Breast Cancer Research and Treatment (2022) 194:683–692
https://doi.org/10.1007/s10549-021-06500-4

ORIGINAL ARTICLE

Surgical margin status and survival outcomes of breast cancer patients treated with breast-conserving surgery and whole-breast irradiation after neoadjuvant chemotherapy

Jong-Ho Cheun[1,2] · Young Joo Lee[3,4] · Jun-Hee Lee[5,6] · Yungil Shin[3] · Jung Whan Chun[3] · Soo Yeon Baek[3] · Hong-Kyu Kim[1] · Han-Byoel Lee[1] · Jonghan Yu[5] · Byung Joo Chae[5] · Wonshik Han[1] · Jeong Eon Lee[5]

Received: 11 October 2021 / Accepted: 23 December 2021 / Published online: 28 June 2022

Abstract

Purpose The definition of "no tumor on ink" is generally applied for clear resection margin (RM) after breast-conserving surgery (BCS). However, few studies reported the effect of RM in the setting of neoadjuvant chemotherapy (NAC). We investigated the association between RM status and survival outcomes for those who underwent BCS after NAC for breast cancer.

Methods We retrospectively reviewed the data of 2,803 patients who underwent BCS and whole-breast irradiation after NAC between January 2008 and December 2016 from three institutions in South Korea.

Results The 786 patients in the pathologic complete response group (R_{pCR}) had significantly longer local recurrence-free survival (LRFS) than the 1,949 patients in clear or close RM and non-pCR group (R_0) and the 68 patients in involved RM and non-pCR group (R_1) (vs. R_0, $p=0.001$; vs. R_1, $p=0.049$). Patients in R_0 showed no benefit in LRFS compared to R_1 on both log-rank test (HR = 1.20; 95% C.I., 0.49–2.93; $p=0.692$) and Cox regression analysis (HR = 2.05; 95% C.I., 0.64–6.58; $p=0.227$). Subgroup analysis according to tumor subtypes revealed that there was no significant difference in LRFS, distant metastasis-free survival, and recurrence-free survival between the R_0 and R_1 group. Additionally, among 286 patients with pCR with residual ductal carcinoma in situ (DCIS) alone, RM status was not significantly associated with LRFS.

Conclusion Clear RM of specimen does not have benefit on LRFS after NAC. Additionally, for the patients showing pCR with residual DCIS in the breast, margin involvement also did not affect the risk of local recurrence.

Keywords Breast neoplasms · Mastectomy, segmental · Margins of excision · Neoplasm recurrence, local

Introduction

Neoadjuvant chemotherapy (NAC) is currently accepted as a preferred option for treating breast cancer, and its usage has increased over time [1]. NAC has several advantages over upfront surgery, including early observation of response to systemic treatment and modification of adjuvant treatment and breast-conserving surgery (BCS) for patients with clinically large tumors who initially require total mastectomy [2, 3]. Furthermore, several trials have shown that NAC has an equivalent effect on survival outcomes as adjuvant chemotherapy [4].

Jong-Ho Cheun, Young Joo Lee and Jun-Hee Lee have equally contributed to this work.

✉ Jeong Eon Lee
jeongeon.lee@samsung.com; paojlus@hanmail.net

1 Division of Breast Surgery, Department of Surgery, Seoul National University College of Medicine, Seoul, South Korea

2 Present Address: Department of Surgery, SMG-SNU Boramae Medical Center, Seoul, South Korea

3 Division of Breast Surgery, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

4 Present Address: Department of Surgery, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

5 Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

6 Present Address: Department of Surgery, Soonchunhyang University College of Medicine, Soonchunhyang University Hospital Seoul, Seoul, South Korea

The major concern regarding BCS is the resection margin (RM). Current guidelines strongly recommend achieving "no tumor on ink" for invasive breast cancer [5–7]. The importance of no ink on the stained margin after BCS is associated with the risk of local recurrence (LR) [8, 9]. However, the application of the RM definition after NAC is unclear. Guidelines lack clear evidence of appropriate width for RM after NAC, and few studies have reported the effect of margin status on oncological outcomes [10]. In addition, the significance of clear RM for surgical specimens could be weakened after NAC because some tumors shrink with scattered or multifocal patterns [11], and minimally remaining lesions might be effectively eradicated in the era of a newly effective regimen of cytotoxic drugs and radiation treatment (RT) [2, 12].

Moreover, previous studies recommended a margin width of ≥ 2 mm for specimens after surgery for ductal carcinoma in situ (DCIS) [13]. The significance of RM status remains unclear when patients show pathologic complete response (pCR) with residual DCIS in the breast. Thus, surgeons are required to consider additional resection for involved or close RM, against the preference to preserve the breasts as much as possible after NAC.

This study aimed to investigate the effect of RM on LR by comparing patients with involved RM and close (≤ 2 mm) or clear RM. Previous studies only included a small number of patients because only few patients refuse further re-excision for RM after BCS. To the best of our knowledge, this is the largest study of three major institutions in South Korea to analyze the effect of RM after BCS following NAC.

Patients and methods

Study design

The study protocol was reviewed and approved by the review board (IRB) of the following three institutions in Korea: Asan Medical Center (AMC), Samsung Medical Center (SNH), and Seoul National University Hospital (SNUH) (IRB No.: AMC, 2017–1341; SMC, 2021–03-096–003; SNUH, 2014–015-1210). The protocol was reviewed and approved by our institution, and the study followed the Declaration of Helsinki and good clinical practice guidelines. The requirement for informed consent was waived.

