factors should be considered when planning BCS. Our systematic approach is an important strategy to reduce surgical reoperations.

Keywords: Intraoperative macroscopic margin assessment; Margin involvement risk factors; Breast-conserving surgery; Breast cancer

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Introduction

Breast-Conserving Surgery (BCS) is the standard surgical treatment of Breast Cancer (BC) [1,2]. Yet, surgical margin involvement remains one of the most controversial aspects in the management of BCS. Surgical margin status after BCS is an important prognostic factor. Positive margins are associated with a twofold increase in the risk of Local Recurrence (LR) [3], thus, requiring reoperation to ensure clear margins. This leads to an increase in morbidity, a delay in the onset of adjuvant therapy, an increase in anxiety and stress for patients, and increased costs [4,5].

Several factors are associated with positive surgical margins after BCS, namely, patient-related factors (age, medical history) [6,7]; factors related to disease presentation (palpable tumor) [6,7]; factors related to diagnostic procedures (mammography, ultrasound, etc.) [7]; factors related to surgical technique (management of non-palpable lesions, intraoperative evaluation of the surgical specimen) [8,9]; and to the characteristics of the tumor (tumor size, histological study) [9,10]. Understanding the relationship between these factors and margin status may reduce the rate of positive margins and consequently the rate of reoperations [4].

Our hospital has an extensive experience in treating patients with BCS and in applying a specific protocol for intraoperative evaluation of the surgical specimen, which we consider may have a

strong impact on the results of BCS.

The objective of the present study was to assess whether the application of our protocol for intraoperative examination of the surgical specimen could affect the rate of margin involvement, as well as, to analyze the association between other risk factors and margin status.

Material and Methods

A retrospective review of 1,054 patients who underwent BCS between 2004 and 2015 at a BC referral center was analyzed. Exclusion criteria included women with metastatic BC, patients who underwent mastectomy as the initial treatment of BC, patients who received neoadjuvant therapy and women diagnosed with ipsilateral BC before 2004.

The variables assessed were, namely:

-Related to patient or demographic variables (age, personal history of benign breast pathology and cancer, patients coming from the Breast Cancer Screening Program (BCSP).

-Related to clinical (palpable lesion) and radiological presentation (presence of micro calcifications in mammography, presence/absence of nodules in ultrasound images).

-Related to surgical details (wire localization procedure, presence/absence of a preoperative histological diagnosis, and presence/absence of an intraoperative pathological evaluation of the margin).

-Related to the definitive histological study (histological type, tumor grade differentiation, immunohistochemical characteristics (Ki67 proliferation index, ErbB2 expression, Estrogen Hormone (ER) and Progesterone Hormone (PR) receptor expression) and to the total tumor size (the sum of the invasive and DCIS component).

Margin management protocol used in our hospital

After the surgical specimen was excised, the margins were identified with metal clips for proper orientation of the specimen, followed by careful inspection and palpation by the surgeon. Wire-localized lesions were first referred to the radiology department to check the inclusion of the lesion. Upon arrival in the pathology department, specimens were inked but only invasive lesions underwent an intraoperative macroscopic pathologic evaluation of the margins. If there were any doubts concerning correct resection of the mass, as indicated by the radiology and pathology results, the corresponding resection margins were intraoperatively widened. In cases of uncertainty due to unexpected lesions, an intraoperative frozen section histological analysis was performed on the doubtful area. The new specimen margins of the additional intraoperative resections were also marked with clips and sutures, inked and assessed in a similar way as the initial surgical margin.

Margins were considered to be involved when cancer cells (invasive or Ductal Carcinoma *in situ* (DCIS)) were present on the inked margins of the excised tissue ("ink on tumor" [6]. The initial surgical margin was defined as the status of the surgical specimen margin at the time of initial excision. It was also considered to be the definitive one, in those patients who did not require additional intraoperative resections. On the other hand, the additional margin excised was considered the definitive one in those patients requiring margin enlargement. In those, with positive definitive margins a second time surgical re-excision was performed.

