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Effect of the Surgery Type, Mastectomy vs. Breast Conserving Surgery, on Outcomes of Patients With Locally Advanced Breast Cancer Receiving Neoadjuvant Therapy

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ABSTRACT

Background: Breast cancer is the most prevalent site-specific cancer and one of the most frequent causes of cancer death in women worldwide. Neoadjuvant chemotherapy, along with surgical treatment—breast conserving surgery (BCS) or mastectomy—is an important part of treatment for locally advanced breast cancer. As BCS is preferred to mastectomy in terms of cosmetic, quality-of-life, and functional outcomes, it would be the preferred treatment for locally advanced breast cancer (LABC), if its oncological safety is confirmed.

Methods: In this study, we retrospectively compared the oncologic outcomes of post-neoadjuvant chemotherapy BCS with mastectomy in 202 patients with LABC.

Results: There were no significant differences between BCS and mastectomy regarding overall survival, local recurrence, contralateral breast cancer, and distant metastasis.

Conclusions: Our study showed that post-neoadjuvant chemotherapy BCS is an oncologically safe surgical treatment in LABC and that BCS can be considered as an acceptable treatment in selected patients with LABC.

Introduction

Breast cancer is the most prevalent site-specific cancer among women. It is the first cause of cancer death among women in less developed regions (324,000 deaths, 14.3% of total), and the second in more developed regions (198,000 deaths, 15.4%).[1] Breast cancer is the leading type of cancer in Iranian females, accounting for 24.6% of all cancer cases, with average annual crude incidence rate of 22.6 per 100,000 (95% CI, 22.1–23.1).[2] It is reported to be the fifth cause of cancer death in Iranian females.[3]

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Stage of the disease is the most important prognostic factor in breast cancer. Patients at earlier stages of cancer have better survival than those at later stages.[4] Nowadays, in most parts of the world, breast cancer is frequently diagnosed at early stages,[1,2] although in some less developed countries diagnosis at later stages is common, probably due to poor access to medical care. The majority of breast cancer cases in Iran are diagnosed at early stages, and the prevalence of stage III (locally advanced breast cancer (LABC)) and metastatic breast cancers are reported to be 17% and 1.6%, respectively.[3]

Surgical treatment for breast cancer has changed over time from traditional Halsted radical mastectomy to less aggressive procedures like breast-conserving surgery (BCS). With the advent of different adjuvant modalities like chemotherapy and radiation therapy, limited surgical procedures with excellent local and distant control have become possible.

Nowadays, the standard treatment for LABC is mastectomy or BCS, followed by adjuvant/neoadjuvant chemotherapy and adjuvant radiation. Neoadjuvant chemotherapy (NAC) is an important part of LABC treatment; NAC not only makes more tumors operable in LABC, but also makes more patients eligible for BCS—patients who otherwise would not be BCS candidates according to their initial tumor size.

As BCS is preferred to mastectomy in terms of cosmetic, quality-of-life, and functional outcomes, it would be the preferred treatment for LABC, if its oncological safety is confirmed. Many studies have shown that, in terms of local recurrence rate, disease-free survival, and overall survival, BCS produces outcomes comparable to or even better than mastectomy in patients with LABC.[5-9] However, as some reports have shown unfavorable results, such as more local recurrence after BCS, there is still some controversy about its safety.[10, 11] Therefor, more investigation is required.

In this study, we compared the outcomes of post-NAC BCS with post-NAC mastectomy to assess the safety of less aggressive procedures in patients with LABC.

Methods

Data on all patients (n = 322) with LABC (stage III breast cancer according to the American Joint Committee on Cancer, 7th edition. 2010) who were admitted to Kaviani Breast Disease Institute (KBDI) in an 8-year period were evaluated retrospectively. Of them, 202 female patients who had undergone standard treatment for LABC, namely, neoadjuvant chemotherapy and surgery (mastectomy or BCS) followed by adjuvant radiotherapy (and adjuvant chemotherapy and hormone therapy as needed according to standard guidelines), were included in the study.

Data included age at diagnosis, number of neoadjuvant chemotherapy courses, histologic type (according to WHO classification), initial clinical tumor size, date of surgery, type of surgery (mastectomy vs BCS), pathologic tumor size after NAC, number of excised lymph nodes, number of involved lymph nodes, ratio of involved lymph nodes to total excised lymph nodes (LNR), hormone receptor status (ER, PR, and HER2, according to WHO classification), overall survival, disease-free survival, local recurrence, contralateral breast cancer, distant metastasis, and all-cause mortality.

