Repeated Intraoperative Margin Re-excision from Frozen Section Analysis during Breast Conserving Surgery and Ipsilateral Breast Tumor Recurrence in Patients who Underwent Neoadjuvant Chemotherapy

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Directed by Professor Joon Jeong

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ABSTRACT

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The utilization of breast-conserving surgery (BCS) grew with the increased rate of neoadjuvant chemotherapy (NAC). Determining the extent of residual tumor can be challenging due to the diverse patterns of tumor reduction observed across different subtypes. Frozen section analysis is a useful tool to determine surgical margin status during surgery, thereby averting the need for subsequent surgery for margin re-excision. Here, we investigated ipsilateral breast tumor recurrence (IBTR) according to additional margin re-excision during a single surgery in patients who had undergone NAC. We identified breast cancer patients who received lumpectomy and NAC in a single institution (Gangnam Severance Hospital, South Korea) between

January 2011 and December 2018. If tumor margins were positive, re-excised margins were sent to frozen sections in a single procedure until all margins achieved tumor-free. Patients who eventually had conversion to total mastectomy were excluded. Among 185 patients, 33 patients had margin re-excision. The re-excision group had a larger residual tumor size and were less likely to achieve pathologic complete response (pCR). Median follow-up was 63 months and 16 IBTR events occurred. The re-excision group demonstrated worse recurrence-free survival and overall survival. However, the subgroup anlaylsis of non pCR group exhibited comparable local recurrence free survival and overall survival between the two groups. Performing intraoperative margin re-excision during a single breast surgery is not linked to an increased risk of IBTR in breast cancer patients who have received NAC.

Key words : breast cancer, breast conserving surgery, frozen section analysis, margin assessment, recurrence

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I. INTRODUCTION

Breast conserving surgery (BCS) followed by adjuvant radiation therapy(RT) has provided patients who are eligible for breast conservation an opportunity to have a surgical option. Previous studies have demonstrated that BCS have equivalent impact on survival compared to mastectomy. Recent stuides show otherwise that having BCS followed by RT may actually result in a more favorable outcome in survival compared to undergoing mastectomy without radiation. This difference over time can be partly attributed to selection bias. A national cohort study conducted in Sweden found that mastectomy treatment patient groups were older, had a higher burden of comorbidities, and a lower socioeconomic status. Despite the adjustment for covariables, BCS followed by RT yielded better

survival than mastectomy irrespective of RT. This finding implies that when both options are valid, choosing BCS should be prioritized. 10-year local recurrence (LR) rates ranged from 3.5% to 6.5% among patients treated with BCS[1]. Meta-analysis confirmed that negative margins reduce the odds of local recurrence, however, increasing the distance of definitive negative margin is not significantly associated with reduced odds of LR[2,3]. Safe margins differ between invasive tumor and in situ disease. “No ink on tumor” is enough minimize the risk of ipsilateral breast tumor recurrence (IBTR), whereas ductal carcinoma in situ (DCIS) needed at least 2mm from tumor to lower the IBTR risk.

Chagpar et al. conducted a randomized controlled trial to undergo further cavity shave margin[4,5.] Patients in the shave group had a significantly lower rate of positive margins than those in the no shave group. Paraffin section of inked surgical margin is gold standard for margin assessment, but time consuming. Several methods of intraoperative margin assessments are being implemented to lower the rates of positive margins at breast tumor resection. Frozen section analysis(FSA) is one of the accurate method that significantly reduces reoperation and medical costs, although it needs a multidisciplinary team effort. Routine use of FSA reduced a reoperation rate from 15% to 3%

Stuides investigating the margin assessments report that BMI, method of localization, presence of microcalcification can affect margin re-excision. However, in patients who had neoadjuvant chemotherapy(NAC), it can be more challenging. The tumor shrinkage pattern cannot be predicted and complete response from after-NAC imaging cannot always guarantee pathologic complete response (pCR). Few studies have investigated the clinicopathologic factors associated with margin excision. Moreover, the percentage of patients receiving NAC has been increasing, and data regarding margin assessment in those who had NAC before surgery are scarce, yet to be studied.

NAC are now being employed more vigorously than before, with treatment like capecitabine or T-DM1 being more actively utilized in post-neoadjuvant setting. NAC plays a crucial role in converting initially inoperable breast cancer cases into operable ones, thereby offering more patients chance to avoid mastectomy. Beyond enhancing body image, NAC demonstrates breast cancer-specific survival rates that are comparable to, if not superior to, those achieved without neoadjuvant therapy. Certain studies suggest that BCS after NAC seemed to have better survival compared to patients having mastectomy without radiation.

