Original Article

Neoadjuvant systemic therapy does not compromise local control after breast-conserving surgery: a single-center, propensity score matching study in China

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Background: To investigate ipsilateral breast tumor recurrence (IBTR) in patients who have undergone breast-conserving surgery (BCS) after neoadjuvant systematic therapy (NST).

Method: Three hundred and twenty-one patients undergoing BCS after NST and 2,534 patients undergoing initial BCS from June 2008 to June 2017 at Fudan University Shanghai Cancer Center were retrospectively enrolled, and statistical analyses, including propensity score matching, were applied to compare IBTR-free survival. The main factors related to IBTR in the NST group were estimated utilizing univariate and multivariate analyses.

Results: After propensity score matching, the 3-year IBTR-free survival rates were 93.7% (95% CI, 90.6–96.8%) in the NST group and 96.9% (95% CI, 94.9–98.9%) in the matched initial BCS group at a median follow-up period of 58 months. IBTR-free survival did not differ statistically between the two groups (P=0.154). According to multivariate analysis in the NST group, tumor-infiltrating lymphocytes (TILs), epidermal growth factor receptor 2 (HER2) status and pathologic ductal carcinoma in situ (DCIS) constituent were the factors related to IBTR after BCS.

Conclusions: BCS after NST and initial BCS have equivalent IBTR-free survival. BCS after NST is a safe and effective therapy in terms of IBTR.

Keywords: Neoadjuvant systematic therapy (NST); breast-conserving surgery (BCS); ipsilateral breast tumor recurrence (IBTR)

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Introduction

Breast cancer is the most commonly diagnosed cancer and the most common cause of cancer-related death among females (1). The development of multidisciplinary systemic therapy has improved the treatment efficacy of breast cancer. In early-stage breast cancer, breast-conserving surgery (BCS) plus radiotherapy has proved to be equivalent to mastectomy in terms of oncologic safety (2,3), but the application of BCS after neoadjuvant therapy remains controversial. Although unable to improve overall

survival (4), neoadjuvant systematic therapy (NST) can degrade the volume of the primary tumor to amplify the possibility of BCS and increase the likelihood of eradicating micrometastatic disease (5,6). BCS after neoadjuvant therapy remains controversial because the improvement in the pathologic complete response (pCR) rate has not been translated into an increase in the BCS rate (7,8). Estimating lesions after NST and surgical decision-making remain challenging for surgeons. A meta-analysis of ten randomized trials investigated long-term outcomes between neoadjuvant and adjuvant therapy in early breast cancer (9). No significant difference was detected for distant metastasis, breast cancer mortality, or overall survival. However, local recurrence was higher in the neoadjuvant group than in the adjuvant group, possibly due to the increase in the BCS rate in the neoadjuvant group. Studies investigating BCS after NST have reported ipsilateral breast tumor recurrence (IBTR) rates ranging from 5% to 11% (10-14). The risk factors associated with IBTR, including clinical stage, pathologic response, a multifocal pattern of residual disease, and lymphovascular space invasion in the specimen, have also been investigated (10-14).

Most studies investigating the outcomes of BCS after NST were one-arm studies or compared BCS after NST with mastectomy (15-18). Two-arm investigations focusing on the IBTR rate are scarce. Our study aimed to explore the IBTR rate of BCS after NST compared to matched initial BCS to estimate the oncologic safety of BCS after tumor downsizing by NST. We also focused on the correlation of IBTR with clinicopathological variables.

Methods

Patients

This retrospective study included 321 consecutive patients undergoing BCS following MST during the period June 2008 to June 2017 at Fudan University Shanghai Cancer Center (FUSCC). We also reviewed 683 patients undergoing initial BCS with noninflammatory invasive breast cancer measuring >2 cm and/or axillary lymph node metastasis as a control group. Patients were excluded if they had any one of the following: (I) stage IV disease; (II) no radiotherapy after BCS; (III) without standard trastuzumab therapy when HER2 status was positive; (IV) unknown data (*Figure 1*). Clinicopathological characteristics and follow-up information were derived from medical records collected by the Department of Surgery of FUSCC. Clinical tumor sizes were assessed on magnetic resonance imaging findings in the baseline assessment.

