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Lobüler Meme Kanserinde Meme Koruyucu Ameliyatlarla Total Mastektomi Ameliyatları Arasındaki Nüks ve Yaşam Oranlarının Karşılaştırılması

Comparison of Recurrence and Survival Rates Between Breast-Conserving Surgery and Mastectomy in Lobular Breast Cancer

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ÖZ

Giriş: İnvaziv lobuler karsinomlar, kendine özgü patogenez, klinik biyoloji ve büyüme paterni olan kanser türüdür. Bu çalışma ile invaziv lobüler karsinomlarda meme koruyucu ameliyatlarla total mastektomi ameliyatları arasında sağ kalım oranlarını karşılaştırmayı ve MKC'nin güvenirliğini araştırmayı amaçladık.

Yöntem: Ocak 2003-Ekim 2012 tarihleri arasında memenin invaziv lobüler karsinomu nedeniyle ameliyat edilen hastaların verileri retrospektif olarak incelendi. Hastalar iki gruba ayırıldı: MKC ve total mastektomi grupları. Her iki grup arasında hastalıskız sağ kalım ve genel sağ kalım oranları değerlendirildi.

Bulgular: Çalışmaya dahil edilen 112 hastanın 79'una (%70,5) total mastektomi ve 33'üne (%29,5) MKC uygulandı. MKC grubundaki yaş ortalaması 53,42±8,66 yıl, Mastektomi grubundaki hastaların yaş ortalaması 55,23±12,19 yıl idi (p: 0,002). Lenfovasküler invazyonun hastalıksız sağ kalımı ve Kİ-67'nin genel sağ kalımı kötü yönde etkilediği görüldü (sırası ile p: 0,018 ve p: 0,014). Her iki grup arasında hastalıksız sağ kalım ve genel sağ kalım açısından anlamlı fark bulunmadı.

Sonuç: İLK'lı hastalara temiz cerrahi sınırlar sağlanma ve adjuvant radyoterapi verme şartı ile meme koruyucu cerrahinin güvenle uygulanabileceği kanaatindeyiz.

Anahtar Kelimeler: invaziv lobüler meme kanseri, meme koruyucu cerrahi, total mastektomi

ABSTRACT

Objective: Invasive lobular carcinoma of the breast is a type of cancer with specific pathogenesis, clinical biology and growth pattern. In this study, we aimed to compare the survival rates between breast conserving surgeries (BCS) and mastectomy in invasive lobular carcinomas and to investigate the reliability of BCS.

Method: Data of patients who underwent breast surgery for invasive lobular carcinoma between January 2003 and October 2012 were analyzed retrospectively. The patients were divided into two groups: BCS and mastectomy. Disease-free survival and overall survival rates were compared.

Results: 112 patients were included in the study. Total mastectomy was performed in 79 (70.5%) and BCS in 33 (29.5%). The mean age of the patients in the BCS group was 53.42±8.66 years and 55.23±12.19 in the mastectomy group (p: 0.002). Lymphovascular invasion was detected as a poor prognostic factor for disease-free survival and Ki-67 for overall survival. (p: 0.018 and p: 0.014, respectively). No statistically significant difference was detected between the groups in disease-free and overall survival.

Conclusion: We suggest that breast conserving surgery with negative surgical margins and adjuvant radiotherapy can be safely performed in patients with invasive lobular cancer.

Keywords: invasive lobular breast cancer, breast-conserving surgery, total mastectomy

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INTRODUCTION

Invasive lobular carcinoma (ILC) is the second common type of breast cancer with a unique pathogenesis and specific clinical biology. 10-15% of invasive breast tumors are lobular cancer. Molecular features of ILCs include E-cadherin mutation, predominantly estrogen receptor positivity and HER2 negativity. The recurrence and metastasis rates are high. It is difficult to diagnose because ILCs tend to be insidious and infiltrative (1-3). Radiological evaluation of ILCs is more difficult than invasive ductal carcinomas. Standard imaging methods, such as mammography and breast ultrasonography, are used to define ILC. Magnetic resonance imaging (MRI) may also be beneficial (3-5). ILC are diagnosed at a later stage than invasive ductal carcinoma (IDC). Despite this, relapse-free survival in ILC patients is higher than in IDC patients with the same tumor and lymph node stage (6).

