RESEARCH ARTICLE

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Locally Advanced Breast Cancer After Neoadjuvant Chemotherapy: Our Clinical Experience

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Objective: The most important prognostic factor in breast cancer is the stage of the disease. Although excellent overall survival rates have been reported with breast breast-conserving therapy (BCT) after neoadjuvant chemotherapy (NAC) in patients with locally advanced breast cancer (LABC), some studies have shown increased local recurrence rates after this therapy. In this study, we aimed to compare the local recurrence, distant metastasis and overall survival rates of patients with LABC who underwent mastectomy and BCT after NAC.

Materials and Methods: This study was conducted to retrospectively examine the oncological results of mastectomy and BCT procedures performed in 31 patients who had received NAC due to LABC in our hospital between July 2017 and December 2021.

Results: No significant difference was found in terms of local recurrence (%5.6 vs. %7.7), distant metastasis (%22.2 vs. %7.7), and overall survival (%94.4 ve %100) in patients who underwent mastectomy and BCT (respectively P=1.00, P=0.368, P=1.00).

Conclusion: This study shows that BCT after NAC is an oncologically safe surgical option in patients with LABC, and it is an alternative surgical procedure to mastectomy in selected patient groups.

Key Words: *Locally advanced breast cancer, breast-conserving surgery, neoadjuvant chemotherapy, mastectomy*

Neoadjuvan Kemoterapi Sonrasi Lokal Ileri Meme Kanseri: Klinik Deneyimimiz

Amaç: Meme kanserinde en önemli prognostik faktör hastalığın evresidir. Lokal ileri meme kanseri (LABC) olan hastalarda neoadjuvan kemoterapi (NAC) sonrası yapılan meme koruyucu cerrahi (BCT) tedavi ile mükemmel genel sağkalım oranları bildirilmiş olsa da bazı çalışmalarda BCT sonrası artmış lokal rekürrens oranları gösterilmiştir. Bu çalışmada LABC' li hastaların NAC sonrası mastektomi ve BCT yapılan hastalarda lokal rekürrens, uzak metastaz ve genel sağkalım oranlarını karşılaştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmada Temmuz 2017 ile Aralık 2021 tarihleri arasında hastanemizde LABC nedeniyle NAC alan 31 hastaya yapılan Mastektomi ve BCT prosedürlerinin onkolojik sonuçlar retrospektif olarak incelendi.

Bulgular: Mastektomi ve BCT yapılan hastalarda lokal rekürrens (%5.6 ve %7.7), uzak metastaz (%22.2 ve %7.7) ve genel sağkalım (%94.4 ve %100) açısından anlamlı farklılık saptanmadı (sırasıyla P=1.00, P=0.368, P=1.00).

Sonuç: Bu çalışmada sonuç olarak; LABC'li hastalarda NAC sonrası BCT'nin onkolojik olarak güvenli bir cerrahi seçenek olduğunu ve seçilmiş hasta grubunda Mastektomiye alternatif, tercih edilebilecek bir cerrahi prosedür olarak kabul edilebileceği gösterilmiştir.

Anahtar Kelimeler: *Lokal ileri meme kanseri, meme koruyucu cerrahi, neoadjuvan kemoterapi, mastektomi*

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Introduction

It is estimated that every year, 2.1 million people are diagnosed with breast cancer across the world, and it is the most common cancer among women (1). In recent years, the incidence of breast cancer has been increasing. Although advances in the diagnosis and treatment of breast cancer in the last few decades have reduced mortality rates, it still remains an important cause of cancer-related death (2).

The most important prognostic factor in breast cancer is the stage of the disease. Patients with early-stage breast cancer have better survival than those at the advanced stage of the disease (3). Today, the majority of breast cancer cases are detected at an early stage in developed countries, but the diagnosis is still delayed until the advanced stage in most developing countries (4). Also, survival rates are lower in developing countries due to the lack of oncological infrastructure and cost-effective treatment modalities (5). Surgery constitutes the main step in the treatment of breast cancer. In recent years, new treatment approaches have emerged with a better understanding of tumor biology and the development of individual treatment options. As a result, surgical treatment has transformed from radical mastectomy to breast -conserving therapy (BCT). It has been proven that the addition of radiotherapy to BCT provides similar treatment results to modified radical mastectomy in the early stages of the disease (6).

