Original Article

Is Local Recurrence Higher Among Patients Who Downstage to Breast Conservation After Neoadjuvant Chemotherapy?

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BACKGROUND: In early studies, local recurrence (LR) rates were higher after neoadjuvant chemotherapy (NAC) in comparison with upfront surgery. Modern outcomes are uncertain, particularly among those who are initially breast-conserving surgery–ineligible (BCSi) and downstage to being breast-conserving surgery–eligible (BCSe). **METHODS:** Among patients with cT1-3 breast cancer treated from 2014 to 2018 who were BCSe after NAC, clinicopathologic characteristics and LR were compared between initially BCSe patients and BCSi patients who downstaged. Breast-conserving surgery (BCS) eligibility was determined prospectively. **RESULTS:** Among 685 patients, 243 (35%) were BCSe before and after NAC and had BCS; 282 (41%) were BCSi before NAC, downstaged to BCSe, and had BCS; and 160 (23%) were BCSi before NAC, downstaged to BCSe, and chose mastectomy. The median age was 52 years, and most cancers were cT1-2 (84%), cN+ (61%), and human epidermal growth factor receptor 2–positive (HER2+; 38%) or triple-negative (34%). Those who were BCSe before NAC had a lower cT stage, whereas those who chose mastectomy were younger ($P < .05$). NAC was usually ACT (doxorubicin, cyclophosphamide, and a taxane)-based (92%), 99% of HER2+ patients received dual blockade, and 99% of BCS patients received adjuvant radiation. At a median follow-up of 35 months, 22 patients (3.2%) had developed LR. The Kaplan-Meier 4-year LR rates were not different among the groups (1.9% for those who were BCSe before and after NAC, 6.3% for those who downstaged to being BCSe and underwent BCS, and 2.7% for those who downstaged and underwent mastectomy; $P = .17$). **CONCLUSIONS:** LR rates are low after NAC and BCS, even among BCSi patients who downstage, and they are not improved in patients who downstage and choose mastectomy. Mastectomy can be safely avoided in BCSi patients who downstage with NAC. ***Cancer* 2021;0:1-8**. © *2021 American Cancer Society*.

KEYWORDS: breast cancer, breast-conserving surgery, chemotherapy, local neoplasm recurrence, mastectomy.

INTRODUCTION

Neoadjuvant chemotherapy (NAC) may be used in operable breast cancer to downstage large primary tumors and permit breast-conserving surgery (BCS) for many patients who would otherwise require mastectomy. Rates of BCS have increased as NAC has become widely used.[1-3] In a consecutive population of 600 patients with large stage I to III tumors initially precluding BCS who were treated at our institution from 2013 to 2019 with modern NAC, 48% successfully avoided mastectomy, and this demonstrated a substantial clinical benefit.[1]

The Early Breast Cancer Trialists' Collaborative Group's patient-level meta-analysis of 4756 patients treated in 10 randomized trials of NAC versus adjuvant therapy between 1983 and 2002 similarly demonstrated a higher rate of BCS in NAC patients in comparison with upfront surgery (65% vs 49%; $P < .001$).[4] However, a higher rate of local recurrence (LR) was observed among those treated with NAC, and this raised concerns regarding the safety of this approach, particularly among those who downstage to BCS after NAC. This was based on the observation of a small but statistically significant difference in 10-year LR among those treated with NAC versus upfront surgery (15.1% vs 11.9%; $P = .01$).[4] The included trials predated targeted systemic therapies and contemporary pathologic, radiologic, and surgical techniques. Rates of LR remain uncertain for patients receiving modern systemic chemotherapy and targeted therapy, particularly those who downstage from mastectomy to BCS with NAC. In this cohort of patients treated with modern NAC, we sought to compare rates of LR between those deemed breast-conserving surgery–eligible (BCSe) who were treated with BCS after chemotherapy, those deemed initially breast-conserving surgery–ineligible (BCSi) who downstaged and underwent BCS, and those who downstaged but chose mastectomy.