The data was collected in a Microsoft Access database and analyzed with the SPSS statistical package (version 25). In univariate analysis, the differences between groups were studied by applying the chi square test or Fisher exact test for the categorical variables and by the Student T test or the U Mann–Whitney test for the continuous variables. Subsequently, using the variables identified in the previous analysis as significant, as well as those considered most relevant in the literature, a multivariate logistic regression analysis was conducted to identify the most important risk factors for surgical margin involvement. Categorical variables were presented as frequencies and 95% Confidence Intervals (CI). Continuous variables were expressed as medians and standard deviations. A p-value ≤ 0.05 was considered statistically significant. P values are derived from two-tailed tests.

This study was approved by the ethical committee of the Complejo Hospitalario de Navarra, Pamplona, Spain.

Results

Patients, clinical, radiological, surgical and tumoral characteristics

The study included 1,054 patients with breast cancer who underwent BCS between January 2004 and December 2015. The mean age was 58.16 ± 12.6 years. A personal history of benign breast pathology was recorded in 12.9% (136) of the patients while 3.9% (41) had a personal history of contralateral BC. 70.7% (745 cases) came from the BC screening program.

Lesions were palpable in 45.3% (478) of the cases. Microcalcifications were present in 28.7% (303) of the patients. A nodular image in ultrasound was present in 74.6% (786) of the cases and 2.7% (29) had no preoperative histological diagnosis. Wire-guided BC surgery was performed in 64.2% (677) of the lesions.

Invasive carcinoma was the definitive diagnosis in 85.4% (900) of the cases and ductal carcinoma in situ in 14.6% (154) of the cases. The mean tumor size was 15.5 ± 9.6 mm. Table 1 shows the clinical, radiological, tumoral and surgical data.

Intraoperative margin assessment

Margin assessment during surgery was performed in 78.3% of the patients (825 of 1,054 patients). It was not assessed in the 229 remaining cases, either due to a preoperative diagnosis of ductal carcinoma *in situ* (132) or on account of the surgeon's treatment decision or technical non-availability (97 patients).

Failure to accomplish an intraoperative assessment of margins was strongly associated with the rate of positive margins: 27.5% compared to 6.1% in the group of patients whose margins were assessed intraoperatively. In fact, we found it to be an independent risk factor of margin involvement in the univariate (OR=5.883; p=0.000) and multivariate (OR=6,198; p=0.000) analysis, showing the greatest OR value in the multivariate study.

Guided by the results of the intraoperative macroscopic evaluation of margins, 348 patients (42.2%) underwent additional margin resection due to close or involved margins. No residual disease was found in 258 cases (74.1%) while cancer cells were present in 90 cases (25.9%). Of these 90 patients, 32 (9.2%) had definitive positive margins.

Margins were not widened during surgery in 706 cases. Of these, 81 (11.5%) had residual disease on the definitive margin (Table 2).

Thus, the overall definitive rates of clear and positive margins were 89.3% (941) and 10.7% (113) respectively. Out of a total of 1,054, 113

Table 1: Univariate analysis of the risk factors for margin involvement in patients undergoing BCS.