Although BCT is widely used in patients with early-stage breast cancer, the application of BCT in those with locally advanced breast cancer (LABC) remains a controversial issue. Patients with LABC should be treated with combined treatment options, including chemotherapy, hormonal therapy, surgery, and radiotherapy, with the adoption of a multidisciplinary approach involving medical, surgical and radiation oncologists (7, 8).

Generally, breast cancers of >5 cm, those invading the skin or pectoral muscle, those infiltrating axillary, supraclavicular or infraclavicular lymph nodes, and those of inflammatory nature are defined as LABC (9). Studies show that 4% of patients with breast cancer in Europe and 8.5% in America have LABC. However, in countries with low socioeconomic status, the rate of LABC among breast cancer cases can reach 60% (8).

Today, neoadjuvant chemotherapy (NAC) is accepted as the standard treatment in patients with LABC to reduce the size and stage of the tumor, increase surgical treatment options, especially the possibility of conversion from mastectomy to BCT, and make inoperable breast cancer operable. In addition, NAC can improve the long-term prognosis in patients with pathologically complete response (10-12).

In this study, we aimed to evaluate early surgical results after NAC in patients with inoperable LABC.

Materials and Methods

Research and Publication Ethics: Ethical approval for this study was obtained from the Non-Invasive Clinical Research Ethics Committee of Adiyaman University (approval date: 23.06.2020, number: 2020/6-27).

This study was retrospectively designed with 31 patients with LABC that had received NAC among 136 cases of breast cancer treated in the surgical oncology clinic of our hospital between July 2017 and December 2021. Patients with early-stage breast cancer or distant metastases, with secondary malignancies, those that underwent palliative breast surgery, and patients with some missing data were excluded from the study. In addition to mammography and breast ultrasonography, the patients were evaluated with contrast-enhanced thoraco-abdominopelvic computed tomography or positron emission tomography (PET)-CT for distant metastasis screening after the diagnosis of breast cancer. In addition, complete blood count analysis, routine biochemical tests, hepatitis serological marker analysis, and CA-15-3 and CEA level measurements were undertaken. Patients with LABC without distant metastases had been evaluated with the magnetic resonance imaging of the breast before NAC. Surgical treatment was applied to the patients at three weeks after NAC treatment. All surgical procedures were performed with the patients under general anesthesia. In patients suitable for BCT, surgical borders were marked and sent to frozen section laboratory for a pathological analysis after lumpectomy. Tumor-negative surgical margins were considered sufficient for lumpectomy, and metallic clips were placed in the lumpectomy site. In patients with suspected surgical margins, re-excision was performed if appropriate and mastectomy otherwise. Mastectomy was performed in patients who were not suitable for BCT. Routine level 2 axillary dissection was applied to the axillary region. Drains were placed in the axilla and mastectomy sites in patients who underwent mastectomy, while a drain was placed only in the axilla in those who underwent BCT. Radiotherapy for the breast was added to the adjuvant treatment of patients undergoing BCT.

Patients' age at the time of diagnosis, histological type of breast cancer (WHO classification), date of surgery, type of breast surgery (mastectomy or BCT), hormone receptor status (ER, PR and HER2 according to the WHO classification), the total number of lymph nodes dissected, number of metastatic lymph nodes, local recurrence, distant metastasis, overall survival, and all-cause mortality were evaluated.

Follow-up: The patients were followed up every month after surgery with complete blood count, routine biochemistry, CA 15-3 and CEA analyses, breast and abdominal ultrasonography, and chest radiography. Besides, a mammogram was taken annually. Breast MRI, tomography, and PET-CT were used when necessary.

Statistical Analysis: Data analysis was performed using SPSS version 25.0 (Chicago, IL, USA). While categorical data were expressed as percentages, numerical data were given as mean values. When categorical variables were appropriate, Fisher's exact and chi-square tests were used, and numerical data were compared with the independent-samples t-test. Survival analysis was performed using the Kaplan-Meier survival charts and log-rank test. $P<0.05$ was considered statistically significant.

Results

All of the patients were female. The median age was 44 (range 27-73) years. Mastectomy was performed in 18 (58.0%) patients and BCT in 13 (42.0%). The demographic characteristics of the patients are presented in Table 1. The median follow-up duration of all patients was 18.63 (range 3-42) months. Twelve (38.7%) of the patients had right breast cancer, 18 (58.0%) had left breast cancer, and one (3.2%) had bilateral breast cancer.

Local recurrence developed in two patients; one at the 12th month after who underwent mastectomy (5.5%) and the other at the 15th month after BCT (7.6%). There was no statistical significance between the two surgery groups in terms of local recurrence according to the Kaplan Meier survival chart (log rank; P=0.70) (Figure1).