Surgical approaches

Neoadjuvant chemotherapy was delivered to 252 of the 321 patients with six to eight cycles of anthracycline and/or taxane regimens, while neoadjuvant endocrine therapy was delivered to 69 patients with four to six months of aromatase inhibitors plus ovarian function suppression or aromatase inhibitors alone. All patients with HER2-positive breast cancer received trastuzumab as part of their neoadjuvant regimen. The clinical and radiological response was measured every two cycles. For all patients, the type of breast surgery and axillary surgery were determined by the multidisciplinary team according to NCCN guidelines. When obtaining positive margins in the final pathology, additional excisions were performed. Axillary lymph node dissection (ALND) was the standard treatment for NST patients. For patients presenting clinically lymph node negative, sentinel lymph node dissection (SLND) without ALND was routinely performed. All patients received adjuvant whole-breast radiotherapy with or without the regional nodal area in 25–30 fractions after adjuvant chemotherapy or after surgery if adjuvant chemotherapy was unnecessary. In the control group, adjuvant chemotherapy was delivered to 597 of 683 patients, while adjuvant endocrine therapy only was delivered to 86 patients.

Pathological assessment

All specimens were fixed in 10% neutral phosphate-buffered formalin and paraffin-embedded. Slices of typical tumor blocks with a thickness of 4 μm were stained with hematoxylin and eosin (H&E). Estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 expression, and Ki67 proliferative index were tested using immunohistochemical staining in both pretreatment core needle biopsy samples and posttreatment surgical excision samples. Evaluation of TILs in core needle biopsy specimens was accomplished by two pathologists. Stromal TILs were appraised according to the standardization of the international TILs working group (19). Pathological complete response (pCR) was defined as the absence of residual tumor cells in both the breast and axillary lymph nodes (ypT0+ ypN0). Lymphovascular invasion (LVI) was observed in the postoperative slices. Negative margins were defined as “no ink-on-tumor”.