We obtained baseline clinicopathologic data and reviewed detailed information of female patients with breast cancer who underwent curative BCS for invasive cancer between January 2008 and December 2016. All patients received NAC followed by surgery and adjuvant whole-breast radiation therapy (WBRT) (Supplementary table S1). We excluded patients with stage IV breast cancer, recurrent breast cancer, bilateral breast cancer, or synchronous or metachronous cancer in other organs. In case of close or involved RM, surgeons further resected the breast in the direction of reported margin based on clinical experience of each physicians. Patients who underwent further resection via total mastectomy were also excluded, whereas those who completed the surgical treatment with partial resection were included. Initial breast cancer was clinically staged according to the 8th American Joint Committee on Cancer staging criteria. All patients were diagnosed with invasive breast cancer using core needle biopsy, fine-needle aspiration or vacuum-assisted breast biopsy of abnormal findings on breast sonography or mammography at each institution. Hormone receptor (HR) status, including estrogen and/or progesterone receptors, was reviewed by pathologists from each institution based on immunohistochemistry findings, with positivity defined as > 1% or Allred scores of 3–8 [14]. Human epidermal growth factor receptor type 2 (HER2) status was assessed using anti-HER2 antibodies and/or fluorescence in situ hybridization (FISH) or silver in situ hybridization (SISH). When the result of HER2/chromosome enumeration probe 17 (CEP17) ratio was > 2.0 on FISH or SISH, tumor was regarded as HER2 positive according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline. Data on the Ki-67 labeling index were not collected because of different cut-off values used in institutions. As we focus on the effect of residual tumors on local recurrence of breast, pCR was defined as the absence of residual invasive cells in the breast. Regarding the preoperative radiographic diagnosis before surgery, all of institutions had conducted breast MRI to assess the response to neoadjuvant chemotherapy before, in the middle of, and after administration of neoadjuvant chemotherapy. Additionally, preoperative sonography was once more conducted to precisely check the tumor size and range before surgery.

Assessment of resection margin

Involved RM was defined as the presence of ink on the radial margin of the final surgical specimen, regardless of the intraoperative frozen section results. Margin widths were reviewed based on data from histology reports from each institution, and RM was classified into close and clear according to widths of ≤ 2 mm and > 2 mm, respectively. Data of superficial and deep RM were not collected because they were previously reported to not be significant factors affecting LR [15]. Furthermore, detailed pathologic reports for close margin were not also collected as one of institutions in our study did not report the type of tumors for close RM.

Recurrence and recurrence-free survival

LR, the primary endpoint of this study, was defined as the first recurrence in any quadrant of the ipsilateral breast. Recurrence at the breast skin was excluded from the LR. LR-free survival (LRFS) was defined as the interval between the dates of surgery and pathologic confirmation of LR. Assuming that neither regional recurrence nor distant metastasis (DM) is associated with the effect of RM on LR, the events without concurrent LR were not regarded as censoring events when analyzing LRFS. DM-free survival (DMFS) was defined as the time interval between the date of surgery and the time of radiologic or pathologic confirmation of distant metastasis. Recurrence-free survival (RFS) was defined as the interval between the date of surgical treatment and the date of diagnosis of any recurrence including LR, regional recurrence and DM.

Statistical analyses

All analyses were performed using SPSS (version 25.0; IBM Corp., Armonk, NY, USA). Demographic and clinicopathologic variables were compared using Student's t-test for continuous variables and Pearson's χ^2 test for categorical variables. Survival analyses were performed using the log-rank test to analyze the difference in survival outcomes between groups, and the curves were derived using the Kaplan–Meier method. Cox proportional hazard regression was used to adjust for variables affecting pathologic response and survival outcomes and it was also used to estimate the hazard ratio. Propensity score matching procedure was also performed to reduce the effects of several clinicopathological variables using "*MatchIt*" R package (version 3.6.3; R Core Team, Vienna, Austria). Statistical significance was set at p values < 0.05. All curves were drawn using GraphPad Prism™ (version 9.0; GraphPad Software, San Diego, USA).

Results

Patient demographics and characteristics

We identified 2,803 patients who underwent NAC followed by BCS and met the inclusion criteria. Nineteen patients who underwent total mastectomy for involved RMs were excluded. The median follow-up period was 62.3 months (range, 0.4–157.2 months). Clinicopathological characteristics of all patients are listed in Supplementary table S2.

Patients were classified into subgroups according to their RM status and pathologic response (Table 1). We divided them into three broad groups: patients with pCR (R_{pCR}, *subgroups 5–8*, $n = 786$), patients with non-pCR and clear or close RM (R_0, *subgroup 1–2*, $n = 1{,}949$), and patients with non-pCR and involved RM (R_1, *subgroups 3–4*, $n = 68$), with median follow-up periods of 70.4, 71.7, and 71.6 months, respectively (Table 2). Patients in the R_{pCR} group were significantly older at the time of operation and had lower clinical T stage, lower HR positivity, higher HER2 positivity, and higher histologic grade than those in the other groups. Among the 786 patients who had pCR in the breast, 500 (*subgroup 8*, 63.6%) had no tumor and 286 (*subgroups 5–7*, 36.4%) had residual in situ lesion.

Survival outcomes

In total, 23, 5, and 121 ipsilateral breast tumor recurrence (IBTR) events were noted in the R_{pCR}, R_1, and R_0 groups, respectively. The five-year LRFS rates were 97.4%, 91.5% and 94.0% for the R_{pCR}, R_1, and R_0 groups, respectively. The Kaplan–Meier curves revealed that patients in the R_{pCR} group had higher LRFS than those in the R_1 (hazard ratio [HR], 2.55; 95% confidence interval [CI], 0.97–6.72; log-rank $p = 0.049$) and R_0 (HR, 2.15; 95% CI, 1.37–3.35; $p = 0.001$) groups (Fig. 1a). In contrast, the LRFS in the R_0 group was not significantly different from that in the R_1 group (HR, 1.20; 95% CI, 0.49–2.93; $p = 0.692$). DMFS and

Table 1 Subgroup classification according to RM status and pathologic response

	non-pCR ($n = 2017$)	pCR with residual DCIS ($n = 286$)	pCR without tumor ($n = 500$)
Clear RM	*Subgroup 1* 1790 (88.7%)	*Subgroup 5* 264 (92.3%)	*Subgroup 8* 500 (100.0%)
Close RM	*Subgroup 2* 159 (7.9%)	*Subgroup 6* 10 (3.5%)	–
DCIS-involved RM	*Subgroup 3* 29 (1.4%)	*Subgroup 7* 12 (4.2%)	–
IDCa-Involved RM	*Subgroup 4* 39 (1.9%)	–	–

pCR: pathologic complete response; *DCIS:* ductal carcinoma in situ; *RM:* resection margin; *IDCa:* invasive ductal carcinoma