Considering that pathologic reporting practice for breast cancer specimen after NAC is more complex, it is anticipated that

intraoperative fresh frozen section of postneoadjuvant specimen would be intricate as well. Here, we aim to study clinicopathologic factors associated with repeated intraoperative margin re-excision and IBTR, especially in patients who received neoadjuvant chemotherapy.

II. MATERIALS AND METHODS

1. Patients and data collection

Between January 1, 2011, and December 31, 2018, a total of 185 women with invasive breast tumors had received NAC and undergone breast conserving surgery at Gangnam Severance Hospital in South Korea. Tumor characteristics, surgical techniques, and adjuvant treatment information of the identified patients were obtained from institutional database. Individual chart review was performed to identify any ipsilateral breast tumor recurrence and regional recurrence until June, 2023. Institutional Review Board approval was waived due to the retrospective nature of the study.

2. Intraoperative margin assessment

Intraoperative margin assessment by frozen section pathologic examination has been a routine procedure in our institute. Cavity shave margin excision was also routinely done after lumpectomy, and shaved margins are sent separately in four directions; superior, inferior, medial, and lateral. Fresh tissue representing each

direction are frozen in dextrin solution and cut in sections in 10mm thick. We proceeded with intraoperative margin re-excision when the fresh frozen tissue reviewed by pathologists contains invasive carcinoma or in situ portion at the margin itself. Margin re-excision was also considered when atypical cells were present, implicating very close safety margins. However, we did not measure the distance of safety margin, and did not incorporate this into the decision of re-excision. Repeated margin re-excision was performed until we obtain “free from tumor (FFT)” without compromising the cosmetic results within the clinical context of the patients. Decision regarding the conversion to total mastectomy was evaluated individually, depending on the residual breast tissue of each patient. Slides with the fresh frozen tissue were reviewed again in permanent deeper section and five patients had undergone secondary operation because the final pathologic report has been changed from “FFT” to “presence of invasive carcinoma or carcinoma in situ”. Those five were classified into margin re-excision group. We excluded those from the analysis who eventually had subsequent mastectomy, and patients who initially had vacuum assisted excision or excision from other hospital before.

3. Statistical analysis

Clinical variables were collected based on electric medical records, including age, BMI, tumor size, grade, invasiveness, lymph node involvement, tumor subtype, localization, presence of microcalcification on mammography, and satellite nodules. Chi-square test was used for categorical variables, and the student t-test was used for continuous variables. Univariate and multivariable logistic regression analysis was utilized to find factors associated with intraoperative margin re-excision. Variables with p-value under 0.1 were included in multivariable analysis. Kaplan-Meier curve was created using log-rank test to compare differences in IBTR. Statistical analysis was performed in SPSS and GraphPad PRISM 7.

III. RESULTS

1. Baseline characteristics

There were 185 patients who had BCS after NAC between January 2011 and December 2018 at Gangnam Severance Hospital. Among them, 28 patients had margin positive from intraoperative FSA. Five of them turned out to be benign in final review of the fresh frozen specimen and one person had secondary margin re-excision even after intraoperative margin re-excision result was negative in initial surgery, because the result changed during final evaluation.

From 157 patients who had “free from tumor” in FSA, five had second operation due to margin positive in final pathology review. Those who had secondary surgery for margin re-excision and did not convert to mastectomy were re-classified in the margin re-excision group, and the one who had benign pathology and did not need margin re-excision in the first place were re-classified to FFT at first group. The final study population did not change from 185 patients.

FFT at first group were 152 and intraoperative margin excision group were 33. FFT at first group was more likely to achieve pCR at a rate of 47.4%, whereas group only 21.2% patients achieved pCR in the intraoperative margin re-excision group (Table 1). Moreover, the mean value of pathologic tumor size and total extent of residual tumor from MRI after neoadjuvant chemotherapy were significantly larger in intraoperative margin re-excision group. Also, the presence of daughter nodule from postNAC MRI was more common in intraoperative margin re-excision group. Other clinical factors, such as age, body mass index (BMI), histologic grade, tumor subtype, Ki67, and presence of daughter nodule in the initial MRI imaging and microcalcification were well balanced between two groups.