Table 1. Clinical pathological characteristics of patients

		n	Mastectomy (n=18)	BCT (n=13)	P Value
Age			46.28 ± 14.02	43.85 ± 10.13	-
Tumor type	IDC	25 (80.6)	12 (66.7)	13 (100.0)	-
	ILC	3 (9.6)	3 (16.7)	-	
	Other	3 (9.6)	3 (16.7)	-	
ER receptor	negative	7 (22.6)	6 (33.3)	1 (7.7)	-
	positive	24 (77.4)	12 (66.7)	12 (92.3)	
PR receptor	negative	14 (45.2)	10 (55.6)	4 (30.8)	-
	positive	17 (54.8)	8 (44.4)	9 (69.2)	
HER2 receptor	negative	20 (64.5)	10 (55.6)	10 (76.9)	-
	positive	11 (35.5)	8 (44.4)	3 (23.1)	
Triple-negative		2 (11.1)	2 (11.1)	-	
Dissected LN		14.52±5.34	15.59±5.30	13.23±5.51	-
Involved LN		4.90±5.61	6.53±6.15	2.1±3.28	-
Local recurrence	Yes	2 (6.5)	1 (5.6)	1 (7.7)	-
	No	29 (93.5)	17 (94.4)	12 (92.3)	
Distant metastasis	Yes	5 (16.1)	4 (22.2)	1 (7.7)	-
	No	26 (83.9)	14 (77.8)	12 (92.3)	
Outcome	Alive	30 (96.8)	17 (94.4)	13 (100.0)	-
	Deceased	1 (3.2)	1 (5.6)	-	

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, LN: Lymph node, BCT: Breast-conserving therapy

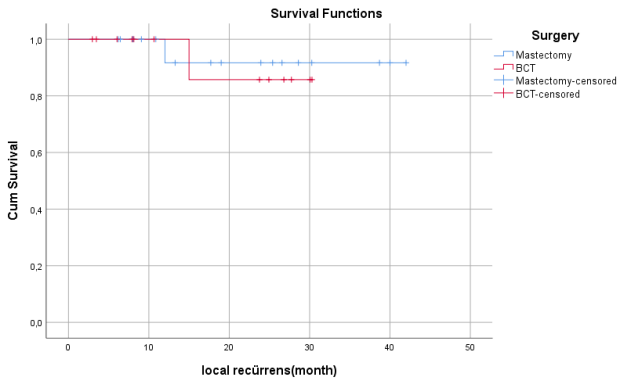

Figure 1. Kaplan-Meier survival analysis graph for local recurrence in patients who underwent mastectomy and BCT (log-rank, P=0.750). BCT: Breast-conserving therapy.

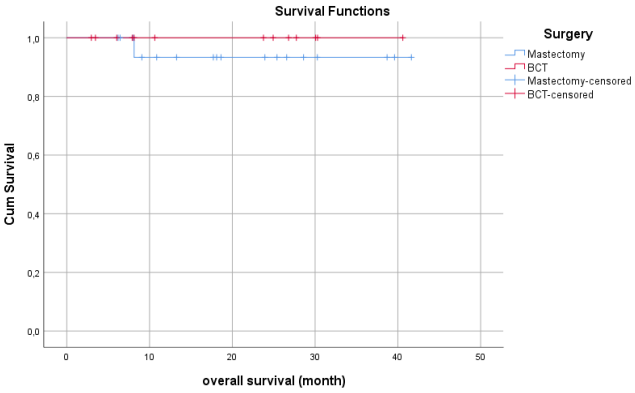

Figure 3. Kaplan-Meier survival analysis graph for overall survival in patients who underwent mastectomy and BCT (log-rank, P=0.439). BCT: Breast-conserving therapy.

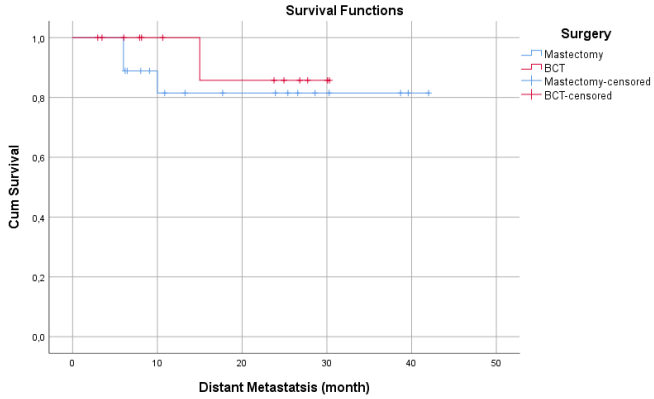

Figure 2. Kaplan-Meier survival analysis graph for distant metastasis in patients who underwent mastectomy and BCT (log-rank, P=0.539). BCT: Breast-conserving therapy.