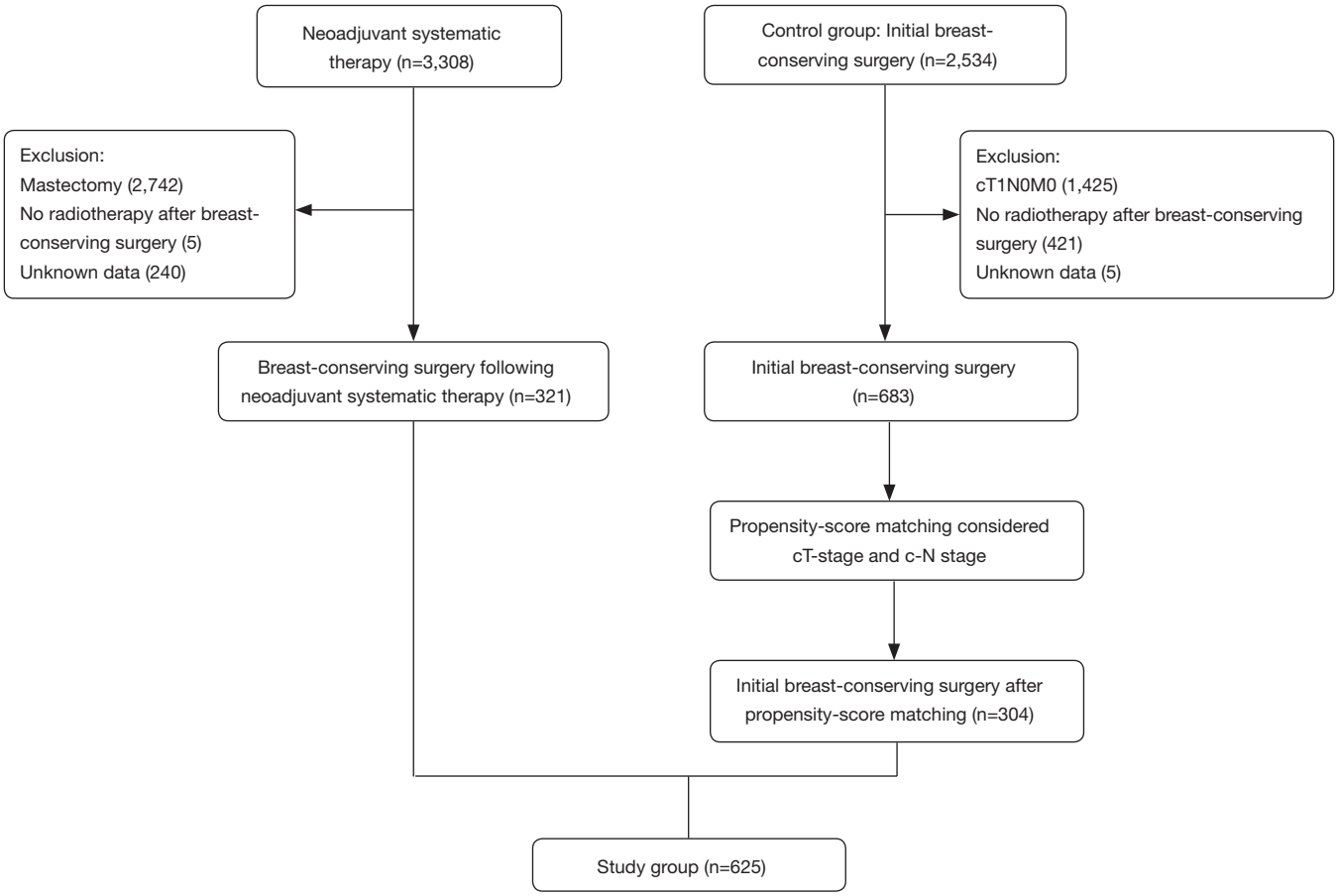

Figure 1 Patient selection and exclusion criteria.

Follow-up protocol

After surgery, patient follow up was scheduled every 3 months in the first 2 years and then every 6 months over the following 3 years. After 5 years, the follow-up frequency was prolonged to once per year. During the follow-up period, patients came to our cancer center to receive a routine examination, comprehensive chest computed tomography (CT), breast MRI, breast ultrasonography, mammography, and abdominal ultrasonography. The follow-up information was compiled by reviewing medical records with a deadline of December 2018. This study was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (No.050432-4-1212B).

Propensity score matching and statistical analyses

To adjust for significant baseline covariates between the two groups, a propensity score matching procedure was used to decrease latent biases between the two groups. Patients' baseline clinical characteristics, including clinical tumor size and clinical lymph node stage, were considered as covariates for matching. The propensity score matching was carried out by IBM SPSS Statistics version 24.0 software with the number of patients in each group set at 1:1 and Caliper set at 0.05. Baseline standardized mean differences were computed before and after propensity score matching.

Baseline characteristics of the patients were described by frequencies and percentages for categorical variables and by means and standard deviations for normally distributed continuous data, including age, menopausal status, clinical T-stage, clinical N-stage, histological type, ER status, PR status, HER2 expression, pathological T-stage, pathological N-stage and neoadjuvant/adjuvant regimen. Tests of distribution between two groups were conducted by Student's t-test or Pearson's x^2 test.

IBTR was considered as recurrence in the ipsilateral

breast and locoregional recurrence (LRR) as recurrence in the ipsilateral breast, ipsilateral axilla, chest wall, internal mammary, and supraclavicular lymph nodes. Kaplan-Meier survival curves for both groups were used to portray IBTR-free survival. Cox proportional hazards regression was used in univariate and multivariate analyses. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant. SPSS software package version 24.0 (Chicago, IL) was used for all analyses.

Results

Before propensity score matching, 321 patients underwent BCS after NST, and 683 patients underwent initial BCS. Their baseline clinical characteristics are shown in *Table 1*. Although we selected patients with breast cancer measuring >2 cm and/or axillary lymph node metastasis as controls, there were still significant differences in clinical T-stage (P<0.001), clinical N-stage (P<0.001), ER status (P<0.001), PR status (P<0.001), HER2 status (P<0.001), pathological T-stage (P<0.001), pathological N-stage (P<0.001) and neoadjuvant/adjuvant regimen (P<0.001). Considering the importance of the clinical T-stage and N-stage for BCS in terms of IBTR, we used a propensity score matching process to reduce potential biases.