Table 1. Baseline characteristics between FFT at first and margin re-exicision group

	FFT at first (N=152)	Margin re-excision (N=33)	p
Before NAC (at biopsy)			
AGE	48.0 ± 10.0	47.1 ± 11.9	0.648
BMI	24.1 ± 3.7	24.0 ± 3.8	0.953
Clinical tumor size (cm)	3.7 ± 1.6	3.6 ± 1.1	0.731
HG			
Low	63 (61.8%)	13 (65.0%)	0.984
High	39 (38.2%)	7 (35.0%)	
Ki-67 (%)			
Low	10 (17.2%)	4 (28.6%)	0.558
High	48 (82.8%)	10 (71.4%)	
Subtype			
HR+HER2-	41 (27.0%)	14 (42.4%)	
HR+HER2+	27 (17.8%)	1 (3.0%)	0.070
HR-HER2+	27 (17.8%)	8 (24.2%)	
HR-HER2-	57 (37.5%)	10 (30.3%)	
NME			
No	98 (73.7%)	25 (78.1%)	0.770
Yes	35 (26.3%)	7 (21.9%)	
daughter nodule			0.563
No	99 (74.4%)	26 (81.2%)	

	FFT at first (N=152)	Margin re-excision (N=33)	p
Yes	34 (25.6%)	6 (18.8%)	
After NAC (surgical spec			
Breast pCR			
No	80 (52.6%)	26 (78.8%)	0.010
Yes	72 (47.4%)	7 (21.2%)	
RCB			0.049
0	47 (45.6%)	5 (23.8%)	
1	13 (12.6%)	1 (4.8%)	
2	35 (34.0%)	14 (66.7%)	
3	8 (7.8%)	1 (4.8%)	
Pathologic tumor size (cm)	0.6 ± 0.9	1.0 ± 0.9	0.044
pN stage			
0	108 (71.1%)	20 (60.6%)	
1	37 (24.3%)	8 (24.2%)	0.158
2	6 (3.9%)	4 (12.1%)	
3	1 (0.7%)	1 (3.0%)	
HG			
Low	67 (71.3%)	23 (76.7%)	0.733
High	27 (28.7%)	7 (23.3%)	
Ki-67 (%)			1.000
Low	44 (46.3%)	14 (48.3%)	

	FFT at first (N=152)	Margin re-excision (N=33)	p
High	51 (53.7%)	15 (51.7%)	
LVI			
No	129 (92.8%)	21 (67.7%)	<0.001
Yes	10 (7.2%)	10 (32.3%)	
Total extent (cm)	0.8 ± 0.9	1.4 ± 1.2	0.003
NME			
No	112 (83.0%)	28 (87.5%)	0.719
Yes	23 (17.0%)	4 (12.5%)	
Daughter nodule			
No	131 (97.0%)	27 (84.4%)	0.016
Yes	4 (3.0%)	5 (15.6%)	
Reduction pattern			
concentric	121 (91.7%)	26 (86.7%)	0.013
scattered	10 (7.6%)	1 (3.3%)	
N/A	1 (0.8%)	3 (10%)	
Localization			
No	12 (7.9%)	4 (12.9%)	0.400
US-guided	82 (54.3%)	13 (41.9%)	
Mammo-guided	57 (37.7%)	14 (45.2%)	
Microcalcification			
No	75 (57.3%)	15 (51.7%)	0.737
Yes	56 (42.7%)	14 (48.3%)	

FFT; free from tumor, BMI; body mass index, HG; histologic grade, NME; non mass enhancement, RCB; residual cancer burden, LVI; lymphovascular invasion

The median follow-up period was 63 months, and during that time 16 IBTR event occurred. FFT at first group had 10 IBTR events and intraoperative margin re-excision group had 6 patients who had IBTR. IBTR-free survival rate were similar between the two groups (p=0.034, data not shown). Margin re-excision group had generally worse survival compared to FFT at first group, apparently related to more patients having non-pCR were included in margin re-excision group.

2. Subgroup analysis in patients with non-pCR

It was inevitable to carry the analysis after excluding patients who received pCR, and there were 106 patients left, 80 and 26 patients each in the FFT at first group and intraoperative margin re-excision group. In the subgroup analysis that compared only those who had residual tumor left in the breast, the clinical characteristics such as clinical tumor size, histologic grade, tumor subtype, and residual cancer burden index were similar (Table 2). However, intraoperative margin re-excision group significantly had more patients who had lymphovascular invasion, although pathologic N stage were similar. Unforeseen finding was that more patients had scattered shrinkage

pattern of the tumor in FFT at first group.