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MATERIALS AND METHODS

Following institutional review board approval, we identified consecutive patients with cT1-3 invasive breast cancers, as defined in the American Joint Committee on Cancer Staging Manual (eighth edition),[5] who were treated with NAC from May 2014 to December 2018 from a prospectively maintained, Health Insurance Portability and Accountability Act–compliant, database. This period was selected because it spanned sufficient time to allow 3 or more years of follow-up after the time at which BCS eligibility began to be recorded in the database. Patients with cT4 disease or multicentric disease who were considered ineligible for downstaging to BCS with NAC and those who had unknown pre- or post-NAC BCS eligibility were excluded from this analysis. BCS eligibility was prospectively determined by the treating surgeon before NAC and at the completion of NAC on the basis of the extent of disease with respect to the breast size. Three groups were identified for analysis: patients who were BCSe before and after NAC and had BCS; patients who were BCSi before NAC, downstaged to BCSe after NAC, and had BCS; and patients who were BCSi before NAC and downstaged to BCSe after NAC but chose mastectomy. The last group was included as a comparator to assess whether resection of the entire original tumor volume in initially BCSi patients would affect LR rates in comparison with BCS. The primary outcome of interest was LR, which was defined as a biopsy-proven in situ or invasive recurrence of the ipsilateral breast or chest wall with or without disease in the regional lymph nodes and without any sites of distant disease relapse. Biopsy to confirm LR was performed after detection by an examination or imaging abnormality.

Clinicopathologic characteristics were compared between groups with the Wilcoxon rank sum test for continuous variables, and with the χ^2 or Fisher exact test for categorical variables. Significant covariates from the univariate analysis along with the clinical T stage and the BCS eligibility group, considered to be important predictors of recurrence regardless of the results of univariate analysis, were then included in the multivariable Cox regression model. Kaplan-Meier methods were used to estimate 4-year LR-free survival estimates by group. The type I error rate was set to .05 (α). To account for the 178 patients whose lymphovascular invasion (LVI) status was not reported, we conducted a sensitivity analysis by performing multiple imputation with the *mice* package in R under the missing-at-random assumption. All analyses were performed with R 3.6.3 (R Core Team, 2020).

RESULTS

From May 2014 to December 2018, 1136 consecutive patients with cT1-3 invasive cancers were treated with NAC; 374 patients were BCSi or had unknown BCS eligibility after NAC and were excluded, as were 71 patients who were BCSe after NAC and chose mastectomy and 6 patients with unknown BCS eligibility before NAC. The remaining 685 patients who were BCSe after NAC comprised the study cohort. Among these patients, 243 (35%) were BCSe before and after NAC and had BCS, 282 (41%) were BCSi before NAC, downstaged to BCSe after NAC, and had BCS, and 160 (23%) were BCSi before NAC and downstaged to BCSe after NAC but chose mastectomy (Fig. 1). All patients underwent pretreatment mammography, 670 (98%) underwent pretreatment ultrasound, and 577 (84%) underwent pretreatment magnetic resonance imaging. After NAC, 635 (93%) underwent mammography, 165 (24%) underwent ultrasound, and 404 (59%) underwent magnetic resonance imaging. The majority of the patients received neoadjuvant dose-dense doxorubicin, cyclophosphamide, and a taxane (92%), and 99% of human epidermal growth factor receptor 2–positive (HER2+) patients received dual-targeted HER2 therapy with trastuzumab and pertuzumab. In the adjuvant setting, 216 of 258 HER2+ patients (84%) completed adjuvant trastuzumab and pertuzumab, whereas the remainder received single-agent HER2 blockade. Most hormone receptor–positive patients (93%) received adjuvant endocrine therapy. Adjuvant radiotherapy (RT) was delivered to 96% of the patients who underwent BCS: it was received by 238 (97.9%) who were BCSe before and after NAC and had BCS and by 267 BCSi patients (94.7%) who downstaged and had BCS. Postmastectomy RT was delivered to 94 BCSi patients (58.8%) who downstaged and chose mastectomy. Standard adjuvant RT to the breast or chest wall used conventional fractionation to a total dose of 5000 cGy in 25 fractions or a hypofractionated regimen of 4240 cGy in 16 fractions for BCS patients at the discretion of the treating physician. A sequential boost to the lumpectomy cavity of 1000 cGy was delivered in 4 to 5 fractions. Comprehensive nodal irradiation, received by 108 patients (44.4%) who were BCSe before and after NAC and had BCS, by 105 patients (37.2%) who were BCSi, downstaged, and had BCS, and by 81 patients (50.6%) who downstaged and chose mastectomy, was delivered to the ipsilateral level I and II axillary nodes, the supraclavicular and infraclavicular fossa, and the internal mammary chain in the first 3 intercostal spaces to a total dose of 5000 cGy in 25 fractions.