After propensity score matching, 304 patients were enrolled in the control group. No significant differences in T-stage and N-stage were observed, as shown in *Table 2*. With a median follow-up period of 58 months (range, 10–153), 23 patients (7.2%) in the NST group had developed LRR, including 20 with IBTR (6.2%, *Table S1*), and 26 patients developed recurrences at other sites: eight bone metastases, five brain metastases, four liver metastases, four lung metastases, and five soft tissue metastases.

The 3-year IBTR-free survival rates were 93.7% (95% CI, 90.6–96.8%) in the NST group and 96.9% (95% CI, 94.9–98.9%) in the matched initial BCS group. The 3-year disease-free survival (DFS) rate was 87.3% (95% CI, 83.4–91.2%) in the NST group. IBTR events were diagnosed mainly by magnetic resonance imaging (*Table S1*). The overall pCR rate in the NST group was 31.5% (101/321). LRR after initial BCS occurred in 22 patients (7.2%), 21 of which had IBTR. *Figure 2* depicts the IBTR-free survival of the NST group and the initial BCS group. There was no significant difference between the two groups (P=0.154, HR =1.53, 95% CI, 0.82–2.87).

To evaluate independent prognostic factors affecting IBTR in patients undergoing BCS after NST, univariate and multivariate analyses were performed. The results are shown in *Table 3* and *Figure 3*. Pre-NST ER status (P=0.013), pre-NST HER2 status (P=0.022), TILs (P=0.001), and pathologic ductal carcinoma in situ (DCIS) constituent (P=0.001) were associated with a high rate of IBTR in univariate analysis. Next, a multivariate analysis taking these four factors into consideration was performed. Three factors reached statistical significance in the Cox proportional hazard model (Pre-NST HER2 status: HR =3.84, 95% CI, 1.26–11.71, P=0.018; TILs: HR =12.12, 95% CI, 2.62–55.97, P=0.001; pathologic DCIS constituent: HR =8.47, 95% CI, 2.76–26.01, P=0.001).

Discussion

Our retrospective study discovered that IBTR-free survival after BCS after NST resembled that after initial BCS in patients with invasive breast cancer measuring >2 cm and/or axillary lymph node metastasis after propensity score matching. Based on our single-institution experience, concerns that the application of BCS after NST may increase the risk of IBTR after BCS should be reconsidered.

Most previous studies that investigated the outcomes of BCS after NST were one-arm studies or compared BCS after NST with mastectomy; two-arm studies focusing on the IBTR rate are scarce, possibly because treating patients undergoing mastectomy as the control group would eliminate the applicability of IBTR as an endpoint. Moreover, patients who have a good response to NST are more likely to receive BCS than mastectomy, which leads to a better outcome. This kind of "treatment by indications" bias has influenced previous studies and cannot be completely avoided. Thus, we enrolled patients undergoing initial BCS and used a propensity score matching procedure to adjust for clinical T-stage and N-stage to conduct this nonrandomized study. BCS after NST has rarely been compared with initial BCS (14,20,21), and those studies suggested worse outcomes in patients who underwent BCS after NST compared with initial BCS. However, Mittendorf EA *et al.* found no differences in LRR-free survival rates when comparing the presenting clinical stage (P=NS) between two groups (14). This observation is in agreement with our result that BCS after NST did not significantly increase the risk for IBTR (BCS after NST *vs.* initial BCS, P=0.154, HR =1.53, 95% CI, 0.82–2.87), as shown in *Figure 2*. These results suggest that the characteristics of the tumor and patients' baseline characteristics underlie the differences in IBTR between BCS and BCS after NST

Table 1 Clinicopathologic characteristics of BCS after NST and initial BCS groups before propensity-score matching