Advanced tumor stage, presence of lobular carcinoma, multifocality and multicentricity are still among the reasons why surgeons prefer total mastectomy (7). However, when patient selection is made correctly and carefully, there is no difference in oncological safety between breast conserving surgery (BCS) and total mastectomy. (7-10). Patients with invasive lobular carcinoma undergoing BCS and adjuvant radiotherapy (RT) have similar oncological outcomes in patients with IDC. BCS has been reported as a safe suitable surgical option, especially in patients with stage I and II invasive lobular breast cancer (11). Although publications on the safety of BCS have increased recently, especially in ILC with large tumor size, total mastectomy is still a more common surgical method for these patients (10,12,13).

In this study, we aimed to examine the recurrence and survival rates among ILC patients who had breast conserving surgery and total mastectomy.

MATERIALS AND METHODS

Patients operated on for invasive lobular carcinoma between January 2003 and October 2012 in the Department of General Surgery of the Ege University Medical Faculty Hospital were included in the study. Approval for the study was received from the University's Ethics Committee. Cases were collected sequentially. The patients were divided into two main groups as BCS and total mastectomy. In order for the data to be used in scientific studies, the consents obtained from the patients were available in their files. The patients data were recorded in a database and analyzed retrospectively.

Patients younger than 18 years of age, with distant metastases at the time of diagnosis, with a previous history of breast cancer, did not receive or complete adjuvant treatment, whose data were missing and could not be followed up were excluded from the study.

Breast ultrasonography, mammography and, if necessary, breast MRI were used as preoperative radiological examinations. Breast and abdominal ultrasonography, mammography, chest X-ray and bone scintigraphy were routinely used in the postoperative follow-up. The patients were followed up in the Breast Surgery outpatient clinic.The decision for BCS or total mastectomy and the adjuvant treatment were made by the multidisciplinary breast cancer council. Breast conserving surgery consisted of excision of the primary tumor with approximately 1 cm of intact surrounding breast tissue. The determination of excision margins was based on obtaining radiologically and pathologically negative surgical margins. Specimens of patients with partial mastectomy were sent to radiology from the operating room. Sentinel lymph node biopsy (SLNB) was performed on clinically negative axillary lymph nodes. Axillary lymph node dissection was performed on clinically positive or SLNB positive lymph nodes. Adjuvant radiotherapy was applied to all patients with BCS.

Demographic data, pathology results, prognostic factors were examined. Prognostic factors were recorded: 1) tumor stage, 2) axillary lymph node involvement, 3) tumor diameter, 4) tumor grade, 5) lymphovascular invasion, 6) steroid receptors (estrogen, progesterone), 7) Cerb-B2, 8) p53, 9) Ki-67. Disease-free survival and overall survival between groups were examined. Recurrence and mortality rates were analyzed between both groups. The effect of prognostic factors on recurrence and mortality in both groups was examined.

Primary evaluation criteria were recurrence and disease-free survival. Recurrence was considered as any local, regional, or distant tumor recurrence. Disease-free survival was defined as the time interval between the date of first diagnosis and the date of first recurrence or last follow-up or death, whichever occurs first. Overall survival was defined as the time interval between the date of first diagnosis and the date of last follow-up or death (developing from breast cancer or any other cause).

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used for statistical analysis. Chi-square test and Fisher's Exact Chi-Square test for comparison of qualitative data as well as descriptive statistical methods (Mean, Standard deviation); The significance test of the difference between the two percentages was used. Kaplan Meier test and Log Rank test were used for survival assessment. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$.