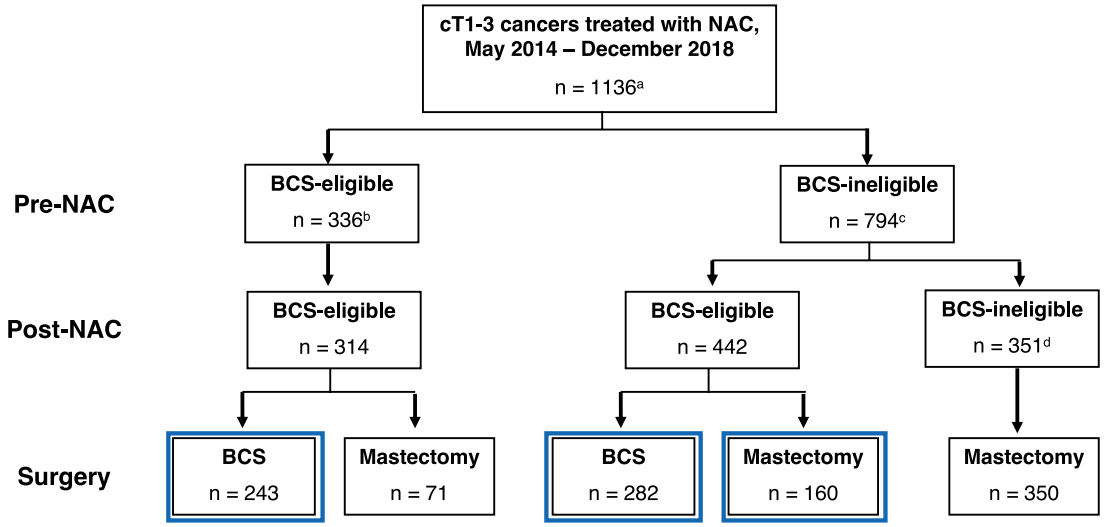


Figure 1. Patient population categorized by BCS eligibility and choice of surgery. Highlighted boxes indicate study groups. [a]BCS eligibility before NAC was unknown in 6 cases. [b]Twenty-two patients were deemed BCS-ineligible after NAC because of progression of disease, a contraindication to radiation, a genetic mutation, or other patient factors discovered during NAC. [c]BCS eligibility after NAC was unknown in 1 case. [d]One patient pursued BCS despite being categorized as BCS-ineligible. BCS indicates breast-conserving surgery; NAC, neoadjuvant chemotherapy.

The clinicopathologic characteristics of all patients and each BCS eligibility group are summarized in Table 1. The median age was 52 years, and most cancers were cT1-2 (84%), cN+ (61%), and HER2+ (38%) or triple negative (34%). Patients who were BCSe before and after NAC and had BCS were older (median age, 56 years) in comparison with BCSi patients who downstaged and had BCS (median age, 51 years) or who downstaged and chose mastectomy (median age, 44 years; $P < .001$). BCSi patients who downstaged had a higher clinical T stage at presentation than BCSe patients ($P < .001$) and more often had poorly differentiated tumors ($P = .04$; Table 1). A breast pathologic complete response (pCR; ypT0) was achieved in 220 patients (32.1%), and this was similar between groups ($P = .6$).

At a median follow-up of 35 months (interquartile range, 24-48 months), 22 patients (3.2%) had developed LR, with 5 occurring in pre-NAC BCSe patients, 13 occurring in BCSi patients who downstaged and had BCS, and 4 occurring in BCSi patients who downstaged and chose mastectomy. None of the 4 patients who developed LR after mastectomy received postmastectomy RT. The Kaplan-Meier 4-year LR rate was 3.8% (95% confidence interval [CI], 2.1%-5.5%) overall and was similar between groups: 1.9% (95% CI, 0.04%-3.8%) among pre-NAC BCSe patients, 6.3% (95% CI, 2.6%-10.0%) among those who downstaged and had BCS, and 2.7% (95% CI, 0.09%-5.4%) among those who downstaged and chose mastectomy ($P = .17$; Fig. 2). The crude median time to LR was 14 months (interquartile range, 10-20 months), and the majority (n = 18 [82%]) were isolated breast or chest wall recurrences, whereas 4 (18%) had synchronous breast or chest wall and regional nodal recurrences. The time to LR and the location of LR were similar between groups ($P = .3$ and $P = .2$, respectively). Distant disease developed in 55 patients (8.0%; 7.4% vs 7.4% vs 10%; $P = .6$), and at last follow-up, 617 patients (90%) were alive with no evidence of disease (92% vs 90% vs 88%; $P = .5$).