Characteristics	Clear definitive margin (N [%]) (N=941)	Involved definitive margin (N [%]) (N=113)	Odds Ratio (CI 95%)	P value
Age (median, SD)	57.34 ± 12.7	52.93 ± 11.5	58.17 ± 12.6	0.008
Personal history of breast cancer				
Yes	36 (87.8)	5 (12.2)	1.164 (0.45-3.03)	0.795
No	905 (89.3)	108 (10.7)	Ref.	
Personal history of benign breast pathology				
Yes	106 (77.9)	30 (22.1)	2,847 (1.80-4.53)	0
No	835 (91)	83 (9)	Ref.	
BC Screening program				
Yes	665 (89.3)	80 (10.7)	1.006 (0.65-1.54)	1
No	276 (89.3)	33 (10.7)	Ref.	
Palpable tumor				
No	502 (87.2)	74 (12.8)	1.659 (1.10-2.50)	0.019
Yes	439 (91.8)	39 (8.2)	Ref.	
Microcalcifications in mammography				
Yes	253 (83.5)	50 (16.5)	2.180 (1.46-3.25)	0
No	684 (91.7)	62 (8.3)	Ref.	
Ultrasound image				
Nodular image	724 (92.1)	62 (7.9)	0.344 (0.23-0.52)	0
Others	201 (80.1)	50 (19.9)	Ref.	
Preoperative diagnosis				
No	11 (37.9)	18 (62.1)	16.019 (7.35-34.92)	0
Yes	930 (90.7)	95 (9.3)	Ref.	
Guided surgical procedure				
Yes	594 (87.7)	83 (12.3)	1.616 (1.04-2.50)	0.039
No	347 (92)	30 (8)	Ref.	
Intraoperative assessment of margins				
No	166 (72.5)	63 (27.5)	5.883 (3.91-8.84)	0
Yes	775 (93.9)	50 (6.1)	Ref.	
Definitive diagnosis				
Intraductal carcinoma	126 (81.8)	28 (18.2)	2.131 (1.34-3.40)	0.001
Invasive carcinoma	815 (90.6)	85 (9.4)	Ref.	
Tumor grade				
High (III)	228 (91.2)	22 (8.8)	0.756 (0.46-1.23)	0.261
Low (I, II)	697 (88.7)	89 (11.3)	Ref.	
Ki 67 proliferation index				
Negative	84 (86.6)	13 (13.4)	1.256 (0.65-2.40)	0.492
Positive	430 (89)	53 (11)	Ref.	
ErbB2 expression				
Negative	683 (89.8)	78 (10.2)	1.033 (0.62-1.72)	1
Positive	190 (90)	21 (10)	Ref.	
ER Expression				
Negative	110 (89.4)	13 (10.6)	1.031 (0.56-1.91)	0.922
Positive	768 (89.7)	88 (10.3)	Ref.	
PR Expression				
Negative	215 (88.8)	27 (11.2)	1.122 (0.70-1.79)	0.629
Positive	661 (89.9)	74 (10.1)	Ref.	
Total tumor size (median, SD)	14.00 ± 9.5	16.00 ± 10.0	15.54 ± 9.6	0.002

SD: Standard Deviation; BC: Breast Cancer; Ki 67: ki 67 Cell Proliferation Marker; ErbB2: Tyrosine Kinase Receptor; ER: Estrogen Receptor; PR: Progesterone Receptor; Ref: Reference Value

Table 2: Positive margin rates, subdivided by additional margin resection v/s. no additional margin resection.

Widened margin	Definitive margin		
	Clear	Involved	Total
Yes	316 (90,8%)	32 (9.2%)	348 (100%)
No	625 (88,5%)	81 (11.5%)	706 (100%)
Total	941 (89,3%)	113 (10.7%)	1054 (100%)

(10.7%) patients required a second operation to ensure clear margins.

Risk factors associated with margin involvement

Our univariate analysis identified 9 additional factors that were significantly associated with margin involvement. With regard to the clinical and diagnostic variables, the median age of the group with involved margins was significantly lower compared to that with clear margins (52.9 *vs.* 57.3; p=0.008). Also, the patients with a personal history of benign breast pathology had a greater risk of having positive margins (22.1% *vs.* 9%; p=0.000).

The presence of Microcalcifications on mammography and a non-nodular image in ultrasound were associated to a higher risk of positive margins in relation to the absence of Microcalcifications and the presence of a nodular image (16.5% *vs.* 8.3% and 19.9% *vs.* 7.9 % respectively).

The variable "absence of preoperative histological diagnosis" was a risk factor for positive margins. Of the 29 (2.7%) patients who did not have a preoperative histological diagnosis, 62.1% had a definitive margin involved compared to 9.3% in the group who had previous histological diagnosis (OR=5.889; 95% CI=1, 65-20.98; p=0.039).

Non-palpable lesions were also associated with positive margins (12.8% *vs.* 8.2%; p=0.019). Lastly, wire-guided surgical procedures had a significantly higher risk of involved margins compared to non-guided procedures (12.3% *vs.* 8%; p=0.039).