RESULTS

The mean age of 112 patients was 54.7±11.26 (35-82) years. The mean follow-up period was 64.58±35.74 (4-132) months. There were 79 patients (70.5%) in the total mastectomy group, and 33 patients (29.5%) in the BCS group. The mean age in the BCS group (53.42±8.66 years) was found to be lower than the total mastectomy group (55.23±12.19 years) and the difference was statistically significant (p:0.002). The mean age of first menstruation was 13.29±1.27 years in all cases. The age at first menstruation was 13.35 years in the total mastectomy group and 13.15 years in the BCS group. The mean age of menopause in 66 menopausal patients was 48.29±5.74 years (48.02 years in the total mastectomy group and 48.95 years in the BCS group). There was no statistically significant difference between the two groups in terms of age at first menstruation and menopause ($p>0.05$). 94 (83.9%) patients were treated with adjuvant chemotherapy (KT) and 101 (90.2%) with hormonotherapy (HT). Adjuvant radiotherapy (RT) was administered to 72 (64.3%) patients.

In both groups 28 (25%) patients had multifocal and/or multicentric tumors. Only 4 patients (12.12%) in the BCS group had multifocal (non-multicentric) tumors. Tumor characteristics of the patients are shown in Table 1.

The mean tumor diameter is 2.9 cm (0.4-11 cm). The largest tumor

diameter was 3.26 cm on average in the total mastectomy group and 2.05 cm in the BCS group. The difference between the two groups was statistically significant (p:0.002).

In both groups, mean number of dissected axillary lymph nodes (LN) was 16.79 (1-48). The number of LNs dissected in the BCS group (mean 13.21 LN) was less than the total mastectomy group (mean 18.28 LN) (p:0.001).

Table 1.Pathological Features of Tumors in Both Groups.

		Surgery type		Total
		Mastectomy	BCS (breast conservative surgery)	
T1		13 (%16,5)	14 (%42,4)	27 (%24,1)
T2		51 (%64,6)	18 (%54,5)	69 (%61,6)
T3		10 (%12,7)	0 (%0)	10 (%8,9)
T4		5 (%6,3)	1 (%3)	6 (%5,4)
Estrogen receptor	Pozitive	68 (%86,1)	29 (%87,9)	97 (%86,6)
	Negative	11 (%13,9)	4 (%12,1)	15 (%13,4)
Progesterone receptor	Pozitive	61 (%77,2)	25 (%75,8)	86 (%76,8)
	Negative	18 (%22,8)	8 (24,2)	26 (%23,2)
p53	Pozitive	33 (%41,8)	14 (%42,4)	47 (%42)
	Negative	46 (%58,2)	19 (%57,6)	65 (%58)
C-erb B2	Pozitive	15 (%19)	5 (%15,2)	20 (%17,9)
	Negative	64 (%81)	28 (%84,8)	92 (%82,1)
Lymphovascular invasion	Yes	14 (%18,2)	4 (%12,5)	18 (%16,5)
	No	63 (%81,8)	28 (%87,5)	91 (%83,5)
Multifocality	Yes	24 (%30,3)	4 (%12,12)	28 (%25)
	No	55 (%69,6)	29 (%87,87)	84 (%75)
MSBRHG	1	12 (%35,3)	7 (%38,9)	
	2	22 (%64,7)	9 (%50)	
	3	0 (%0)	2 (%11,1)	
NG	1	12 (%31,6)	9 (%47,4)	
	2	24 (%63,2)	9 (%47,4)	
	3	2 (%5,3)	1 (%5,3)	
HG	1	4 (%10,5)	5 (%15,8)	
	2	2 (%5,3)	2 (%10,5)	
	3	32 (%84,2)	12 (63,2)	

MSBRHG-Modified Scarff-Bloom-Richardson Histologic Grading, NG-Nuclear Grade, HG-Histological Grade

Lymph node metastasis (LNM) was detected in 50% of all patients. 44 (55.7%) patients in the total mastectomy group and 12 (36.4%) patients in the BCS group had LNM and it was not statistically significant (p>0.05). The mean number of metastatic lymph nodes (MLN) in all patients was 3.74 (0-34) and 4.09 in the total mastectomy group, 2.91 in the BCS group patients respectively (p>0.05).