Table 2 Clinical characteristics of patients according to the resection margin and pCR status

	R_1 ($n=68$)	R_0 ($n=1,949$)	R_{pCR} ($n=786$)	p value
Age at operation (years) *	44.2 ± 8.7	46.4 ± 9.7	47.4 ± 10.1	0.003
< 50	48 (70.6%)	1243 (63.8%)	437 (55.6%)	< 0.001
≧ 50	20 (29.4%)	706 (36.2%)	349 (44.4%)	
Clinical T stage†				< 0.001
cT1	8 (11.8%)	156 (8.0%)	109 (13.9%)	
cT2	39 (57.4%)	1437 (73.7%)	572 (72.8%)	
cT3	18 (26.5%)	300 (15.4%)	88 (11.2%)	
cT4	3 (4.4%)	56 (2.9%)	17 (2.2%)	
Clinical N stage†				0.001
cN0	9 (13.2%)	371 (19.0%)	115 (14.6%)	
cN1	32 (47.1%)	950 (48.7%)	350 (44.5%)	
cN2	18 (26.5%)	369 (18.9%)	187 (23.8%)	
cN3	9 (13.2%)	259 (13.3%)	134 (17.0%)	
Clinical Stage†				0.029
I	2 (2.9%)	20 (1.0%)	5 (0.6%)	
II	31 (45.6%)	1138 (58.4%)	428 (54.5%)	
III	35 (51.5%)	791 (40.6%)	353 (44.9%)	
HR status‡				< 0.001
Positive	45 (66.2%)	1208 (62.0%)	280 (35.6%)	
Negative	22 (32.4%)	740 (38.0%)	502 (63.9%)	
Unknown	1 (1.5%)	1 (0.1%)	4 (0.5%)	
HER2 receptor status‡				< 0.001
Positive	21 (30.9%)	510 (26.2%)	345 (43.9%)	
Negative	45 (66.2%)	1384 (71.0%)	427 (54.3%)	
Unknown	2 (2.9%)	55 (2.8%)	14 (1.8%)	
Subtype‡				< 0.001
HR + /HER2-	34 (50.0%)	874 (44.8%)	135 (17.2%)	
HR + /HER2 +	11 (16.2%)	292 (15.0%)	137 (17.4%)	
HR-/HER2 +	10 (14.7%)	218 (11.2%)	207 (26.3%)	
HR-/HER2-	11 (16.2%)	510 (26.2%)	290 (36.9%)	
Unclassified	2 (2.9%)	55 (2.8%)	17 (2.2%)	
Histologic grade‡				< 0.001
I	2 (2.9%)	21 (1.1%)	2 (0.3%)	
II	21 (30.9%)	806 (41.4%)	233 (29.6%)	
III	7 (10.3%)	414 (21.2%)	324 (41.2%)	
Unknown	38 (55.9%)	708 (36.3%)	227 (28.9%)	
NAC regimen				< 0.001
Combine A and T	51 (75.0%)	1461 (75.0%)	588 (74.8%)	
A-based	10 (14.7%)	330 (16.9%)	81 (10.3%)	
T-based	1 (1.5%)	61 (3.1%)	54 (6.9%)	
Others	6 (8.8%)	97 (5.0%)	63 (8.0%)	
HER2 targeting treatment				< 0.001
Yes	13 (19.1%)	372 (19.1%)	267 (34.0%)	
No	55 (80.9%)	1577 (80.9%)	519 (66.0%)	
Follow-up (months) *	71.6 ± 30.8	71.7 ± 30.0	70.4 ± 28.3	0.289
Local recurrence	5 (7.4%)	121 (6.2%)	23 (2.9%)	
Reginal recurrence	5 (7.4%)	94 (4.8%)	13 (1.7%)	
Distant metastasis	12 (17.6%)	304 (15.6%)	43 (5.5%)	
BC-specific mortality	0 (0.0%)	170 (8.7%)	21 (2.7%)	

pCR: pathologic complete response; $R_{1:}$ involved resection margin group; $R_{0:}$ clear or close resection margin group; $R_{pCR:}$ pCR group; *HR*: hormone receptor; *HER2:* human epidermal growth factor receptor 2; *NAC:* neoadjuvant chemotherapy; *A:* anthracycline; *T:* taxane; *BC:* breast cancer

*Values are median ± standard deviation

†Stratified according to the American Joint Committee on Cancer (AJCC) 7th TNM stage