With regard to the tumor-related variables, DCIS had 2.3 times greater risk of having positive margins than invasive carcinomas (18.2% *vs.* 9.4%; p=0.001). The overall total tumor size (sum of the invasive and non-invasive tumors) was also identified as a risk factor (median of 16 mm and 14 mm in the groups with positive and clear margins, respectively, p=0.002). Table 1 shows the univariate analysis of the above-mentioned risk factors.

In the multivariate study the following variables remained statistically significant: Absence of intraoperative pathologic assessment of the margin, younger patient age, personal history of benign breast pathology, lack of preoperative histological diagnosis, ductal carcinoma in situ, and overall total tumor size. The variable "localization technique" touched statistical significance in our multivariate analysis. While, the variable tumor differentiation grade was also included in the model but showed no statistically significant correlation with positive margins. The results of our multivariate study are shown in Table 3.

Discussion

The main objective of this study was to determine whether the protocol applied for intraoperative assessment of margin status could affect the rate of margin involvement in BCS. A positive margin was defined according to the 2014 ASCO/ASTRO consensus guidelines as "ink on tumor" [6,7]. On this basis, our overall positive margin rate was 10.7%, which is comparable to previously reported results [8-11]. However, this rate decreased to 6.1% when intraoperative pathologic examination was performed (825 of 1,054 patients, 78.3%) while it increased to 27.5% when it was not analyzed (OR=6.198; 95% CI= 3.28-11.71; p=0.000).

Our results coincide with various studies in which a similar protocol to evaluate margin involvement was employed [12-15]. In their retrospective study, Fleming and col., analyzed and compared the rate of positive margins in patients with and without intraoperative macroscopic assessment of margin status, reporting a rate of 9.1% *vs.* 21.4% respectively. Likewise, margins were assessed intraoperatively only in patients with invasive carcinomas since DCIS have less defined margins [15]. In comparison to their results, we obtained a slightly lower rate of inadequate margins that could be probably explained by the fact that they used a different criteria to define a positive margin (distance margin/tumor <10 mm) [12].

There are other diagnostic methods for intraoperative assessment of surgical margins that have been evaluated in the literature. In addition, in many of these studies, the rate of margin involvement was not directly, but indirectly assessed by reporting the rates of reoperations or re-excisions needed to achieve a clear margin. Intraoperative evaluation by frozen sections analysis or imprint cytology was significantly associated with lower re-excision rates, by enabling intraoperative resection of additional tissue [13,16]. Re-excision rates of 10% and 11% for patients that underwent frozen sections analysis and imprint cytology, have been respectively reported, compared to 35% in those lacking intraoperative pathologic assessment.

Table 3: Multivariate analysis of the risk factors for margin involvement in patients undergoing BCS.

Variables	Odds Ratio (CI 95%)	P Value
Age, years	0.978 (0.96-0.99)	0.03
Personal history of benign breast pathology: Yes v/s No	2.488 (1.42-4.35)	0.001
Palpable tumor: No v/s Yes	1.082 (0.53-2.23)	0.831
Pathological diagnosis: Intraductal carcinoma v/s Invasive carcinoma	3.573 (1.67-7.62)	0.001
Tumor grade: High (III) v/s low (I, II)	0.718 (0.40-1.30)	0.276
Microcalcifications in mammography: Yes v/s No	1.067 (0.56-2.04)	0.844
Ultrasound image: Nodular v/s non - nodular image	0.623 (0.32-1.21)	0.164
Histological preoperative diagnosis: No v/s Yes	5.889 (1.65-20.98)	0.006
Guided surgical procedure: Yes v/s No	1.990 (0.91-4.35)	0.085
Intraoperative assessment of margins: No v/s Yes	6.198 (3.28-11.71)	0
Tumor size, mm	1.041 (1.02-1.06)	0

Other methods employed were intraoperative ultrasound or specimen radiography. The proportion of patients in whom margins had to be widened intraoperatively was similar to ours (33%). A recent meta-analysis compared these methods of intraoperative specimen management to assess surgical resection margins. The results of the study indicate that frozen section analysis and imprint cytology had greater diagnostic precision than intraoperative ultrasound and specimen radiography. But, they also found that these methods are more time and resource consuming, thereby, hindering their widespread use [14].