Although distant metastasis was detected in four (22.2%) patients who underwent mastectomy and one (7.6%) patient who underwent BCT, no significant difference was found in the survival analysis graphs (P=0.539) (Figure 2).

One patient (5.5%) in the mastectomy group died due to brain metastasis at the postoperative eighth month. In the analysis of total survival, no statistical difference was found between the two surgery groups (P=0.439) (Figure 3).

Discussion

BCT is a sensible and attractive option for early-stage breast cancer cases. With the development of chemotherapy regimens, it has become possible to perform BCT after NAC in patients with LABC (13, 14). Surgery and adjuvant radiotherapy in addition to NAC

have resulted in significant local recurrence and overall survival (15). In recent publications, it is stated that BCT is an oncologically safe surgical option in patients with LABC after NAC (3, 16).

In a study conducted to evaluate BCT rates after NAC in 119 cases in which mastectomy was initially the only surgical option, the median age of the patients was 49.6 years (range 26.9-75.9) (17). In another study, da Costa Viera et al. (18) evaluated 78 patients with LABC in terms of surgical results after NAC. The mean age of the patients was 48.8 (range 21.3-75.1) years. The median age of the patients in our study was 44 (range 27-73) years.

In a study by Barranger et al. (17), BCT was performed in 86 (72.3%) of 119 patients. The authors reported that with the use of NAC, there was a significant conversion from mastectomy to BCT among chemosensitive breast cancer cases, and the type of surgery had no effect on local recurrence and survival. Similarly, in our study, we observed that the type of breast surgery (BCT or mastectomy) performed after NAC in patients with LABC did not affect local recurrence, distant metastasis, and overall survival in the survival analysis.

Zhou et al. (19) evaluated eight studies including a total of 3,215 patients with LABC that had undergone NAC and reported the rate of local recurrence as 9.2% in the BCT group and 8.3% in the mastectomy group, indicating no statistically significant difference. In the current study, we observed local recurrence in one patient in both groups, but this did not result in a statistically significant difference between the two surgery groups.

Mauriac et al. (20) performed surgery on 134 patients with LABC after NAC and did not find a significant difference in survival between those who underwent BCT and mastectomy. They argued that in patients with tumors that are initially too large for BCT, NAC followed by BCT could be a gold standard surgical treatment option. They also emphasized that patients should be informed about the possibility of local recurrence. In our study, 48% of the patients underwent BCT, and we did not find any difference in survival between the BCT and mastectomy groups.

Recently, Sisi et al. conducted a prospective study to make patients with LABC suitable for BCT with the use of NAC and to evaluate oncological outcomes (21). BCT was performed on 50 female patients, and no local recurrence was detected during the one-year follow-up. The authors reported that traditional NAC was effective in reducing tumor size and metastatic axillary lymph nodes in patients with LABC, and BCT after NAC was safe in terms of preventing local recurrence.

Similarly, in our study, no local recurrence was observed in the one-year follow-up in the BCT group. However, local recurrence developed in one patient at the 15th month after surgery.

Mashoori et al. (3) conducted a retrospective study to evaluate the oncological results of BCT and mastectomy in 202 patients with LABC who had undergone NAC. They found no significant difference in terms of local recurrence, distant metastasis, and overall survival between patients who underwent BCT and mastectomy. They reported that BCT after NAC was an oncologically safe option in selected patients. Consistently, in our study, no statistically significant difference was found between the patients who underwent BCT and mastectomy in relation to local recurrence, distant metastasis, and overall survival.

The limitations of our study are its retrospective nature, a small number of patients, short follow-up period, and single-center design. Although the oncological data of BCT after NAC in patients with LABC were similar to previous studies, there is a need for prospective studies with a large number of patients and long-term follow-up to make more reliable inferences.

In conclusion, BCT is a surgical treatment that can be safely performed oncologically in selected patients with LABC after NAC. Surgeons can safely perform BCT after NAC in patients who are planned to undergo mastectomy due to the large tumor size.

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