Associations with the development of LR were examined with Cox regression models and are summarized in Table 2. In a univariate analysis, breast pCR (hazard ratio [HR], 0.20; 95% CI, 0.05-0.87; $P = .032$) and LVI (HR, 3.95; 95% CI, 1.55-10.0; $P = .004$) were associated with the development of LR, whereas the clinical T stage and BCS eligibility before NAC were not ($P > 0.5$). In a multivariable analysis, only LVI was independently associated with LR (HR, 3.06; 95% CI, 1.2-7.9; $P = .02$; Table 2). A multiple imputation analysis to account for missing data did not affect this result; LVI remained the only covariate associated with LR (HR, 3.24; 95% CI, 1.33-7.86; $P = .01$).

DISCUSSION

This study in a large, consecutive cohort of patients with T1-3 breast cancer treated with modern NAC provides

TABLE 1. Clinicopathologic Characteristics of the Overall Cohort and Each BCS Eligibility Group

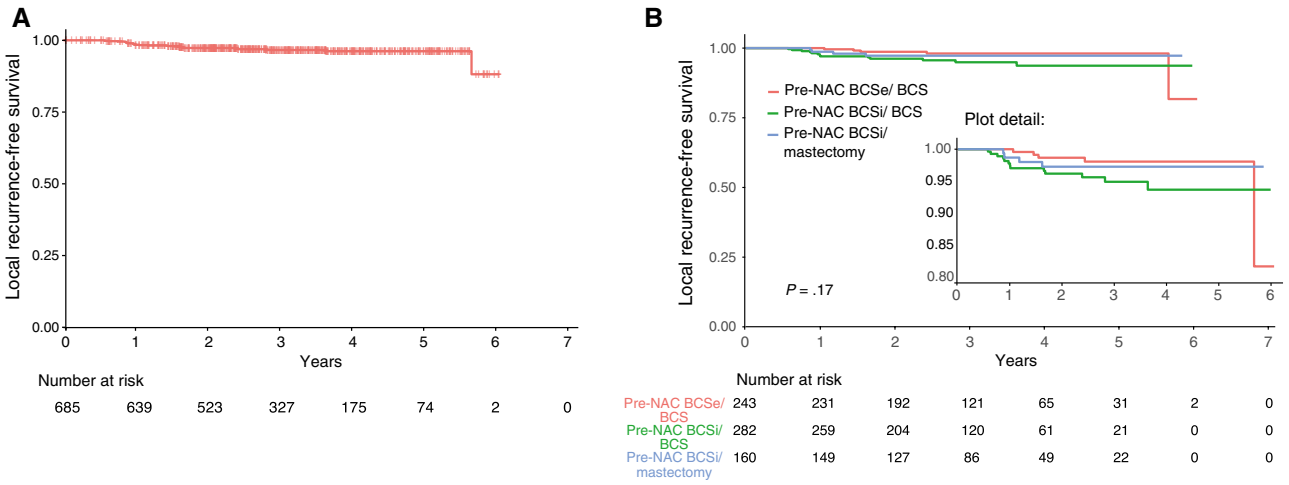
Characteristic	All Patients (n = 685)	Post-NAC BCSe, Had BCS			P
		Pre-NAC BCSe (n = 243)	Pre-NAC BCSi (n = 282)	Pre-NAC BCSi, Downstaged to BCSe, Chose Mastectomy (n = 160)	
Age, median (range), y	52 (25-82)	56 (30-82)	51 (25-82)	44 (26-72)	<.001
Clinical T stage, No. (%)					<.001
1	114 (16.6)	82 (33.7)	21 (7.4)	11 (6.9)	
2	459 (67.0)	156 (64.2)	200 (70.9)	103 (64.4)	
3	112 (16.4)	5 (2.1)	61 (21.6)	46 (28.8)	
Clinical N stage, No. (%)					.3
0	267 (39.0)	79 (32.5)	121 (42.9)	67 (41.9)	
1	372 (54.3)	145 (59.7)	142 (50.4)	85 (53.1)	
2	23 (3.4)	10 (4.1)	9 (3.2)	4 (2.5)	
3	23 (3.4)	9 (3.7)	10 (3.5)	4 (2.5)	
Histology, No. (%)					.073
Invasive ductal	645 (94.2)	223 (91.8)	273 (96.8)	149 (93.1)	
Invasive lobular	33 (4.8)	15 (6.2)	8 (2.8)	10 (6.3)	
Other	7 (1.0)	5 (2.1)	1 (0.4)	1 (0.6)	
Receptor status, No. (%)					.3
ER+/HER2–	196 (28.6)	81 (33.3)	70 (24.8)	45 (28.1)	
ER+/HER2+	164 (23.9)	52 (21.4)	78 (27.7)	34 (21.3)	
ER–/HER2+	94 (13.7)	30 (12.3)	39 (13.8)	25 (15.6)	
ER–/HER2–	231 (33.7)	80 (32.9)	95 (33.7)	56 (35.0)	
Lymphovascular invasion, No. (%)[a]	161 (23.5)	56 (23.0)	61 (21.6)	44 (27.5)	.9
Differentiation, No. (%)					.04
Well	6 (0.9)	3 (1.2)	2 (0.7)	1 (0.6)	
Moderate	167 (24.4)	73 (30.0)	54 (19.1)	40 (25.0)	
Poor	512 (74.7)	167 (68.7)	226 (80.1)	119 (74.4)	
Breast pCR (ypT0), No. (%)	220 (32.1)	73 (30.0)	92 (32.6)	55 (34.4)	.6
Breast pCR (ypT0/Tis), No. (%)	272 (39.7)	93 (38.3)	116 (41.1)	63 (39.4)	.8
Final margin status, No. (%)					>.9
No tumor	684 (99.9)	243 (100)	281 (99.6)	160 (100)	
Positive	1 (0.1)	0 (0)	1 (0.4)	0 (0)	
Developed LR, No. (%)	22 (3.2)	5 (2.1)	13 (4.6)	4 (2.5)	.3