Factor	BCS after NST (n=321)	Initial BCS (n=683)	P
Age, years, median(range)	48.2±16.3 (21 to 85)	47.0±12.01 (19 to 87)	0.638
Menopausal status, n (%)			0.148
Pre-menopause	195 (60.7)	447 (65.4)	
Post-menopause	126 (39.3)	236 (34.5)	
Tumor histology, n (%)			0.085
Invasive ductal carcinoma	210 (65.4)	644 (94.3)	
Others	6 (1.9)	39 (5.7)	
Unknown (pCR)	105 (32.7)		
Clinical T-stage, n (%)			<0.001*
T1	51 (15.9)	74 (10.8)	
T2	220 (68.5)	604 (88.4)	
T3	50 (15.6)	5 (0.7)	
Clinical N-stage, n (%)			<0.001*
N0	109 (34.0)	391 (57.2)	
N1	113 (35.2)	250 (36.6)	
N2	68 (21.2)	40 (5.86)	
N3	28 (8.7)	1 (0.1)	
Nx	3 (0.9)	1 (0.1)	
ER status, n (%)			<0.001*
Positive	166 (51.7)	490 (71.7)	
Negative	155 (48.3)	193 (28.3)	
PgR status, n (%)			<0.001*
Positive	141 (43.9)	471 (69.0)	
Negative	180 (56.1)	212 (31.0)	
HER2 status, n (%)			<0.001*
Positive	102 (31.8)	121 (17.7)	
Negative	219 (68.2)	562 (82.3)	
Pathological T-stage, n (%)			<0.001*
Breast pCR	105 (32.7)		
(yp)Tis	15 (4.7)		
(yp)T1	165 (51.4)	82 (12.0)	
(yp)T2	33 (10.3)	596 (87.3)	
(yp)T3	3 (0.9)	5 (0.7)	

Table 1 (*continued*)

Table 1 (*continued*)

Factor	BCS after NST (n=321)	Initial BCS(n=683)	P
Pathological N-stage, n (%)			<0.001*
(yp)N0	224 (69.8)	367 (53.7)	
(yp)N1	65 (20.2)	175 (25.6)	
(yp)N2	29 (9.0)	105 (15.4)	
(yp)N3	3 (0.9)	29 (4.2)	
Nx		7 (1.0)	
Neoadjuvant/adjuvant regimen, n (%)			<0.001*
Anthracycline, not taxane	68 (21.2)	158 (23.1)	
Taxane-based	107 (33.3)	389 (57.0)	
Only endocrine	69 (21.5)	86 (12.6)	
Other	77 (24.0)	50 (7.3)	

*, P<0.05. BCS, breast-conserving surgery; NST, neoadjuvant systematic therapy; pCR, pathologic complete response; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 2 Clinicopathologic characteristics of BCS after NST and initial BCS groups after propensity-score matching

Factor	BCS after NST (n=321)	Initial BCS (n=304)	P
Age, years, median (range)	48.2±16.3 (21 to 85)	45.9±10.96 (23 to 85)	0.490
Menopausal status, n (%)			0.068
Pre‐menopause	195 (60.7)	206 (67.8)	
Post‐menopause	126 (39.3)	98 (32.2)	
Tumor histology, n (%)			0.124
Invasive ductal carcinoma	210 (65.4)	287 (94.4)	
Others	6 (1.9)	17 (5.6)	
Unknown (pCR)	105 (32.7)		
Clinical T-stage, n (%)			0.144
T1	51 (15.9)	36 (11.8)	
T2-3	270 (84.1)	268 (88.2)	
Clinical N-stage, n (%)			0.744
N0	109 (26.7)	108 (35.5)	
N1-3	209 (71.7)	196 (64.5)	
Nx	3 (1.7)		
ER status, n (%)			<0.001*
Positive	166 (51.7)	213 (70.1)	
Negative	155 (48.3)	91 (29.9)	

Table 2 (*continued*)

Table 2 (*continued*)

Factor	BCS after NST (n=321)	Initial BCS (n=304)	P
PgR status, n (%)			<0.001*
Positive	141 (43.9)	207 (68.1)	
Negative	180 (56.1)	97 (31.9)	
HER2 status, n (%)			
Positive	102 (31.8)	119 (39.1)	0.054
Negative	219 (68.2)	185 (60.9)	
Neoadjuvant/adjuvant regimen, n (%)			<0.001*
Anthracycline, not taxane	68 (21.2)	77 (25.3)	
Taxane-based	107 (33.3)	188 (61.8)	
Only endocrine	69 (21.5)	27 (8.9)	
Other	77 (24.0)	12 (3.9)	