Table 2. Baseline characteristics between FFT at first and margin re-exicision group in non-pCR patients

	FFT at first (N=80)	Margin re-excision (N=26)	p
Before NAC (at biopsy)			
AGE	48.8 ± 10.5	48.0 ± 12.6	0.741
BMI	23.9 ± 3.9	23.7 ± 2.7	0.767
Clinical tumor size (cm)	3.7 ± 1.7	3.6 ± 1.2	0.762
HG			
Low	34 (64.2%)	11 (68.8%)	0.969
High	19 (35.8%)	5 (31.2%)	
Ki-67c			
Low	8 (29.6%)	3 (27.3%)	1.000
High	19 (70.4%)	8 (72.7%)	
Subtype			
HR+HER2-	35 (43.8%)	14 (53.8%)	
HR+HER2+	12 (15.0%)	1 (3.8%)	0.192
HR-HER2+	5 (6.2%)	4 (15.4%)	
HR-HER2-	28 (35.0%)	7 (26.9%)	
NME			
No	53 (81.5%)	19 (76.0%)	0.769
Yes	12 (18.5%)	6 (24.0%)	

	FFT at first (N=80)	Margin re-excision (N=26)	p
Daughter nodule			
No	50 (76.9%)	20 (80.0%)	0.975
Yes	15 (23.1%)	5 (20.0%)	
After NAC (surgical spec			
RCB			
1	9 (17.3%)	1 (6.2%)	0.289
2	35 (67.3%)	14 (87.5%)	
3	8 (15.4%)	1 (6.2%)	
Pathologic tumor size (cm)	1.2 ± 0.9	1.2 ± 0.9	0.830
pN stage			
0	46 (57.5%)	13 (50.0%)	
1	28 (35.0%)	8 (30.8%)	0.402
2	5 (6.2%)	4 (15.4%)	
3	1 (1.2%)	1 (3.8%)	
HG			
Low	48 (71.6%)	20 (80.0%)	0.586
High	19 (28.4%)	5 (20.0%)	
Ki-67 (%)			
Low	41 (61.2%)	12 (48.0%)	0.367
High	26 (38.8%)	13 (52.0%)	
LVI			0.006

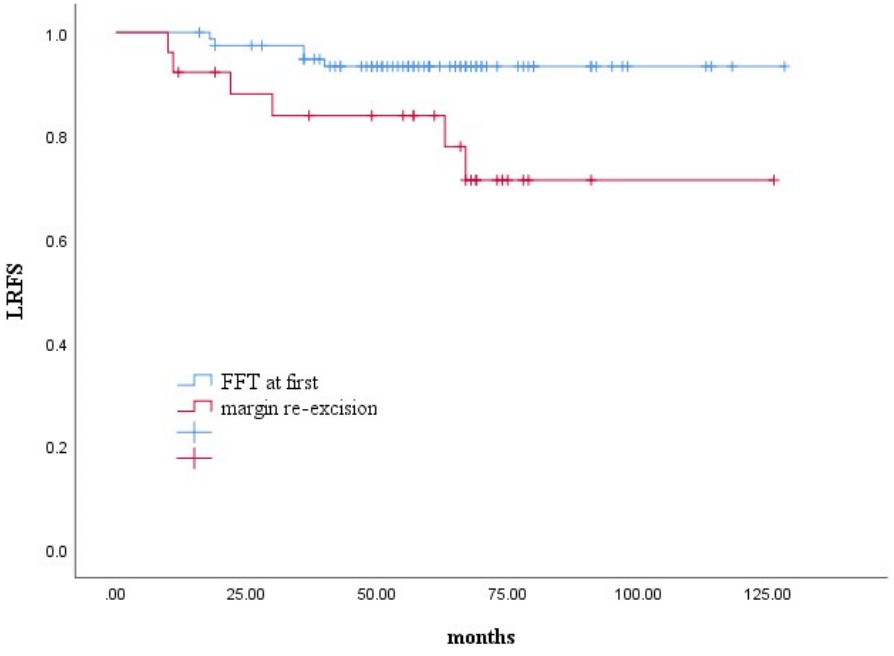
	FFT at first (N=80)	Margin re-excision (N=26)	p
No	61 (87.1%)	14 (58.3%)	
Yes	9 (12.9%)	10 (41.7%)	
Total extent (cm)	3.9 ± 1.8	3.6 ± 1.2	0.410
NME			
No	57 (85.1%)	22 (88.0%)	0.982
Yes	10 (14.9%)	3 (12.0%)	
Daughter nodule			
No	64 (95.5%)	21 (84.0%)	0.158
Yes	3 (4.5%)	4 (16.0%)	
Reduction pattern			
concentric	56 (87.5%)	20 (87.0%)	0.034
scattered	7 (10.9%)	0 (0.0%)	
N/A	1 (1.6%)	3 (13%)	
Localization method			
No	11 (13.8%)	4 (16.7%)	0.259
US-guided	51 (63.8%)	11 (45.8%)	
Mammo-guided	18 (22.5%)	9 (37.5%)	
Microcalcification			
No	36 (57.1%)	11 (47.8%)	0.601
Yes	27 (42.9%)	12 (52.2%)	