Data were analyzed using R statistical software (version 3.3.3). Qualitative variables were analyzed using the chi-square test and the Fisher exact text, when appropriate. Survival analysis was preformed using the Kaplan-Meier method and log-rank test. The Cox proportional hazard test was used for multivariate analysis, as needed. P value was considered significant when it was less than 0.05.

Table 1. Summary of patients' demographics

		Mastectomy	BCS	P-value
N		161	41	
Age, mean (SD), y		50.53 (11.96)	43.52 (10.51)	0.004
No. of neoadjuvant chemotherapy, median [IQR]		6 (4–7)	6 (6–8)	0.164
Histological type				0.234
	IDC	136 (95.8)	31 (91.2)	
	ILC	4 (2.8)	3 (8.8)	
	other	2 (1.4)	0 (0.0)	
Tumor size after NAC, median [IQR]		25 (15–40)	20 (15–30)	0.066
No. of LN excised, median [IQR]		9 (6–12)	8.00 (5.25–11)	0.291
No. of LN involved, median [IQR]		2 (0–6)	1 (0–2.75)	0.013
ER (%)				0.394
	Positive	99 (69.7)	25 (78.1)	
	Negative	43 (30.3)	7 (21.9)	
PR (%)				0.326
	Positive	85 (59.9)	24 (70.6)	
	Negative	57 (40.1)	10 (29.4)	
HER2 (%)				0.839
	Positive	47 (33.3)	10 (29.4)	
	Negative	94 (66.7)	24 (70.6)	
Triple-negative (%)		21 (15.1)	2 (6.2)	0.255
Involved/excised LNR (%)				0.587
	< 0.25	31 (34.1)	8 (44.4)	
	0.25–0.65	29 (31.9)	6 (33.3)	
	> 0.65	31 (34.1)	4 (22.2)	
Status				0.253
	Alive	98 (73.1)	30 (85.7)	
	Deceased	5 (3.7)	2 (5.7)	
	Local recurrence	3 (2.2)	1 (2.9)	
	Contralateral recurrence	3 (2.2)	0 (0.0)	
	Distant metastasis	25 (18.7)	2 (5.7)	

Results

Data on 208 patients with LABC were evaluated. After excluding cases with missing data, 202 patients were analyzed, of whom 161 had undergone mastectomy, and 41 had undergone BCS after NAC.

The mean age at diagnosis was 50.53 and 43.52 years for the mastectomy and the BCS group, respectively (P = 0.004). The median number of chemotherapy courses for both groups was 6 cycles. The most prevalent histologic type in both groups was invasive ductal carcinoma (95.8% and 91.2% in the mastectomy and the BCS group, respectively). The median pathologic tumor size after NAC was 25 mm in the mastectomy group and 20 mm in the BCS group (P = 0.066). The median number of excised lymph nodes (LNs) were 9 and 8 in the mastectomy and the BCS group respectively (P = 0.291), and the median number of involved LNs were 2 and 1 in the mastectomy and the BCS group, respectively (P = 0.013).

The difference in LNR was not significant between the two treatment groups. Although more patients in the BCS group were hormone receptor–positive and HER2-negative than in the mastectomy group, no statistically significant difference was observed.

After a median follow-up of 556 days (range, 22–2622 days), there were 5 deaths, 3 local recurrences, 3 contralateral breast cancers, and 25 distant metastases in the mastectomy group; and in the BCS group there were 2 deaths, 1 local recurrence, no contralateral breast cancer, and 2 distant metastases. However, the difference between the two treatment groups on these events was not significant (P = 0.253) (Table 1).

The two groups did not differ significantly on both overall 1-year survival (P = 0.38) and 5-year survival (P = 0.99) (Tables 2 and 3). Five-year disease-free survival rate was 98% for the mastectomy group and 96.1% for the BCS group (P = 0.39) (Table 4).

Also, no significant difference was observed between the two groups in terms of recurrence (either local or contralateral) (P = 0.57) (Figures 1, 2, and 3). Mean and median survival times are presented in Tables 5 and 6.

Table 2. Breast cancer survival probability by type of surgery by Log-Rank test

Survival	Mastectomy	BCS	P-value
1-year	98.2%	100%	0.38
5-year	85.6%	96.6%	0.99

Table 3. Restricted mean survival time of breast cancer by type of surgery

Group	N	event	Restricted Mean Survival time (Days)	SE
Mastectomy	128	5	2028	58.5
BCS	30	1	1699	0

Table 4. One-year and five-year disease-free survival rates for the two groups

Disease-free survival	Mastectomy	BCS	P-value
1-year	100%	100%	NA
5-year	98%	96.1%	0.39

Table 5. Mean and median survival time (in days) for all patients

		Mean[a]				Median	
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Lower Bound
1701.587	133.615	1439.701	1963.473	1729.000	183.291	1369.749	1369.749

a. Estimation is limited to the largest survival time if it is censored.