*, P<0.05. BCS, breast-conserving surgery; NST, neoadjuvant systematic therapy; pCR, pathologic complete response; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

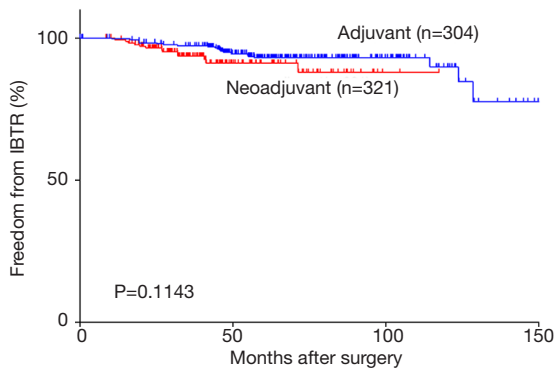

Figure 2 IBTR-free survival of patients undergoing breast-conserving surgery in the neoadjuvant group and adjuvant group after propensity score matching (P=0.154, HR =1.53, 95% CI, 0.82–2.87).

rather than neoadjuvant therapy itself.

Previous studies revealed the IBTR after BCS after NST was associated with clinical T-stage, clinical N-stage, nuclear grade, lymph node metastasis, LVI, and pathologic response (10,13,22). However, information about nuclear grade and LVI is difficult to estimate in surgical specimens after NST and are not reported for pre-NST core needle biopsy specimens. Given this situation, we applied propensity score matching to balance the clinical T-stage and N-stage. Propensity score matching was used recently to compare BCS and mastectomy in several retrospective studies (23,24). After propensity score matching, clinical T-stage (P=0.144) and clinical N-stage (P=0.744) were no longer significantly different between the two groups (*Table 2*). ER status (P<0.001), PR status (P<0.001) and neoadjuvant/adjuvant regimen (P<0.001) remained significantly different, but these variables are not thought to be related to IBTR.

The most challenging question for the application of BCS after NST is the reduction of IBTR. We analyzed factors that might influence IBTR. Several factors including tumor stage, surgical margins, and residual pathologic tumor size have been reported. Akay *et al.* established a prognostic index named the MD Anderson prognostic index (MDAPI) to distinguish patients at high risk of LRR who underwent BCS after NAC (25). The MDAPI considered factors including clinical N2/N3 disease, LVI, residual tumor size >2 cm and multifocal residual disease. In our single-institution cohort, HER2 status, TILs and pathologic DCIS constituent were significantly associated with IBTR in univariate and multivariate analyses. The diversity of predictive factors might reflect the enrollment of patients with early-stage breast cancer in our study, whereas previous studies included only local advanced breast cancer. The value of TILs in effectively predicting outcomes in both neoadjuvant and adjuvant settings has been confirmed (26,27), especially in HER2-positive and triple-negative molecular subtypes. TILs were associated

Table 3 Univariate analysis and multivariate analysis of time to IBTR

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (<50 *vs.* ≥50)	0.71	0.30–1.72	0.452			
Clinical T-stage						
cT1	1					
cT2	0.94	0.18–4.67	0.937			
cT3	0.84	0.25–3.08	0.839			
Clinical N-stage						
cN0	1					
cN1	1.02	0.34–3.05	0.966			
cN2	1.35	0.39–4.68	0.635			
cN3	1.96	0.51–7.58	0.330			
Pre-NST ER (negative *vs.* positive)	1.76	1.13–2.76	0.013*	3.02	0.982–9.28	0.054
Pre-NST PgR (negative *vs.* positive)	1.56	0.99–2.45	0.056			
Pre-NST HER2 status (positive *vs.* negative)	2.80	1.16–6.76	0.022*	3.84	1.26–11.71	0.018*
Pre-NST Ki67(≤20% *vs.* >20%)	1.04	0.34–3.17	0.951			
TIL (≤10% *vs.* >10%)	12.11	2.71–54.13	0.001*	12.12	2.62–55.97	0.001*
Neoadjuvant regimen (chemotherapy *vs.* endocrine therapy)	2.99	0.69–12.91	0.142			
Margin (negative *vs.* positive)	20.29	0.00–NA	0.864			
pCR (no *vs.* yes)	1.28	0.51–3.21	0.601			
Pathologic ductal carcinoma *in situ* constituent (yes *vs.* no)	5.28	2.11–13.25	0.001*	8.47	2.76–26.01	0.001*
Multifocality (yes *vs.* no)	6.83	0.91–51.48	0.062			
Pathologic Lymph node metastasis						
ypN0	1					
ypN1	0.62	0.34–1.13	0.119			
ypN2-3	1.27	0.64–2.51	0.500			
Lymphovascular invasion (positive *vs.* negative)	1.24	0.33–4.73	0.751			
Post-operative chemotherapy (no *vs.* yes)	0.84	0.24–2.73	0.814			