‡Pathology report of pre-treatment

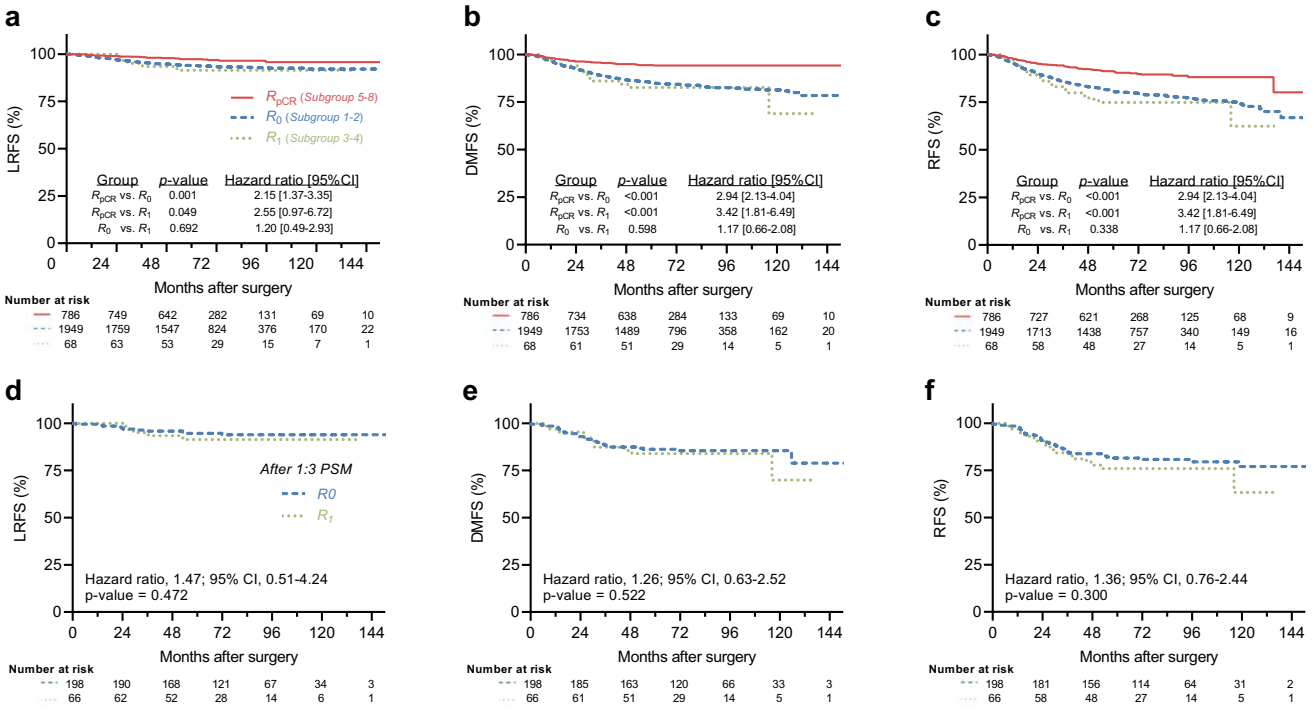

Fig. 1 The Kaplan–Meier curves showing the survival outcomes according to the resection margin status and pathologic response for all patients (**a-c**) and after propensity score matching (d-f). The hazard ratio was calculated using a univariate Cox regression analysis. Abbreviations: R_1: involved resection margin group; R_0: clear or close resection margin group; R_{pCR}: pathologic complete response group; *CI:* confidence interval; *LRFS:* local recurrence-free survival; *DMFS:* distant metastasis-free survival; *RFS:* recurrence-free survival

RFS of patients in the R_{pCR} group were also significantly higher than those in the other groups ($p < 0.001$, Fig. 1b-c). There was no significant difference in DMFS ($p = 0.598$) and RFS ($p = 0.338$) between patients in the R_1 and R_0 groups ($p < 0.001$).

Importantly, to minimize the effect of confounding factors between the R_0 and R_1 groups (supplementary table S3), we performed 1:3 propensity score matching by incorporating clinicopathologic variables, yielding 66 and 198 patients in the R_0 and R_1, respectively. The variables were not significantly different between the two groups after propensity score matching, and no significant difference in survival outcomes was observed between the two groups (Fig. 1d-f).

Among patients with non-pCR, there was no significant difference in LRFS between those with involved (*subgroup 3,4*), close (*subgroup 2*), and clear RMs (*subgroup 1*) ($p = 0.492$) (Fig. 2a). Additionally, for the 68 patients with involved RM in the R_1 group (*subgroups 3,4*), no difference in LRFS was observed with respect to the pathology of tumors with RM (DCIS vs. invasive cancer, HR, 0.54; 95% CI 0.09–3.26; $p = 0.497$) (Fig. 2b).

Focusing on the surgeon's point of view, we analyzed the LRFS of non-pCR patients, including those with pCR and residual DCIS (*subgroup 6–7*). Similarly to the aforementioned results, the log-rank test showed RM status was not a risk factor for LRFS (*subgroup 1, 5 vs. subgroup 2, 6 vs. subgroup 3, 4, 7,* $p = 0.317$).

Multivariate analysis for LRFS between R_0 and R_1

Clinical T and N stage, HR status, and histologic grade were significantly associated with LR according to the log-rank test. Cox regression analysis that was adjusted for other prognostic variables revealed no significant difference in LRFS between the R_0 and R_1 groups (HR, 2.05; 95% CI, 0.64–6.58, $p = 0.227$) (Table 3, Supplementary fig. S1). Moreover, all the abovementioned factors were not significant variables predicting LR.

Subgroup analysis according to subtypes

Depending on pre-chemotherapy pathology reports, 1,960 patients could be distinguished according to different tumor subtypes: 908 (46.3%) with HR + /HER2-, 303 (15.5%) with HR + /HER2 + , 228 (11.6%) with HR-/HER2 + , and 521 (26.6%) with HR-/HER2-. The beneficial effect of clear RM on LRFS was not observed for all subtypes of non-pCR tumors (Fig. 3a–d). Furthermore, the log-rank test showed no difference in DMFS and RFS