Table 6. Mean and median disease-free survival time (in days) for all patients

		Mean[a]				Median	
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Lower Bound
2217.446	110.616	2000.638	2434.254	.	.	.	.

a. Estimation is limited to the largest survival time if it is censored.

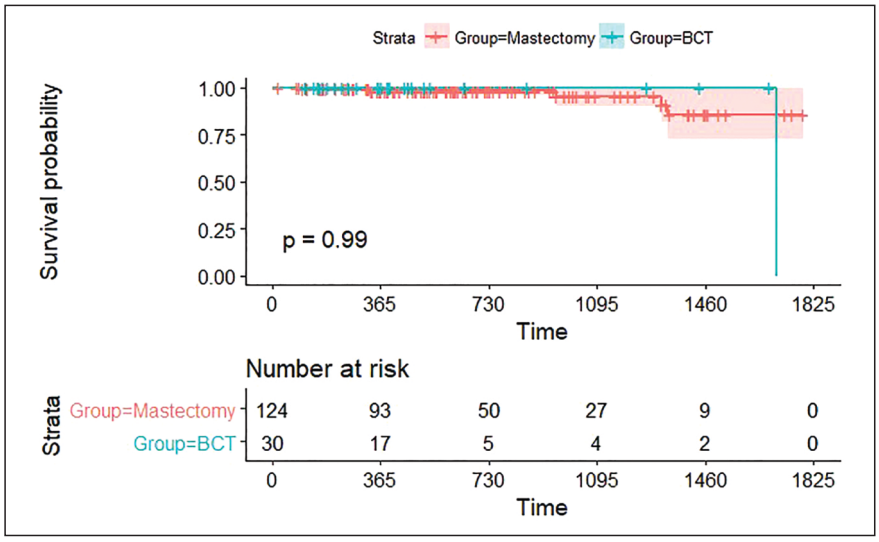

Figure 1. Probability of breast cancer overall survival by type of surgery

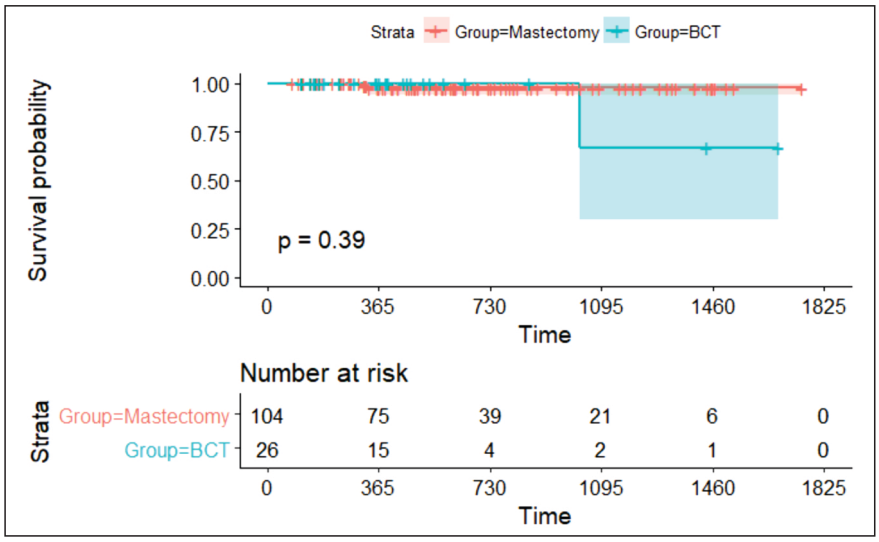

Figure 2. Probability of breast cancer disease-free survival by type of surgery

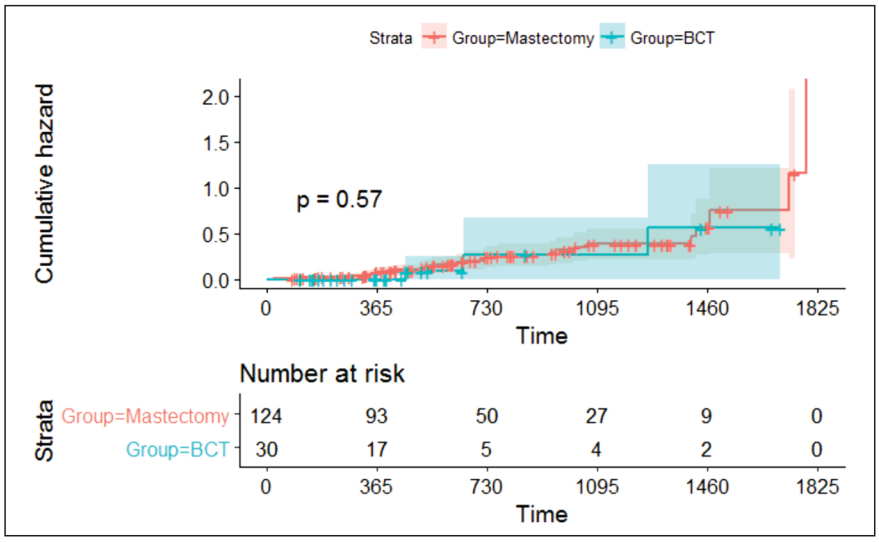

Figure 3. Cumulative hazard of breast cancer recurrence by type of surgery

No significant difference was observed in overall survival between patients with ER+ and ER- tumors (P = 0.35), but the difference in survival between PR+ and PR- patients was significant (P = 0.012), with PR+ patients having better