FFT; free from tumor, BMI; body mass index, HG; histologic grade, NME; non mass enhancement, RCB; residual cancer burden, LVI; lymphovascular invasion

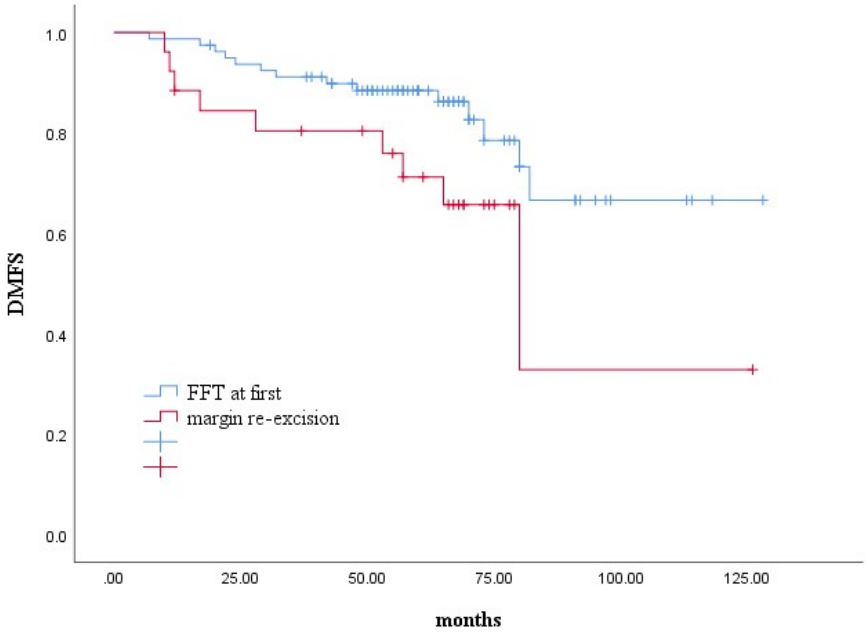
3. Survival analysis in non-pCR patients according to margin re-excision

Survival analysis was conducted in non-pCR patients only. There were 11 IBTR events during follow-up period, five from FFT at first group and 6 from margin re-excision group. IBTR-free survival rate was much worse in margin re-excision group (p=0.015). As a secondary endpoint, distant metastasis free survival (DMFS), recurrence free survival (RFS) and overall survival (OS) were also analyzed. There were more distant relapses than local recurrences, as 23 distant relapses occurred, and 13 of them had concurrent local and distant recurrence. 14 distant metastasis were from FFT at first group and 9 distant metastasis were from margin re-excision group. This also led to significantly worse DMFS in margin re-excision group (p=0.038). Margin re-excision group had significantly worse RFS (p=0.027), however, this finding was not consistent in OS (p=0.301).

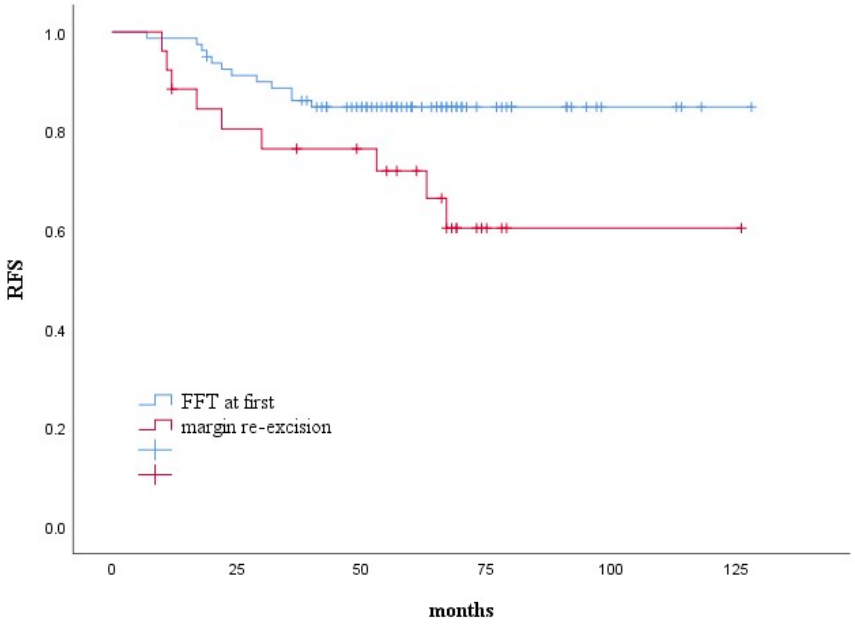
(A) IBTR free survival (p=0.015)