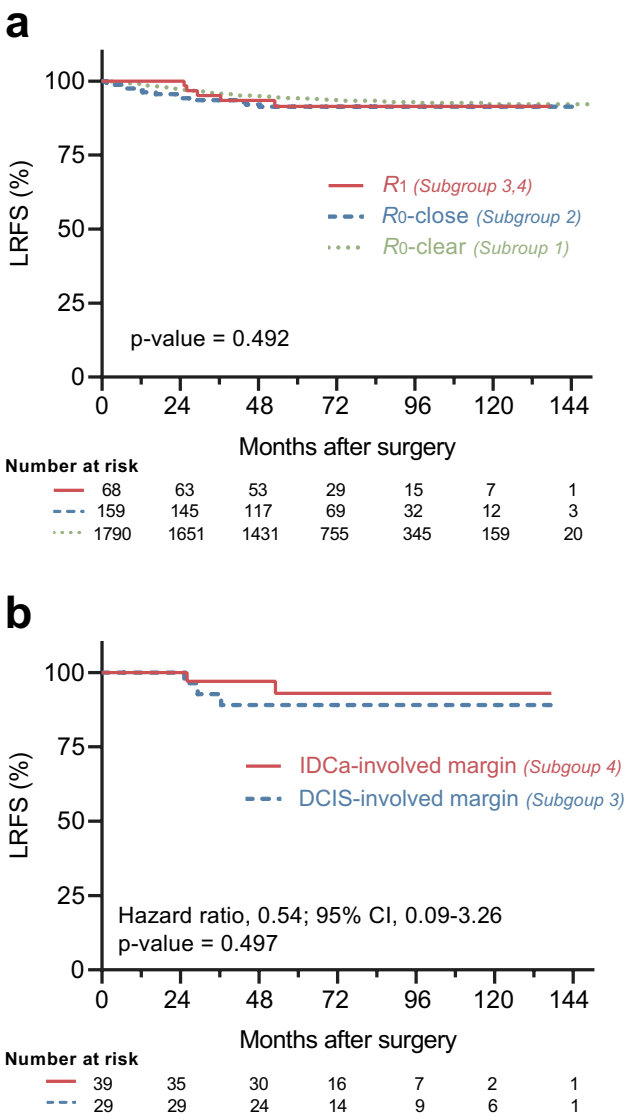

Fig. 2 Kaplan–Meier curves of the patients without pCR according to margin widths (**a**) and involved tumor types (**b**). The hazard ratio was calculated using a univariate Cox regression analysis. Abbreviations: *LRFS:* local recurrence-free survival; $R_{1:}$ involved resection margin group; R_0: clear or close resection margin group; *IDCa:* invasive ductal carcinoma; *DCIS:* ductal carcinoma in situ; *CI:* confidence interval; *pCR:* pathologic complete response

between the R_0 and R_1 groups for all subtypes (Fig. 3e, f, Supplementary fig. S2). Especially, patients with HR-/HER2- subtype in the R_1 group had a tendency of having poorer DMFS and RFS rates than those in the R_0 group.

Survival analysis among patients with residual DCIS

We further investigated the effect of residual DCIS on RM in the R_{pCR} group (*subgroups 5–8*). We identified 286 patients with pCR with DCIS alone after surgery: 12 with involved (*subgroup 7*), 10 with close (*subgroup 6*), and 264 with clear (*subgroup 5*) RM. During the follow-up period, there were 1 LR events and 11 LR events in patients with involved RM (*subgroups 7*) and clear or close RM (*subgroup 5–6*), respectively. The five-year LRFS rates were 96.1% and 90.0% for the *subgroup 5–6* and *subgroup 7*, respectively. The log-rank test revealed no significant difference in LRFS between the two groups (HR, 2.49; 95% CI, 0.32–19.37; $p = 0.366$) (Fig. 4).

Discussion

In the current study, we could not determine whether clear RM status after NAC and BCS followed by WBRT was associated with improved benefit for LRFS in all subtypes. However, we observed that achieving clear RM in cases of tumors showing pCR with residual DCIS would not result in a survival benefit. Our results suggest that struggling to gain a clear RM to reduce LR risk, as opposed to the expectation for cosmetic benefit after NAC, does not always lead to better prognosis.

A few retrospective studies have investigated the effect of clear RM on LR. Wimmer et al. [16] retrospectively analyzed 416 patients who underwent BCS after NAC and observed no significant difference in LRFS, DFS, and overall survival with respect to margin widths (RM > 1 mm vs. 0 < RM ≤ 1 mm; 5-year LRFS, 91% vs. 94%; $p = 0.940$). Similarly, Lin et al. [10] analyzed 161 patients who underwent BCS after excluding those with involved RM and reported similar results that specimens with RM ≥ 1 mm had no benefit for LRFS compared with those with RM < 1 mm (HR, 0.44; 95% CI 0.14–1.38; $p = 0.161$). All the above-mentioned studies suggested that the definition of RM as "no tumor on ink" would be safe for application in the NAC setting. However, these studies analyzed for a small number of patients, including patients with pCR into the R_0 group and excluded patients with involved RM. In another study investigating a large number of patients, Tyler et al. [17] conducted a population-based analysis of 10,863 patients and reported similar LRFS between patients with involved, close, and clean margins ($p = 0.084$). Additionally, a lower BCSS rate was observed in patients with positive RM than in those with clear RM (Cox regression analysis, $p = 0.024$). They concluded that omitting further re-excision would be acceptable for carefully selected patients with positive margin status. However, systemic chemotherapy was administered to only 36.4% of patients in this study, and there was no mention of whether it was administered in the adjuvant or neoadjuvant setting.

The risk of RM involvement after NAC was three times higher (2.5%–7.8%) than that after upfront surgery in a

Table 3 Univariate and multivariate analyses for local recurrence-free survival among patients without pCR

Characteristics	Univariate analysis		Multivariate analysis	
	Hazard ratio [95% CI] *	*p* value	Hazard ratio [95% CI]	*p* value
Clinical T stage		0.006		0.054
cT1	Ref		Ref	
cT2-T4	5.63 [1.39 – 22.8]		6.97 [0.96 – 50.41]	
Clinical N stage		0.021		0.232
cN0	Ref		Ref	
cN1-3	1.90 [1.09 – 3.32]		1.45 [0.79 – 2.67]	
HR status		< 0.001		0.279
Positive	Ref		Ref	
Negative	1.87 [1.32 – 2.66]		1.34 [0.79 – 2.27]	
HER2 receptor status		0.172		0.103
Positive	Ref		Ref	
Negative	0.77 [0.53 – 1.12]		0.66 [0.40 – 1.09]	
Histologic grade		0.042		0.183
I-II	Ref		Ref	
III	1.66 [1.01 – 2.70]		1.43 [0.84 – 2.43]	
Resection margin status		0.692		0.227
R_0	Ref		Ref	
R_1	1.20 [0.49 – 2.93]		2.05 [0.64 – 6.58]	

pCR: pathologic complete response; *CI:* confidence interval; *Ref:* reference; *HR:* hormone receptor; *HER2:* human epidermal growth factor receptor 2; R_1: involved resection margin group; R_0: clear or close resection margin group

*Hazard ratio was calculated with univariate Cox regression analysis

meta-analysis study [18]. Of all patients in our study, 2.9% of patients had involved RM but they did not have worse LRFS compared to patients with clear or close RM. We assumed several explanations for this result. First, although the ink on the specimen is present, there is a possibility of no residual tumor in the remnant cavity. Tang et al. [19] compared pathologic reports of lumpectomy margins with those of shaved cavitary margins and concluded that the lumpectomy margin is not reliable for predicting cavity status with an overall accuracy of 64.9%. Second, improvement in high-resolution magnetic resonance imaging and multiparametric evaluation enables precise measurement of residual tumors after NAC [20, 21]. This would allow surgeons to include all residual lesions in the resection volume, although some tumors shrink in a multifocal pattern. Third, a retrospective study reported a negative correlation between clinical tumor size and BCS conversion rate [22]. Patients with large tumors at the time of pre-treatment might have undergone mastectomy, which could lead to selection bias, making it impossible for clinically large tumors to be analyzed in this study. Lastly, a high dose of RT boost would have affected the better prognosis for patients with positive RM [23].