Several recent studies recommend resecting an additional margin of tissue at each of the margins around the tumor cavity intraoperatively (Cavity Shave Margins [CSM]) [17-19]. This technique achieved a significant decrease in the rate of positive margins in BCS. However, it considerably altered the cosmetic result since the volume of tissue resected was bigger and also increased surgical time. The authors report a higher rate of positive margins compared to the ones that we obtained with gross pathologic evaluation (6.1% in our study and 9.7% in CSM) [18]. Guided by the results of the macroscopic evaluation, when additional margins had to be resected, we actually performed a "selective shaving of a margin". In this way, less volume of tissue was resected with a better esthetic result. Also, unlike other methods, ours barely influenced surgical time since pathological assessment was carried out while we continued with sentinel node biopsy or reconstruction of the breast in the operating room.

Analysis of risk factors for margin involvement

In addition to intraoperative evaluation of the margins, there are other factors that have been associated with positive surgical margins in BCS. In the second part of our study we performed a multivariate analysis of these risk factors in order to evaluate possible interactions among them.

Within the epidemiological factors we found that younger age was associated with a higher rate of margin involvement (OR=0.978; 95% CI = 0.96-0.99; p=0.030). This was consistent with findings previously described in the bibliography [9,20-22].

In addition, the results or our study showed that patients with a personal history of benign pathology (benign tumors, radial scars, etc.), had a significantly higher risk of having positive margins (OR=2.488, 95% CI 1.42-4.35) compared to those without a personal history. In the bibliography reviewed, we have not found any reports describing this relationship, although several studies associate BC and benign breast pathology. A meta-analysis published by Dyrstad et al. reports a fourfold risk of BC in women with non-proliferative breast pathology with and without atypia [23].

With regard to the diagnostic variables, in the univariate analysis, the presence of Microcalcifications in the mammogram was also significantly associated with margin involvement (OR=2.180; 95% CI = 1.46-3.25; p=0.000). These findings were consistent with multiple previous studies [16,24-26]. In addition, we found that the absence of a nodular image on ultrasound was a risk factor for positive margins (OR=0.344; 95% CI = 0.23-0.52; p=0.000). Other studies associate the absence of a mass on mammography with margin involvement [9,27], but, we have not found in the literature any mention of ultrasound findings as predictors of margin involvement. None of these variables were confirmed as risk factors in the logistic regression model.

The absence of a preoperative histological diagnosis was previously described as a risk factor to foresee in order to avoid margin involvement [8,9,27,28]. This group of patients underwent lumpectomy or surgical biopsy instead of segmentectomy. Considering that an intraoperative analysis of the margin was not carried out in these specimens, it was reasonable to expect that these 29 patients without preoperative histological diagnosis had a higher rate of positive margins (62.1% compared to 9.3% in the group with preoperative histological diagnosis).

Although, the terms "non-palpable lesions" and "localization techniques" are often used indistinctly, we considered them as two independent variables. The reason was that certain lesions are difficult to palpate and need the placement of a guide wire to facilitate resection. In our sample, the percentage of guided procedures (64.2%) was greater than the overall number of non-palpable tumors (54.6%). This was because, in addition to non-palpable lesions that required a localization technique, 22.8% of the palpable lesions also required the placement of a guide wire. Our study found that guided surgical procedures had a higher risk of having positive margins than non-guided procedures (OR 1.616; 95% CI 1.04-2.50; p=0.039). This correlated with increased risk of involved margins in non-palpable versus palpable lesions (OR=1.659; 95% CI = 1.10-2.50; p=0.019). None of these two variables reached statistical significance in the multivariate model, although the variable localization procedure touched it (p=0.085). These results were consistent with previous reports [8,9,28,29].

With regard to tumor-related factors, our study found a 3.57 times higher risk of involved margins in cases of DCIS with respect to invasive lesions (OR=3.57; 95% CI = 1.67-7.62; p=0,001). A larger tumor size also significantly increased the risk of positive margins (OR=1.04; 95% CI = 1.02-1.06; p=0.000). Both data are concordant with various previous descriptions [9,10,20,21,24,30].