*, P<0.05. IBTR, ipsilateral breast tumor recurrence; pCR, pathologic complete response; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TILs, tumor infiltrating lymphocytes

with pCR, DFS and overall survival in breast cancers treated with neoadjuvant therapy (28,29). We also observed potential utility of TILs in predicting IBTR after BCS after NST. With respect to molecular subtype, triple-negative and HER2-positive subtypes have been reported to predict higher rates of IBTR (30,31). In our study, this trend was not so obvious, but we found that HER2 positivity was an independent predictive factor for IBTR (*Table S2*). We previously found that the presence of DCIS was significantly related to positive margins (32). In the present study, we found that DCIS was significantly associated with IBTR, possibly because of the smaller

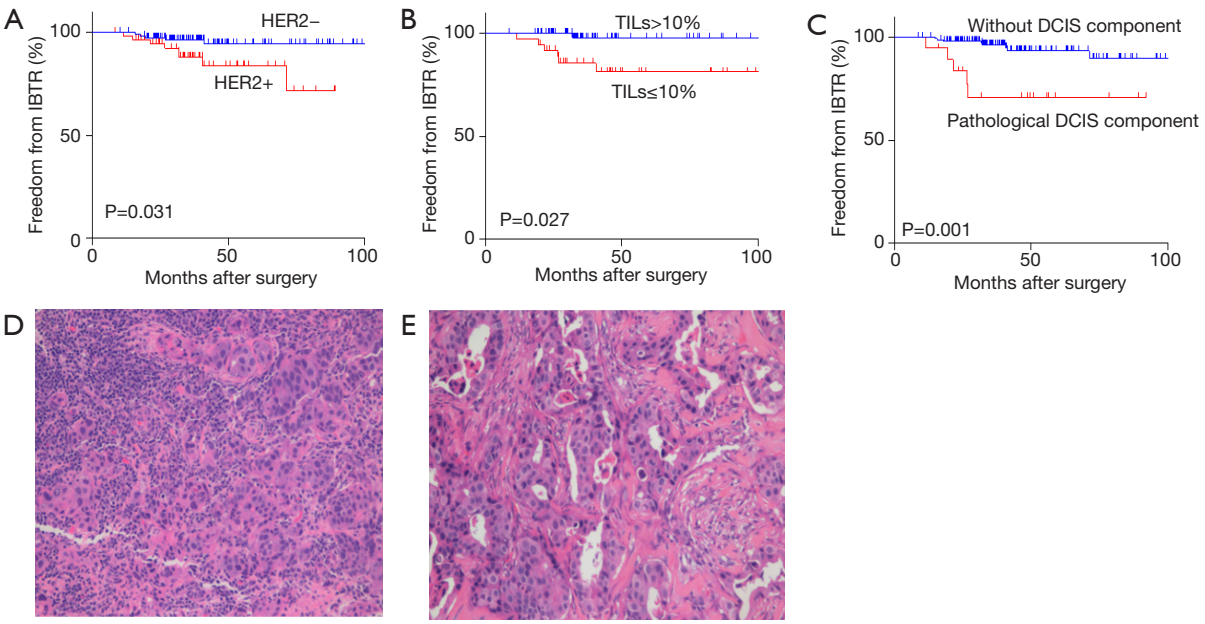

Figure 3 IBTR-free survival by HER2 status, TILs and pathological DCIS constituent. Actuarial rates of IBTR were calculated by the Kaplan-Meier method, and differences between groups were compared by log-rank test. Different TIL scores in core needle biopsy. D 80%, E 10%. H&E, original magnification (D, E) 200×.

tumor-to-margin distance. Tumor multifocality is always considered a factor in IBTR. The most common shrinkage pattern following NST of this kind of tumor is nest-like (33). Multifocal residual disease was not common in our study because mastectomy was performed only when the tumor magnetic resonance imaging shrinkage pattern resembled a nest.