Abbreviations: BCS, breast-conserving surgery; BCSe, breast-conserving surgery–eligible; BCSi, breast-conserving surgery–ineligible; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LR, local recurrence; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response.
[a]Unknown in 178 patients.

evidence that rates of LR after NAC and BCS are low, even among patients who are initially BCSi and are downstaged with NAC.

Because NAC is increasingly being used to downstage large primary tumors to BCS, evidence supporting the oncologic safety of this approach is of paramount importance. Although early trials demonstrated no difference in survival or LR with the use of NAC versus postoperative chemotherapy,[2,3] the recent Early Breast Cancer Trialists' Collaborative Group meta-analysis of 10 randomized trials, including 4756 patients treated between 1983 and 2002, raised concerns regarding the safety of this approach. This analysis revealed a statistically significant higher rate of LR among patients treated with NAC versus upfront surgery followed by adjuvant therapy at a median follow-up of 9 years.[4] Although the included trials were performed in the pre-trastuzumab era, did not report details on RT, and likely used dated pathologic and localization techniques, the authors hypothesized that the increase in LR might be attributable to those who converted from initially being BCSi to being BCSe after NAC and underwent BCS.

LR rates among patients who downstage to BCSe have been examined in small subgroup analyses of 2 early randomized trials. In the National Surgical Adjuvant Breast and Bowel Project B-18 trial of 1523 women randomized to NAC versus adjuvant chemotherapy, the 9-year rate of LR was 15.9% among those who downstaged to BCS (n = 69) and 9.9% among those who were BCSe before NAC and had BCS (n = 434). This was not statistically significant after adjustments for age and tumor size ($P = .14$).[6] The European Organisation for Research and Treatment of Cancer 10902 trial also reported comparable 10-year rates of LR among those who underwent BCS followed by adjuvant chemotherapy (n = 64; reference), those who were initially BCSe and had NAC followed by BCS (n = 63; HR, 1.0; 95% CI, 0.46-2.15), and those who



Group	n	4-year LR-free survival	95% CI
Overall	685	96.2%	94.5–97.9%
Pre-NAC BCSe/ BCS	243	98.1%	96.2–99.9%
Pre-NAC BCSi/ BCS	282	93.7%	89.9–97.4%
Pre-NAC BCSi/ mastectomy	160	97.3%	94.6–99.9%

Figure 2. LR-free survival: (A) overall and (b) stratified by BCS eligibility and type of surgery. BCS indicates breast-conserving surgery; BCSe, breast-conserving surgery–eligible; BCSi, breast-conserving surgery–ineligible; CI, confidence interval; LR, local recurrence; NAC, neoadjuvant chemotherapy.

downstaged with NAC to BCS (n = 58; HR, 1.1; 95% CI, 0.5-2.39; $P = .97$).[7] These findings are consistent with the results of our study, with 4-year LR rates of 1.9% (observed among initially BCSe patients who had NAC and BCS), 6.3% (observed among BCSi patients who downstaged and had BCS), and 2.7% (observed among BCSi patients who downstaged but chose mastectomy; $P = .2$). Furthermore, our observed LR rates after NAC are comparable to the 10-year cumulative incidences of LR of up to 9% reported in the National Surgical Adjuvant Breast and Bowel Project trials after upfront BCS followed by RT and adjuvant chemotherapy among both node-positive and node-negative breast cancers.