According to lymph node status, 56 (50%) patients were graded as N0, 29 (25.9%) as N1, and 27 (24.1%) as N2+N3. Since the number of N3 patients was only two in total, they were evaluated together with the N2 group. Both patients with N3 were in the total mastectomy group. According to breast cancer stage, 19 (17%) patients were Stage 1, 42 (37.5%) Stage 2A, 20 (17.9%) Stage 2B, and 31 (27.7%). Stage 3A+B (table 2).

Table 2. Distrubition of LN and Cancer Stage in Both Groups

		Mastectomy n (%)	BCS n (%)
N	0	35 (%44,3)	21 (%63,6)
	1	23 (%29,1)	6 (%18,2)
	2+3	21 (%26,6)	6 (%18,2)
Stage	1	8 (%10,1)	11 (%33,3)
	2A	29 (%36,7)	13 (%39,4)
	2B	17 (%21,5)	3 (%9,1)
	3A+B	25 (%31,6)	6 (%18,2)

Disease Free Survival

Patients who subsequently developed metastases and had cancer recurrence were combined. In both groups metastasis or recurrence was detected in 17 patients (15.2%). The rate of metastasis or recurrence was 6.1% in the BCS group and 19% in the total mastectomy group. There was no statistically significant difference between the two groups according to disease free survival (p>0.05) (Figure 1).

During the follow-up, the mortality rate was 7.1% (8 patients). The mortality rate was 7.6% (6 patients) in the total mastectomy group and 6.1% (2 patients) in the BCS group. The difference in overall survival between the two groups was not statistically significant (p>0.05) (Figure 1).

According to the relation between disease free survival and progesterone receptor, estrogen receptor, p53, C-erb B2, histologic grade (HG) and modified Bloom-Richardson grade (MBRG) status, there was no statistically difference detected (p>0.05).

In the Log Rank (Mantel-Cox) test, no statistically significant difference was detected between the groups in the relationship between Ki-67 and disease-free survival. However, it was detected that the risk of metastasis and recurrence increased as the Ki-67 value increased in the Cox Regression test (p<0.005) (Figure 2).

In the Log Rank (Mantel-Cox) test, it was detected that metastasis or recurrence increased and the disease-free period decreased in cases with high nuclear grade (NG). A statistically significant difference was detected between NG 1 and NG 3 according to disease-free survival (p:0.01) (Figure 2).

aA statisticlly significant difference was detected between T2, T4B and stage 2A, 3A+B groups according to disease-free survival (p:0.005 and p:0.003, respectively) (Figure 3).

A statistically significant difference was detected between the N0 and N2+3 groups according to disease-free survival (p:0.03) (Figure 4). Lymph node involvement was evaluated in 3 groups: 0-no metastasis, 1-3 metastatic lymph nodes and ≥4 lymph node metastases. A statistically significant difference was detected between patients without lymph node metastasis and with 4 or more lymph node metastases according to disease-free period (p:0.03) (Figure 4).

According to the results of the Cox Regression test, the risk of metastasis-recurrence increased as the number of lymph node metastases increased (p<0.05).

A statistically significant difference was detected between patients with positive lymphovascular invasion and with negative according to disease-free period (p:0.01).

Overall Survival

Kaplan-Meier and Log Rank tests were performed to examine the relation between estrogen receptor, p53, C-erb B2, HG, NG, MBRG status and overall survival. It was detected that these parameters were not statistically significant according to overall survival (p>0.05).

In the Log Rank test, positive or negative progesterone receptors were detected to be statistically significant and associated with overall survival (p:0.04). In the Cox Regression test, the overall survival decreased as the Ki-67 value increased (p:0.03).

As a result of the statistical analysis, lymphovascular invasion was associated with the overall survival (p:0.01). A statistically significant difference was detected between patients without lymph node metastasis and with 4 or more lymph node metastases according to overall survival (p:0.02). The tumor stage and size were associated with overall survival (Figure 5).