Other factors that have been related to the rate of margin involvement in the literature are: Multifocality [21], tumor grade [20], or lymph node involvement [21,22]. The variable tumor grade was also included in our model, but it did not reach statistical significance. The molecular characteristics of the tumor did not show statistical differences in margin involvement, although immunohistochemical techniques could not be performed on all patients.

The limitations of our study include its retrospective study design and the large time frame of our study (2004-2015). Although the criteria for assessing margin involvement have not changed in this period, the availability of techniques to assess Ki67, ErbB2, as well as imaging techniques such as MRI evaluation were limited during the initial years. However, these inconveniences have been compensated by warranting long-term follow-up of patients.

Conclusion

Intraoperative margin assessment of the specimen by gross pathological examination manages to significantly reduce the rate of involved margins. It enables a targeted approach of the surgical margin involved reducing the amount of tissue excised.

In our opinion, our systematic approach is an important strategy that should be considered in order to reduce the number of surgical reoperations, provided that the center has the economic and technical means to carry it out.

Intraoperative evaluation of surgical margins, as well as younger age, history of benign breast pathology, the absence of a preoperative diagnosis, DCIS, and tumor size were all independent predictors of

margin involvement. All of these factors should be taken into account when planning BCS to reduce the rate of margin involvement.

Highlights

1. Intraoperative margin assessment of the specimen by gross pathological examination manages to significantly reduce the rate of involved margins in breast cancer-conserving surgery.

2. Absence of intraoperative pathologic assessment of the margin, younger age, personal history of benign breast pathology, lack of preoperative diagnosis, intraductal histology and tumor size are independent predictors of margin involvement in breast cancer-conserving surgery.

3. Our overall definitive rate of inadequate margins was 10.7% When the protocol for intraoperative evaluation of the surgical specimen was applied, this rate improved to 6.1%.