[8,9] To our knowledge, this is the first contemporary study to evaluate local control in a cohort with prospectively determined BCS eligibility, and it included more than 400 patients who successfully downstaged from BSCi to BCSe. Although longer follow-up of our cohort will establish long-term LR rates, the absence of any significant association between BCS eligibility before and after NAC and LR in univariate and multivariable analyses suggests that the eligibility status at presentation by itself is not a predictor of local failure.

Recent studies have demonstrated that a poor response to NAC is predictive of LR. In a single-institution analysis of 751 patients treated with modern NAC and BCS from 2005 to 2012, a failure to achieve pCR was independently associated with LR (HR, 8.9; 95% CI, 2.1-37; $P = .003$), with 5-year LR-free survival rates of 98.6% for those who experienced a pCR and 89.9% for those who did not ($P = .007$).[10] Similarly, a lack of breast pCR was predictive of LR (HR, 1.4; 95% CI, 1.1-1.8; $P = .02$) in a patient-level meta-analysis including 4125 patients from 9 studies of breast-conserving therapy after NAC.[11] In our current study, breast pCR was associated with LR in a univariate analysis, but this did not reach statistical significance in a multivariable analysis. This may be due to the low LR event rate in our study as well as our short median follow-up; with longer follow-up, associations with breast pCR may become evident. Notably, LVI, a known risk factor for recurrence,[12] was strongly associated with LR in the univariate and multivariable analyses, and this highlights the clinicopathologic feature as a primary driver of local failure. The observation that choosing mastectomy did not lower rates of LR among patients who downstaged from being BCSi to being BCSe further underscores the impact of tumor biology (and not the extent of local surgery) on local control.

The findings in this study support the safety of BCS after NAC among initially BCSi patients who downstage

TABLE 2. Univariate and Multivariable Regression Analyses of Risk Factors for the Development of Local Recurrence

	Univariate Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Eligibility/surgery group						
Initially BCSe and had BCS	Reference	—	—	Reference	—	—
Downstaged and had BCS	2.43	0.9-6.8	.09	2.70	0.8-9.4	.1
Downstaged and chose mastectomy	1.28	0.3-4.8	.7	0.78	0.2-3.9	.8
Age, y	1.00	0.96-1.0	>.9			
Clinical T stage						
1	Reference	—	—	Reference	—	—
2	0.87	0.2-3.1	.8	0.90	0.2-4.4	.9
3	2.72	0.7-10.3	.14	2.06	0.4-11.6	.4
Clinical N stage						
0	Reference	—	—			
1	1.04	0.5-2.4	>.9			
2[a]	NA	NA	>.9			
3[a]	NA	NA	>.9			
Receptor status						
ER+/HER2–	Reference	—	—			
ER+/HER2+	0.30	0.06-1.4	.13			
ER–/HER2+	1.18	0.3-4.0	.8			
ER–/HER2–	1.14	0.4-3.1	.8			
Differentiation[b]						
Moderate	Reference	—	—			
Poor	1.12	0.4-3.0	.8			
Lymphovascular invasion						
Absent	Reference	—	—	Reference	—	—
Present	3.95	1.6-10.0	.004	3.06	1.2-7.9	.02
Breast pCR (ypT0)						
No	Reference	—	—	Reference	—	—
Yes	0.20	0.05-0.8	.03	0.18	0.02-1.4	.10