The response to NAC differs across various breast cancer subtypes. Among the subtypes, TNBC shows the highest sensitivity to NAC and pCR rate [24, 25]. Additionally, the shrinkage pattern of tumor regression after NAC is different among the subtypes, and the HR + /HER2- subtype usually shrinks in a scattered pattern, while HER + or TNBC tumors show concentric patterns [26, 27]. It can be inferred that the effect of RM status on recurrence may differ across subtypes; however, we did not find a difference in LR risk according to RM for all subtypes. Especially, patients with TNBC in the R_1 group had a tendency of poorer DMFS and RFS than those in the R_0 group. TNBC has no benefit owing to hormone therapy or HER2-targeted therapy, implying that entire tumor resection without residual lesion might be important for survival outcomes. Moreover, the number of TNBC tumors which were down-staged in tumor size after NAC was significantly higher in the R_0 group than in the R_1 group in our study (73.9% vs. 37.5%, $p = 0.035$). As TNBC with residual lesion or refractory to NAC has a higher probability of systemic recurrence than other subtypes, the difference in response rates to NAC between the two groups may have resulted in the tendency of poorer survival of patients in the R_1 group [25, 28]. Although there was no statistically significant difference, it may be due to the small number of patients with TNBC subtype.

While the margin width for DCIS is well known to be enough with < 2 mm at upfront surgery, there is no criteria of allowed width for residual DCIS after NAC [13, 29]. Few studies have investigated how residual DCIS, which is regarded as pCR, would affect survival outcomes. We

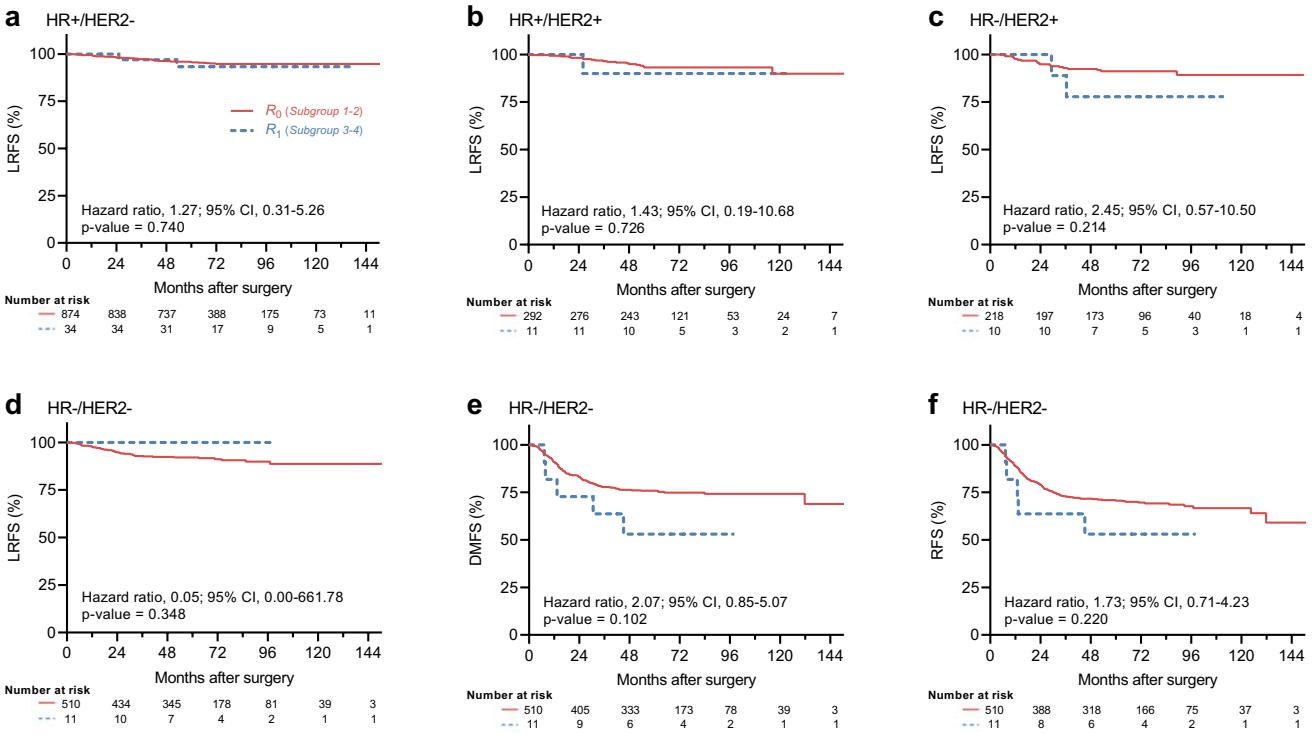

Fig. 3 The Kaplan–Meier curves of survival outcomes stratified according to HR and HER2 status. The Kaplan–Meier curves of LRFS between the R_0 and R_1 according to tumor subtypes are shown (**a–d**). Additionally, the survival graphs of DMFS and RFS of HR-/HER2- subtype are shown (**e–f**). The hazard ratio was calculated using a univariate Cox regression analysis. Abbreviations: *LRFS:* local recurrence-free survival; *HR:* hormone receptor; *HER2:* human epidermal growth factor receptor 2; R_1: involved resection margin group; R_0: clear or close resection margin group; *CI:* confidence interval

demonstrated that the prognosis of patients with residual DCIS was not significantly affected by RM status despite the small number of subgroups. Several reports have shown that patients with residual DCIS after NAC do not have different survival outcomes compared with patients with no tumors in the breast [30, 31]. The results suggest that residual DCIS after NAC is clinically or pathologically different from usual DCIS; thus, there may be no need to worry about residual DCIS on RM.