(B) DMFS (p=0.038)



(C) RFS (p=0.027)



(D) OS (p=0.301)

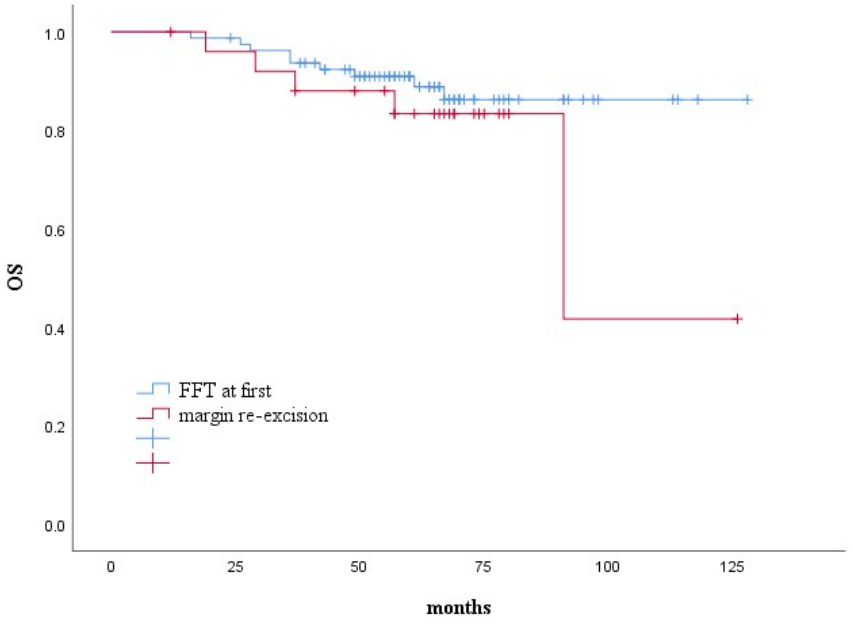


Figure 1. (A) IBTR-free survival and (B) distant metastasis free survival (C) recurrence free survival (D) overall survival according to margin re-excision in the subgroup of non-pCR patients

4. Factors associated with margin re-excision

Factors associated with margin re-excision in patients who had NAC

were further analyzed. Patient related factor such as age and BMI, tumor factors from pathologic diagnosis, and radiologic factors including non-mass enhancement, daughter nodule, total extent from MRI, tumor reduction pattern were considered in the analysis. Univariable analysis showed LVI and the presence of daughter nodule associated with possible margin re-excision. After adjustment, multivariable analysis exhibited that LVI is the only significant factor associated with margin re-excision (Table 3).

Table 3. Factors associated with margin re-excision

	univariable			multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Before NAC (at biopsy)						
Age	0.6	0.223-1.614	0.312			
BMI	0.826	0.337-2.025	0.675			
HG	0.921	0.275-3.089	0.894			
Ki67	0.932	0.192-4.539	0.933			
LVI	4.725	1.586-14.079	0.005	4.247	1.288-14.001	0.018
Pathologic tumor size (cm)	1.186	0.705-1.996	0.52			

Subtype	ref		0.569			
	0.231	0.027-1.954	0.179			
	0.791	0.145-4.308	0.786			
	0.692	0.244-1.965	0.49			
NME	0.536	0.109-2.629	0.536			
Daughter nodule	4.963	1.017-24.211	0.048	4.778	0.827-27.609	0.081
After NAC (surgical specimen)						
Total extent	1.256	0.748-2.109	0.389			
Reduction pattern	<0.001		0.999			
Microcalcification	1.454	0.542-3.901	0.458			
Localization method	ref		0.221			
US-guided	0.864	0.211-3.542	0.839			
Mammo-guided	0.403	0.136-1.196	0.102			

5. Risk factors associated with IBTR

Risk factors associated with IBTR were evaluated using Cox regression hazard model. Margin re-excision increased the risk of

IBTR at HR 3.93 (95% CI 1.198-12.919, p=0.024) compared to FFT at first (Table 4). The number of margin re-excision was also included as a variable in the analysis. Among those who had margin re-excision, about half of the patients had only once, and the rest had more than twice. Increase in the frequency of margin re-excision did not lead to a rise in the IBTR rate. Conventional prognostic factors such as clinical tumor size, pathologic tumor size, and nodal staging were not significant, except histologic grade and Ki67 index. Multivariable analysis revealed that margin re-excision and histologic grade statistically significant risk factors. Adjusted HR was 5.776 (95% CI 1.639-20.285, p=0.006) compared to FFT at first group.