Abbreviations: BCS, breast-conserving surgery; BCSe, breast-conserving surgery–eligible; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NA, not applicable; pCR, pathologic complete response.
[a]There were too few patients with cN2 and cN3 tumors (n = 46) to report the HR.
[b]There were too few patients with well-differentiated tumors (n = 6) to report the HR.

to BCSe. The perception that all breast tissue initially involved by the tumor must be excised at the time of surgery may lead to unnecessary mastectomies in this setting.[13,14] Although guidelines such as those published by the St. Gallen International Expert Consensus advise that resection of the entire tumor bed after neoadjuvant treatment is not necessary,[15] practice remains highly variable. In a recent survey of all multidisciplinary teams from breast units in the United Kingdom, 26% of centers reported resection of the original tumor footprint, regardless of clinical and radiologic responses.[13] Similarly, in the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALLTO) trial of neoadjuvant treatment for HER2+ cancers, despite dramatic improvements in pCR rates with dual HER2 blockade, BCS rates did not increase, and the use of BCS remained most frequent among those who were deemed BCSe at diagnosis.[16] However, data from past studies, including a retrospective study of 509 consecutive patients with T1-3N0-2 cancers treated in prospective trials of chemotherapy from 1998 to 2005, have demonstrated the safety of limiting resection to residual viable tumor. That study found that after NAC, there was a significant reduction in the lumpectomy volume among tumors larger than 2 cm at presentation, and there was no difference in the re-excision rate or LR at 33 months, in comparison with those who received postoperative chemotherapy.[17] The appropriate margin width after NAC also remains controversial, but multiple studies have demonstrated that no tumor on ink, similarly to the primary surgery setting, is associated with excellent local control after NAC and BCS.[18-21] Although long-term outcome data are forthcoming, contemporary data, including results from our current study, emphasize the opportunity for optimizing surgical therapy and decreasing the burden of overtreatment.

The limitations of our study include its retrospective, single-institution nature and relatively short median follow-up of 35 months. However, we have examined a large, consecutive cohort of patients treated with modern NAC along with prospective

determination of BCS eligibility by the treating surgeon and standardized medical, surgical, and pathologic techniques. Additionally, although most recurrences among HER2+ and triple negative patients, who comprised more than 70% of our study population, occur within 5 years,[22-24] further follow-up will be valuable for establishing long-term LR rates after treatment with NAC and BCS.

In conclusion, in this contemporary population of operable breast cancers treated with NAC, the 4-year rates of LR were similar for initially BCSi patients who downstaged to BCSe and had BCS, and those who were BCSe throughout and had BCS. Choosing to undergo mastectomy did not improve LR rates among those who downstaged. These results support the safety of avoiding mastectomy in initially ineligible patients who downstage with modern NAC. For many patients, this approach affords an opportunity for surgical de-escalation to minimize the burden of treatment without compromising oncologic outcomes.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Anita Mamtani: Conceptualization, data curation, formal analysis, investigation, methodology, resources, validation, visualization, writing–original draft, and writing–review and editing. **Varadan Sevilimedu:** Formal analysis, methodology, resources, validation, visualization, and writing–review and editing. **Tiana Le:** Data curation. **Monica Morrow:** Conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Andrea V. Barrio:** Conceptualization, data curation, formal analysis, methodology, resources, supervision, validation, visualization, writing–original draft, and writing–review and editing. Data were analyzed by a statistician employed by the authors' institution. Medical editors employed by the authors' institution assisted in preparing the article under the direction of the authors. All authors helped to prepare, review, and approve the article.

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