To the best of our knowledge, this is the largest study to analyze the effect of RM after BCS following NAC; however, our study had several limitations. The study was conducted in multiple institutions; thus, there was hidden bias owing to the heterogeneity of data, such as surgeon factors, methods for pathologic review, and surveillance strategies. Nevertheless, we could include a large number of cases from three institutions and combine the patient population more closely with real-world data. In addition, due to the nature of retrospective study, we could not review several clinical, radiologic and pathologic variables such as patients' preference or feasibility, microcalcification and multiplicity that would have affected the

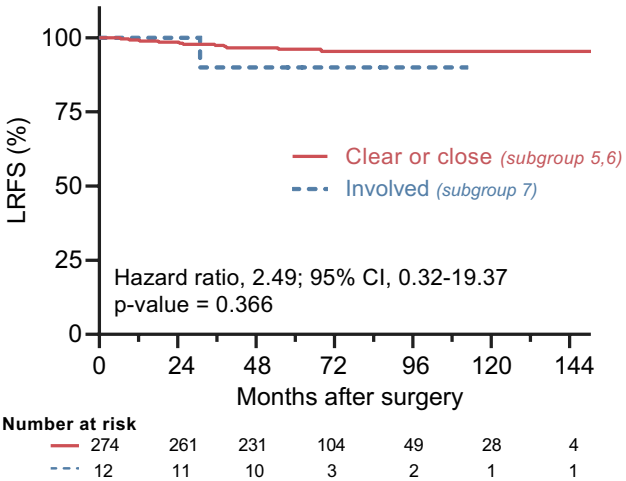

Fig. 4 The Kaplan–Meier LRFS curves according the RM status among 286 patients showing pCR with residual in situ lesion in the R_{pCR} group. The hazard ratio was calculated using a univariate Cox regression analysis. Abbreviations: *RM:* resection margin; R_{pCR}: pathologic complete response group; *LRFS:* local recurrence-free survival; *CI*: confidence interval; *pCR:* pathologic complete response

pathologic response and survival outcomes. Further study would be needed for more reliable results incorporating abovementioned features in the analysis. Additionally, we classified patients who had no more breast tissue for resection in the direction of the involved or close margin into the R_1 group, raising the possibility of selection bias. But the number of those patients was so small according to medical records that it could be ignored. Also, we defined the pCR as the absence of invasive breast tumor in the breast instead of both breast and axilla that are widely accepted. This can lead to selection bias, but the results would not be different from ours as our study focused on the effect of RM on local recurrence in the breast. Finally, patients who received NAC generally had a high probability for systemic recurrence, and almost half of the patients (53.5%) showed DM without LR. Focusing on the primary endpoint, we did not censor patients at the time of distant metastasis so the LR rate could have been overestimated considering the competing risk. To overcome this issue, we further analyzed LRFS after censoring patients at the time of all recurrences, but still no significant difference in LRFS was observed according to RM status ($p > 0.05$, *data not shown*).

In conclusion, our study showed no difference in LRFS rates for involved or close RM compared with clear RM after BCS following NAC. We suggest that the relative risk of LR according to margin status after NAC might differ from that of upfront surgery, and the definition of "no tumor on ink" should be revisited. Additionally, for patients who achieved pCR with DCIS alone, DCIS on RM did not increase the risk of LR. Clinicians should not overlook the importance of clear surgical margins; however, re-excision for close or involved margins after enough volume excision to reduce the LR risk can be omitted for selected patients. Further studies comparing patients with involved or close RM after NAC and those after upfront surgery would validate our results.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-021-06500-4.

Acknowledgements The authors would like to sincerely appreciate Mr. Yong Seop Lee and Ms. Sun Hee Kang for financial support to conduct research in the department of breast surgery, Samsung Medical Center. Additionally, we thank Dr. Sae Byul Lee, Jisun Kim, Il Yong Chung, Hee Jeong Kim, Beom Seok Ko, Jong Won Lee, Byung Ho Son, and Sei-hyun Ahn (Division of Breast Surgery, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea) for critical advice and consultation.

Author contributions All authors whose names appear on the submission made substantial contributions to the conception of design of the work or the acquisition, analysis, or interpretation or data; drafted the work or revised it critically for important intellectual content; approved the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This study was conducted with the support of the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2018R1D1A1A09081884) and by the MSIT (Ministry of Science and ICT), Korea, under the ICT Creative Consilience program (IITP-2020–0-01821) supervised by the IITP (Institute for Information & communications Technology Planning & Evaluation) and by SMC-SKKU Future Convergence Program (Grant SMO1190341).

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Han-Byoel Lee and Wonshik Han report being a member on the board of directors of and holding stock and ownership interests at DCGen, Co., Ltd., not relevant to this study. Other authors declare no competing interests.

Ethical approval The study was performed in accordance with the Declaration of Helsinki or comparable ethical standards. Approval was granted by the ethics committee or institutional review board at the participating sites.

Informed consent Requirement for informed consent was waived for all patients.

Consent to publication All authors have read the paper and consent to its publication.

References

1. Puig CA, Hoskin TL, Day CN et al (2017) National trends in the use of neoadjuvant chemotherapy for hormone receptor-negative breast cancer: A national cancer data base study. Ann Surg Oncol 24:1242–1250. https://doi.org/10.1245/s10434-016-5733-y
2. Colomer R, Saura C, Sánchez-Rovira P et al (2019) Neoadjuvant management of early breast cancer: A clinical and investigational position statement. Oncologist 24:603–611. https://doi.org/10.1634/theoncologist.2018-0228
3. Schott AF, Hayes DF (2012) Defining the benefits of neoadjuvant chemotherapy for breast cancer. J Clin Oncol 30:1747–1749. https://doi.org/10.1200/JCO.2011.41.3161
4. Rastogi P, Anderson SJ, Bear HD et al (2008) Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol 26:778–785. https://doi.org/10.1200/JCO.2007.15.0235
5. National Comprehensive Cancer Network (2021) Breast Cancer (Version 3.2021). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 19 Apr 2021
6. Cardoso F, Kyriakides S, Ohno S et al (2019) Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 30:1194–1220. https://doi.org/10.1093/annonc/mdz173
7. Moran MS, Schnitt SJ, Giuliano AE et al (2014) Society of surgical oncology-American society for radiation oncology consensus guideline on margins for breast-conserving surgery with