survival (Figure 4). There was also no significant difference in overall survival between HER2- and HER2+ patients (P = 0.17). The difference in overall survival after adjusting for histologic types was also not significant (P = 0.89). The survival in patients with LNR > 0.65 was significantly lower than in patients with LNR < 0.65 (P = 0.045) (Figure 5).

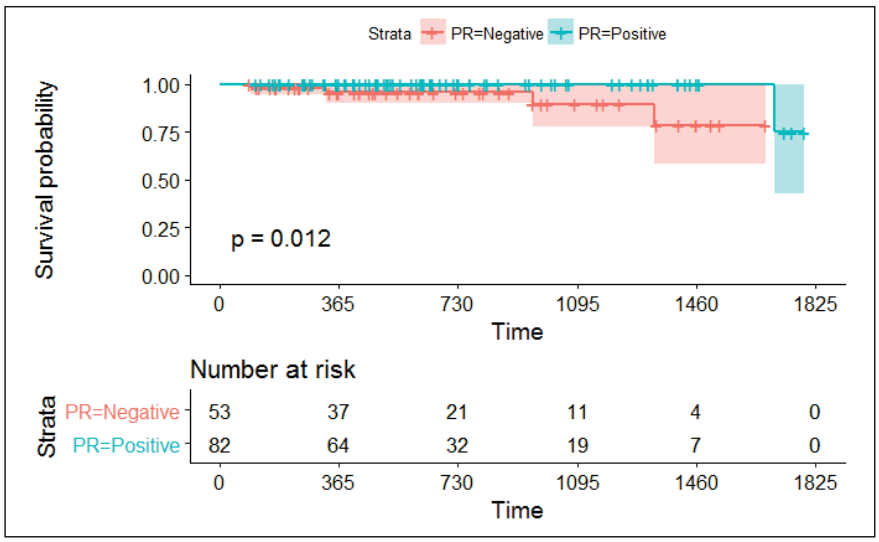

Figure 4. Probability of breast cancer survival by PR receptor status

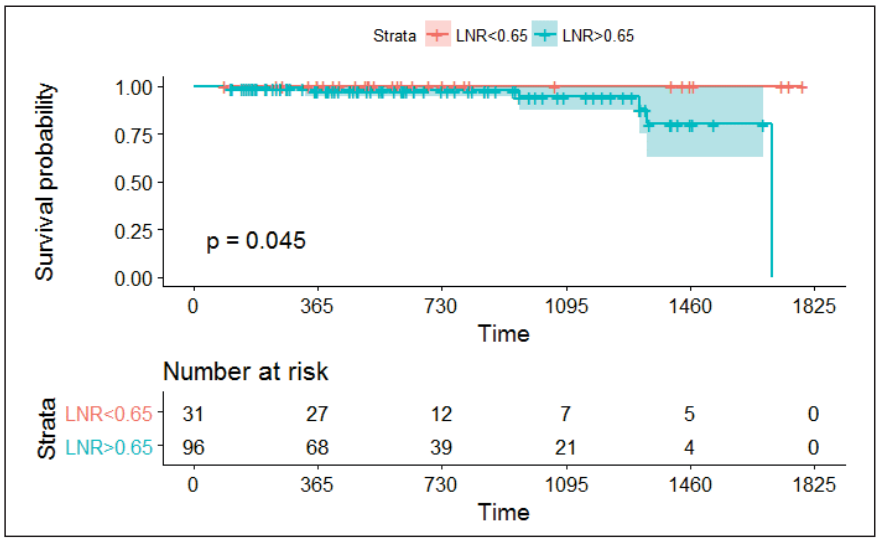

Figure 5. Probability of breast cancer survival by LNR

Discussion

This study showed that, in patients with LABC who had received NAC, there is no significant difference between BCS and mastectomy in terms of overall survival, local recurrence (one of the main concerns when substituting BCS for mastectomy), contralateral breast cancer, and distant metastasis.