Table 4. Risk factors associated with IBTR

	univariable			multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
Before NAC (at biopsy)						
Age	0.96	0.906-1.017	0.164			
BMI	1.018	0.861-1.203	0.834			
HG (biopsy)	8.003	0.894-71.635	0.063			
Ki67 (biopsy)	36.625	0.005-265996.04	0.427			

		8				
Clinical tumor size	0.953	0.639-1.422	0.814			
NME	1.59	0.422-5.994	0.493			
Daughter nodule	0.757	0.163-3.503	0.722			
Subtype						
HR+HER2-	ref					
HR+HER2+	<0.001		0.983			
HR-HER2+	3.203	0.586-17.510	0.179			
HR-HER2-	1.983	0.532-7.395	0.308			
After NAC (surgical specimen)						
Margin re-excision	3.935	1.198-12.919	0.024	5.766	1.639-20.285	0.006
LVI	0.943	0.204-4.367	0.94			
Pathologic tumor size(cm)	1.21	0.635-2.306	0.562			
pN stage			0.968			
0	1.357	0.414-4.448	0.614			
1	<0.001	0	0.986			
2	<0.001	0	0.994			

HG	3.874	1.181-12.706	0.025	6.216	1.764-21.907	0.004
Ki67	4.174	1.106-15.745	0.035	2.053	0.437-9.642	0.362
NME	1.313	0.283-6.083	0.728			
Daughter nodule	2.522	0.545-11.676	0.237			
Total extent	1.18	0.643-2.164	0.593			
Reduction pattern						
concentric		ref				
scattered	5.006	0.616-40.711	0.132			
Microcalcification	0.822	0.232-2.913	0.761			
Localization method	ref		0.274			
Us-guided	0.524	0.135-2.032	0.35			
Mammo-guided	0.161	0.017-1.551	0.114			

IV. DISCUSSION

Routine use of intraoperative frozen section pathologic analysis spared secondary operation in about 15% of patients who had additional margin excision in a single operation and obtained tumor-free margin from both frozen section and permanent

pathologic assessment. There were significant differences in IBTR between those who had margin re-excision and those who achieved tumor-free margin at once with a median follow up of 63 months. Prior to the exclusion of patients who achieved pCR, the margin re-excision cohort exhibited inferior local recurrence free survival and distant metastasis free survival (data not shown). This discrepancy may be attributed to the higher proportion of non-pCR patients within the margin re-excision group. Notably, within the subset of patients failing to achieve pCR after NAC, there was a consistent observation of poorer rates of IBTR and RFS in the margin re-excision group. While overall survival remained unaffected, this study stands as the first study showing an adverse prognosis in the margin re-excision group from FSA within the specific patient subgroup that underwent NAC.

Diagnostic accuracy and usefulness of intraoperative margin assessment by frozen section has been examined in various studies. Olson once described sensitivity and specificity of frozen section assessment compared to paraffin section in other studies, 73.08% and 99.59%, respectively.[6] The duration of surgery was also similar between two groups with or without intraoperative evaluation of the extent of primary lumpectomy by frozen section method.[7] This may suggest that frozen section method saves time and cost from

unnecessary secondary surgery without extending the duration of surgery.[8,9] Furthermore, real-time visualization of margin makes it easier to perform re-excision rather than delayed subsequent operation when postoperative change has taken place. In those cases, localizing the affected margin is harder and a difference in survival may be generated.[10]

Many factors were investigated to determine the association that affects intraoperative, repeated margin re-excision. Key factors include tumor size, invasiveness, palpability, and presence of combined suspicious microcalcification. However, in our study tumor size and presence of NME were not significant. Considering SSO-ASTRO guideline says that in case of in situ, a margin of 2mm thickness must be secured, unlike in the case of invasive cancer (no ink on tumor), it is presumable that invasiveness might play a role. Margin excised during surgery is mostly greater than 2mm which is enough to achieve safe margin. Plus, it is widely studied from several retrospective studies that BCS plus re-excision surgery by either mastectomy or further BCS have similar survival as those treated with BCS without re-excision, especially if there was focally positive lesion.[11, 12] Omission of re-excision can be performed in low risk patients[13], however, intraoperative margin assessment leaves no choice but to perform re-excision, reflecting

the advantages of the procedure.