whole-breast irradiation in stages i and II invasive breast cancer. Int J Radiat Oncol Biol Phys 88:553–564. https://doi.org/10.1016/j.ijrobp.2013.11.012
8. Russo AL, Arvold ND, Niemierko A et al (2013) Margin status and the risk of local recurrence in patients with early-stage breast cancer treated with breast-conserving therapy. Breast Cancer Res Treat 140:353–361. https://doi.org/10.1007/s10549-013-2627-6
9. Park CC, Mitsumori M, Nixon A et al (2000) Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: Influence of margin status and systemic therapy on local recurrence. J Clin Oncol 18:1668–1675. https://doi.org/10.1200/JCO.2000.18.8.1668
10. Lin J, Lin KJ, Wang YF et al (2020) Association of surgical margins with local recurrence in patients undergoing breast-conserving surgery after neoadjuvant chemotherapy. BMC Cancer 20:1–9. https://doi.org/10.1186/s12885-020-06955-6
11. Chen AM, Meric-Bernstam F, Hunt KK et al (2004) Breast conservation after neoadjuvant chemotherapy: the M.D. Anderson cancer center experience. J Clin Oncol 22:2303–2312. https://doi.org/10.1200/JCO.2004.09.062
12. Haussmann J, Corradini S, Nestle-Kraemling C et al (2020) Recent advances in radiotherapy of breast cancer. Radiat Oncol 15:71. https://doi.org/10.1186/s13014-020-01501-x
13. Morrow M, van Zee KJ, Solin LJ et al (2016) Society of surgical oncology-American society for radiation oncology-American society of clinical oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. J Clin Oncol 34:4040–4046. https://doi.org/10.1200/JCO.2016.68.3573
14. Allison KH, Hammond MEH, Dowsett M et al (2020) Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol 38:1346–1366. https://doi.org/10.1200/JCO.19.02309
15. Yoon TI, Lee JW, Lee SB et al (2018) No association of positive superficial and/or deep margins with local recurrence in invasive breast cancer treated with breast-conserving surgery. Cancer Res Treat 50:275–282. https://doi.org/10.4143/crt.2017.041
16. Wimmer K, Bolliger M, Bago-Horvath Z et al (2020) Impact of surgical margins in breast cancer after preoperative systemic chemotherapy on local recurrence and survival. Ann Surg Oncol 27:1700–1707. https://doi.org/10.1245/s10434-019-08089-x
17. Tyler S, Truong PT, Lesperance M et al (2018) Close margins less than 2 mm are not associated with higher risks of 10-year local recurrence and breast cancer mortality compared with negative margins in women treated with breast-conserving therapy. Int J Radiat Oncol Biol Phys 101:661–670. https://doi.org/10.1016/j.ijrobp.2018.03.005
18. Volders JH, Haloua MH, Krekel NMA et al (2016) Neoadjuvant chemotherapy in breast-conserving surgery – consequences on margin status and excision volumes: a nationwide pathology study. Eur J Surg Oncol 42:986–993. https://doi.org/10.1016/j.ejso.2016.02.252
19. Tang R, Coopey SB, Specht MC et al (2015) Lumpectomy specimen margins are not reliable in predicting residual disease in breast conserving surgery. Am J Surg 210:93–98. https://doi.org/10.1016/j.amjsurg.2014.09.029
20. Mann RM, Cho N, Moy L (2019) Reviews and Commentary • State of the Art. Radiology 292:520–536
21. Loo CE, Straver ME, Rodenhuis S et al (2011) Magnetic resonance imaging response monitoring of breast cancer during neoadjuvant chemotherapy: relevance of Breast Cancer Subtype. J Clin Oncol 29:660–666. https://doi.org/10.1200/JCO.2010.31.1258
22. Mo H, Kim Y, Rhu J et al (2017) Actual conversion rate from total mastectomy to breast conservation after neoadjuvant chemotherapy for stages II–III breast cancer patients. J Breast Disease 5:51–56. https://doi.org/10.14449/jbd.2017.5.2.51
23. Cho WK, Choi DH, Park W et al (2019) Is higher dose radiation necessary for positive resection margin after breast-conserving surgery for breast cancer? Breast 47:16–21. https://doi.org/10.1016/j.breast.2019.06.005
24. Kim S, il, Sohn J, Koo JS, et al (2011) Molecular subtypes and tumor response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. Oncology 79:324–330. https://doi.org/10.1159/000322192
25. Liedtke C, Mazouni C, Hess KR et al (2008) Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26:1275–1281. https://doi.org/10.1200/JCO.2007.14.4147
26. Pastorello RG, Laws A, Grossmith S et al (2020) Clinico-pathologic predictors of patterns of residual disease following neoadjuvant chemotherapy for breast cancer. Mod Pathol. https://doi.org/10.1038/s41379-020-00714-5
27. Ballesio L, Gigli S, di Pastena F et al (2017) Magnetic resonance imaging tumor regression shrinkage patterns after neoadjuvant chemotherapy in patients with locally advanced breast cancer: Correlation with tumor biological subtypes and pathological response after therapy. Tumor Biology. https://doi.org/10.1177/1010428317694540
28. Sharma P, López-Tarruella S, García-Saenz JA et al (2018) Pathological response and survival in triple-negative breast cancer following neoadjuvant carboplatin plus docetaxel. Clin Cancer Res 24:5820–5829. https://doi.org/10.1158/1078-0432.CCR-18-0585
29. Pilewskie M, Morrow M (2018) Margins in breast cancer: how much is enough? Cancer 124:1335–1341. https://doi.org/10.1002/cncr.31221
30. Mazouni C, Peintinger F, Wan-Kau S et al (2007) Effect on patient outcome of residual DCIS in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy. J Clin Oncol 25:530–530. https://doi.org/10.1200/jco.2007.25.18_suppl.530
31. Jones RL, Lakhani SR, Ring AE et al (2006) Pathological complete response and residual DCIS following neoadjuvant chemotherapy for breast carcinoma. Br J Cancer 94:358–362. https://doi.org/10.1038/sj.bjc.6602950