These findings have been confirmed by other reports. In two studies on 284 and 147 patients, 10 years of follow-up did not reveal any significant difference in local recurrence and overall survival between those undergoing BCS and mastectomy after NAC.[5,6] In another study by Barranger *et al*. on 119 patients who initially were mastectomy candidates, 5-year overall survival after BCS or mastectomy was 77%, and 5-year disease-free survival rates after BCS and mastectomy were 74% and 59%, respectively (not statistically significant). They concluded that, in patients with chemosensitive breast tumor, NAC results in a significant "mastectomy to BCS" conversion rate and that the type of surgery does not appear to affect the patient's overall and disease-free survival rates.[7] Chen and colleagues studied the patterns of local-regional recurrence (LRR) and ipsilateral breast tumor recurrence (IBTR) among 340 breast cancer cases treated with breast conservation therapy following neoadjuvant chemotherapy. After a median follow-

up of 60 months, 5-year LRR-free and IBTR-free survival rates were calculated to be 91% and 95%, respectively.

They concluded that breast-conserving therapy following neoadjuvant chemotherapy would lead to reduced rates of LRR and IBTR in appropriately selected patients, even those with T3 or T4 disease.[8] Finally, Zhou and associates reviewed 8 trials with a total number of 3215 patients, and reported a 9.2% prevalence of local recurrence in the BCS group versus 8.3% in the mastectomy group (P = 0.66). They also found a non-significantly lower rate of 5-year local recurrence–free survival (LRFS) in the mastectomy group versus the BCS group (P = 0.74). They concluded that BCS after NCT is safe in terms of local recurrence and LRFS in LABC.[9]

Although most reports confirm excellent overall survival in patients with LABC treated with NAC and BCS, some studies mention higher rates of local recurrence after BCS. This poses a real concern as it has been proposed that local recurrence can have a detrimental effect on overall survival. In the study by Mauriac *et al*. on 134 women with T2 (> 3 cm) or T3N0–1M0 breast tumors, the majority of patients had undergone BCS at the end of neoadjuvant chemotherapy, with no significant difference in survival when compared with the mastectomy group. They considered post-NAC BCS as the new gold-standard treatment for patients with tumors too large to be treated immediately by conserving surgery. However, they deemed it necessary to inform the patient of the risk of local recurrence in breast-conserving therapy.[10] In another study by Rouzier *et al*., the incidence and the prognostic value of IBTR were evaluated in 257 patients treated with primary chemotherapy and BCS and radiotherapy. At a median follow-up of 93 months, they reported relatively high rates of local recurrence: 16% (± 2.4%) at 5 years and 21.5% (± 3.2%) at 10 years.[11] However, the higher rates of local recurrences in these studies may be explained by the use of different chemotherapeutic agents (epirubicin, vincristine, MTX, etc.) or adoption of non-precise criteria to make decision for a conserving surgical treatment (BCS was performed if the residual tumor, taking into account the breast size, could be removed with clear margins).[10,11]

This study suffers from some shortcomings. It was non-randomized and retrospective, making it difficult to draw a definite conclusion about post-NAC BCS outcomes. The relatively small number of patients, especially in the BCS group, is another weakness of this study. Relatively short follow-up of patients is another drawback of our study, as a remarkable number of recurrences in BCS patients occur after 2 years of treatment; therefor, longer follow-ups would be better. Although our results about the oncologic safety of post-NAC BCS are in concordance with most previous studies, prospective randomized trials with larger sample sizes and long-term follow-up will help draw a definitive conclusion.

According to the results of our study, post-NAC BCS is an oncologically safe surgical treatment for eligible patients with LABC. This kind of surgical management has potentially more favorable functional and cosmetic outcomes, which is especially important to younger patients. BCS can be considered an acceptable treatment in selected patients with LABC, and having an initially advanced stage of cancer in itself should not prevent the patient or the surgeon from pursuing BCS.

Conflict of Interest

There is no conflict of interests in this study.

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