This study also has limitations. Clinical T-stage and clinical N-stage, which were considered as covariates for propensity score matching, are both categorical data; however, the potential for bias still exists. Large, randomized controlled trials would provide the best evidence. The second limitation is the small sample size and the relatively short follow-up period. There were only a few IBTR events, which could have influenced the results. The third limitation is missing data, especially TILs, which may have affected our results. The comparison of initial BCS and BCS with NST requires additional evidence to achieve a better understanding.

Conclusions

In conclusion, our study demonstrates that BCS after NST and initial BCS have equivalent IBTR-free survival. BCS after NST is a safe and effective surgery for patients. Furthermore, HER2 positivity, TILs ≤10% and pathologic DCIS constituent are factors associated with higher IBTR rates in patients undergoing BCS after NST.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.11.23). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (No.050432-4-1212B). Informed consent was waived.

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Supplementary

Table S1 The diagnosis and treatment of patients who developed IBTR

No.	Primary breast cancer		Diagnosis and treatment of IBTR		
	Pathologic stage	Molecular subtype	Imaging diagnosis	Salvage local therapy	Systemic therapy
1	ypT1N1M0	HR+/HER2−	MRI	No	Chemotherapy
2	ypT0N2M0	HR+/HER2−	Ultrasonography	Mastectomy	Chemotherapy
3	ypT0N0M0	HR+/HER2+	MRI	Mastectomy	Chemotherapy
4	ypT0N0M0	HR-/HER2+	MRI	Mastectomy	Chemotherapy
5	ypTisN0M0	HR-/HER2+	MRI	No	Chemotherapy
6	ypTisN0M0	HR+/HER2−	Needle core biopsy	Mastectomy	Chemotherapy
7	ypT2N0M0	TNBC	MRI	Mastectomy	Chemotherapy
8	ypT1N0M0	HR+/HER2+	MRI	Mastectomy	Endocrine therapy
9	ypT1N1M0	TNBC	MRI	No	Chemotherapy
10	ypT1N1M0	HR+/HER2+	MRI	Breast-conserving surgery	No
11	ypT1N1M0	HR+/HER2+	MRI	Mastectomy	Endocrine therapy
12	ypTisN0M0	HR-/HER2+	Mammography	Mastectomy	Endocrine therapy
13	ypT1N0M0	HR-/HER2+	MRI	No	Chemotherapy
14	ypT1N0M0	HR+/HER2+	MRI	Mastectomy	Endocrine therapy
15	ypT1N1M0	HR+/HER2+	MRI	Mastectomy	Chemotherapy
16	ypT1N3M0	TNBC	MRI	Mastectomy	Chemotherapy
17	ypT2N0M0	TNBC	MRI	Mastectomy	Chemotherapy
18	ypTisN0M0	TNBC	MRI	Mastectomy	Chemotherapy
19	ypT1N1M0	TNBC	MRI	Mastectomy	Chemotherapy
20	ypT2N1M0	HR+/HER2+	MRI	Mastectomy	Chemotherapy

MRI, magnetic resonance imaging; IBTR, ipsilateral breast tumor recurrence; HR, estrogen receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Table S2 Pathologic complete response, ipsilateral breast tumor recurrence and locoregional recurrence events by constructed molecular subtype

Molecular subtype	HR+/HER2−, N=149	HR+/HER2+, N=58	HR−/HER2+, N=44	TNBC, N=70
pCR	16 (10.7%)	14 (24.1%)	29 (65.9%)	36 (51.4%)
IBTR	3 (2.0%)	7 (12.1%)	4 (9.1%)	6 (8.6%)
LRR	5 (3.4%)	7 (12.1%)	5 (11.4%)	6 (8.6%)

IBTR, ipsilateral breast tumor recurrence; pCR, pathologic complete response; HR, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TILs, tumor infiltrating lymphocytes.