Previous studies have reported several other factors associated with positive margins in lumpectomy specimens. These factors include an extensive intraductal component of disease, the presence of multifocal disease, human epidermal growth factor receptor 2 (HER2) receptor-positive disease, high BMI, nodal involvement, caudal location, and the presence of microcalcifications on mammography.[14-16] This study recapitulated some of the already known factors, and some of them were not. Age is in close relation with redistribution of the fat, causing fatty change in the breasts, and high BMI can make localization difficult.[17] Here in, we tried to interpret the association between re-excision and age as an association of BMI, and failed to show statistical significance. LVI is known as predictive factors for the development of IBTR after BCS and poor OS after IBTR. One study demonstrated that LVI can predict for residual disease after wide local excision for breast cancer. Clinical significance is still unclear. Malignant microcalcification was another factor related to multiple margin re-excision[18, 19], however, we found the presence of daughter nodule can be relevant, rather than microcalcification. Some studies support that residual microcalcification after NAC does not necessarily be removed, because there are often cases where

microcalcification still remain even after pCR.

Notably, this study demonstrated significant difference in the rate of IBTR between patients who had FFT with the initial lumpectomy compared to those who undergone margin re-excision due to frozen section pathologic assessment. Few studies have shown the effect of multiple margin re-excision based on intraoperative pathologic assessment on IBTR. Contrary to current study findings, prior study by Racz et al demonstrated no statistical difference in IBTR by intraoperative repeated margin re-excision.[20] Nonetheless, our study is distinguished that study population was exclusively focused on patients who received NAC, posing an additional challenge in determining the optimal extent of lumpectomy due to tumor regression[21, 22]. The clinical significance of radiologic factors responsible for residual tumor after NAC warrants further investigated.

In non-pCR cohort, the proportion of patients with HR+HER2- subtype were major subtype. The 10-year IBTR was largely reliant on tumor subtype. Cheun et al. showed that HR-/HER2- subtype were more than twice likely to experience IBTR compared to HR+/HER2- subtype. The survival analysis was restricted to non pCR patients in our study.

There is limitation in our study that central assessment of

histopathology was not performed, and we lack the data involving margin distance and the extent of cancer on specimen tissue for some patients. Additionally, retrospective design of the study can be another limitation. Also, patients who had received primary systemic therapy were included in the study and these patients should be separately evaluated in a large-scale study. However, this study has strength for its large sample size and because the intraoperative margin assessment procedure is not readily available in many institutions, we are able to offer the meaningful evidence to the knowledge of the procedure.

V. CONCLUSION

Repeated margin resection in breast conserving surgery can be a concern regarding IBTR. Since it represents the group with more prominent residual tumor. Patients who had intraoperative repeated margin re-excision after NAC need active surveillance with higher risk of IBTR in mind.

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ABSTRACT(IN KOREAN)

선행항암화학요법을 받고 유방보존술을 시행한 환자에서 수술 중 동결절편 조직검사 결과에 따라 반복적 변연부 절제술 여부에 따른 동측 유방암 재발율 차이

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선행항암화학요법(NAC)의 비율이 증가함에 따라 유방보존술(BCS)의 활용이 증가했다. 유방암 아형에 따라 달라지는 종양 감소의 다양한 패턴으로 인해 잔여 종양의 크기 및 수술 범위를 결정하는 것이 어려울 수 있다. 동결절편 조직검사는 수술 중 수술 마진 상태를 확인하여 마진 재절제를 위한 2차 수술의 필요성을 방지하는 데 유용한 도구로 이 논문에서는 NAC를 시행한 환자의 단일 수술 중 추가 마진 재절제에 따른 동측 유방 종양 재발(IBTR)을 알아보고자 한다. 2011년 1월부터 2018년 12월까지 단일 기관(강남세브란스병원)에서 유방보존술과 NAC를 받은 유방암 환자의 의무기록을 바탕으로 데이터를 수집하였다. 종양 절제면이 양성인 경우, 재절제된 절제면에 대하여 동결절편 조직검사로 절제면에 종양이 없음을 확인한 이후 수술을 마쳤다. 최종적으로 유방전절제술로 전환한 환자는 제외한 이후, 총

185명의 환자 중 33명의 환자가 마진 재절제를 받았다. 재절제군은 잔존 종양 크기가 더 컸으며 병리학적 완전 반응(pCR)을 달성할 가능성이 더 낮았다. 추적관찰기간 중앙값은 63개월이었고 16건의 IBTR이 관찰되었다. 재절제군에서는 무재발 생존율과 전체 생존율이 더 불량했다. non-pCR 그룹을 따로 분석했을 때에도 재절제군에서 동측 유방 재발율과 재발율이 더 불량한 것으로 나타났다. 이로써, 단일 유방 수술 중 수술 중 마진 재절제를 수행하는 것은 NAC를 받은 유방암 환자의 IBTR 위험 증가와 연관이 있다고 결론 내릴 수 있다.

핵심되는 말: 유방암, 유방보존술, 동결절편조직검사, 절제연 평가, 재발