References

1. 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(16):1227-32.
2. Kaye BL, Veronesi U. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. Plast Reconstr Surg. 1982;69(2):383.
3. Houssami N, MacAskill P, Marinovich ML, Dixon JM, Irwig L, Brennan ME, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. Eur J Cancer. 2010;46(18):3219-32.
4. Grant Y, Al-Khudairi R, Carter A, Barschkett M, Cunningham D, Al-Mufti R, et al. Patient-level costs in margin excision for breast-conserving surgery. Ann Surg Oncol. 2018;25:319-20.
5. Baliski CR, Pataky RE. Influence of the SSO/ASTRO Margin Reexcision Guidelines on costs associated with breast-conserving surgery. Ann Surg Oncol. 2017;24(3):632-7.
6. Houssami N, Macaskill P, Marinovich ML, Morrow M. The Association of Surgical Margins and Local Recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: A meta-analysis. Ann Surg Oncol. 2014;21(3):717-30.
7. Buchholz TA, Somerfield MR, Griggs JJ, El-Eid S, Hammond MEH, Lyman GH, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American society of clinical oncology endorsement of the society of surgical oncology/ American society for radiation oncology consensus guideline. J Clin Oncol. 2014;32(14):1502-6.
8. 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(6):740-6.
9. Lai HW, Huang RH, Wu YT, Chen CJ, Chen ST, Lin YJ, et al. Clinicopathologic factors related to surgical margin involvement, reoperation, and residual cancer in primary operable breast cancer-an analysis of 2050 patients. Eur J Surg Oncol. 2018;44(11):1725-35.
10. Laws A, Brar MS, Bouchard-Fortier A, Leong B, Lynn Quan M. Does intra-operative margin assessment improve margin status and re-excision rates? A population-based analysis of outcomes in breast-conserving surgery for ductal carcinoma in situ. J Surg Oncol. 2018;118(7):1205-11.
11. Van Deurzen CHM. Predictors of surgical margin following breast-conserving surgery: A large population-based cohort study. Ann Surg Oncol. 2016;23(suppl 5):627-33.
12. Fleming FJ, Hill ADK, Mc Dermott EW, O'Doherty A, O'Higgins NJ, Quinn CM. Intraoperative margin assessment and re-excision rate in breast conserving surgery. Eur J Surg Oncol. 2004;30(3):233-7.
13. Esbona K, Li Z, Wilke LG. Intraoperative imprint cytology and frozen section pathology for margin assessment in breast conservation surgery: A systematic review. Ann Surg Oncol. 2012;19(10):3236-45.
14. St John ER, Al-Khudairi R, Ashrafian H, Athanasiou T, Takats Z, Hadjiminas DJ, et al. Diagnostic accuracy of intraoperative techniques for margin assessment in breast cancer surgery a meta-analysis. Ann Surg. 2017;265(2):300-10.
15. Butler-Henderson K, Lee AH, Price RI, Waring K. Intraoperative assessment of margins in breast conserving therapy: A systematic review. Breast. 2014;23(2):112-9.
16. Jorns JM, Visscher D, Sabel M, Breslin T, Healy P, Daignaut S, et al. Intraoperative frozen section analysis of margins in breast conserving surgery significantly decreases reoperative rates: One year experience at an ambulatory surgical center. Am J Clin Pathol. 2012;138(5):657-69.
17. Landercasper J, Attai D, Atisha D, Beitsch P, Bosserman L, Boughey J, et al. Toolbox to reduce lumpectomy reoperations and improve cosmetic outcome in breast cancer patients: The American Society of Breast Surgeons Consensus Conference. Ann Surg Oncol. 2015;22(10):3174-83.
18. Dupont E, Tsangaris T, Garcia-Cantu C, Howard-McNatt M, Chiba A, Berger AC, et al. Resection of cavity shave margins in stage 0-III breast cancer patients undergoing breast conserving surgery. Ann Surg. 2021;273(5):876-81.
19. Gray RJ, Pockaj BA, Garvey E, Blair S. Intraoperative margin management in breast-conserving surgery: A systematic review of the literature. Ann Surg Oncol. 2018;25(1):18-27.
20. Findlay-Shirras LJ, Outbih O, Muzyka CN, Galloway K, Hebbard PC, Nashed M. Predictors of residual disease after breast conservation surgery. Ann Surg Oncol. 2018;25(7):1936-42.
21. 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(13):3797-801.
22. Eaglehouse YL, Georg MW, Jatoi I, Shriver CD, Kangmin Zhu. Factors related to re-excision procedures following primary breast-conserving surgery for women with breast cancer in the U.S. Military Health System. J Surg Oncol. 2019.
23. Dyrstad SW, Yan Y, Fowler AM, Colditz GA. Breast cancer risk associated with benign breast disease: Systematic review and meta-analysis. Breast Cancer Res Treat. 2015;149(3):569-75.
24. Murphy BL, Boughey JC, Keeney MG, Glasgow AE, Racz JM, Keeney GL, et al. Factors associated with positive margins in women undergoing breast conservation surgery. Mayo Clin Proc. 2018;93(4):429-35.
25. Pleijhuis RG, Kwast ABG, Jansen L, de Vries J, Lanting R, Bart J, et al. A validated web-based nomogram for predicting positive surgical margins following breast-conserving surgery as a preoperative tool for clinical decision-making. Breast. 2013;22(5):773-9.
26. Edwards SB, Leitman IM, Wengrofsky AJ, Giddins MJ, Harris E, Mills CB, et al. Identifying factors and techniques to decrease the positive margin rate in partial mastectomies: Have we missed the mark? Breast J. 2016;22(3):303-9.
27. 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(9):2542-9.
28. Mann GB, Wong J, Skandarajah A, Elder K, Gorelik A, Mann GB. Factors influencing reoperation following breast-conserving surgery. ANZ J Surg. 2018;88(9):922-7.
29. Dillon MF, Hill ADK, Quinn CM, McDermott EW, O'Higgins N. A

pathologic assessment of adequate margin status in breast-conserving therapy. Ann Surg Oncol. 2006;13(3):333-9.

30. Langhans L, Jensen MB, Talman MLM, Vejborg I, Kroman N, Tvedskov TF. Reoperation rates in ductal carcinoma *in situ vs.* invasive breast cancer after wire-guided breast-conserving surgery. JAMA Surg. 2017;152(4):378-84.