The results of the Log Rank test performed with cancer stage, T-stage, N-stage, and patient age are shown in Table 3.

Parameters that were significant according to disease free and overall survival in the Kaplan-Meier test were included in the multifactorial Cox Regression test. Except for lymphovascular invasion and Ki-67, other parameters were not included in the regression model. According to the results of this test, in the presence of lympho-vascular invasion, the disease-free period decreased and the risk of metastasis and recurrence increased by 3.8 times (p: 0.018). Ki-67 was detected as the prognostic factor and associated with poorer overall survival (p:0.014). Lymph node metastasis was detected to be close to statistically significant with a p:0.054 according to overall survival.

Table 3. Relationship Between Tumor Stage, Patient Age and Overall Survival				
Stage	1	2A	2B	3A+B
	p	p	p	p
1 2A 2B 3A+B	 0,4 0,8 0,2	0,4 0,4 0,02	0,8 0,4 0,1	0,2 0,02 0,1
Tumor	T1	T2	T3	T4B
	p	p	p	p
T1 T2 T3 T4B	 0,6 0,3 0,006	0,6 - 0,4 0,001	0,3 0,4 - 0,1	0,006 0,001 0,1
Lymph node status (N)		N0	N1	N2+N3
		p	p	p
N0 N1 N2+N3		 0,9 0,02	0,9 0,059	0,02 0,059
Age		<45	45-55	>55
		p	p	p
<45 45-55 >55		 0,3 0,04	0,3 0,1	0,04 0,1

Figure 1. Overall Survival and Disease-Free Survival Between the Groups (1-Mastectomy Group, 2-BCS Group)

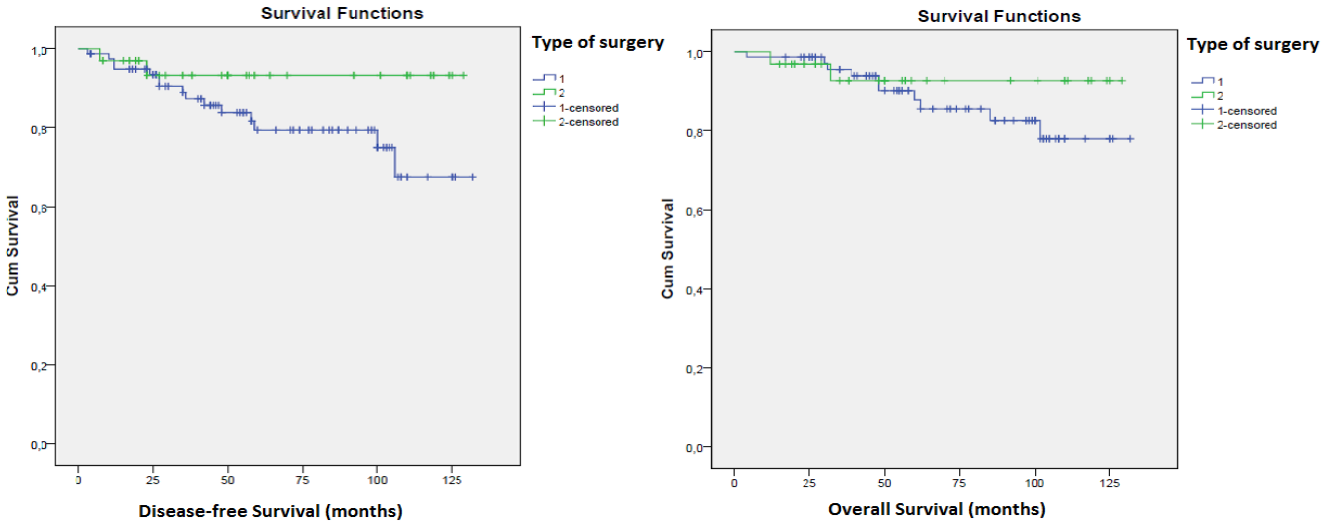


Figure 2. Relationship Between Ki-67, Nuclear Grade and Disease Free Survival

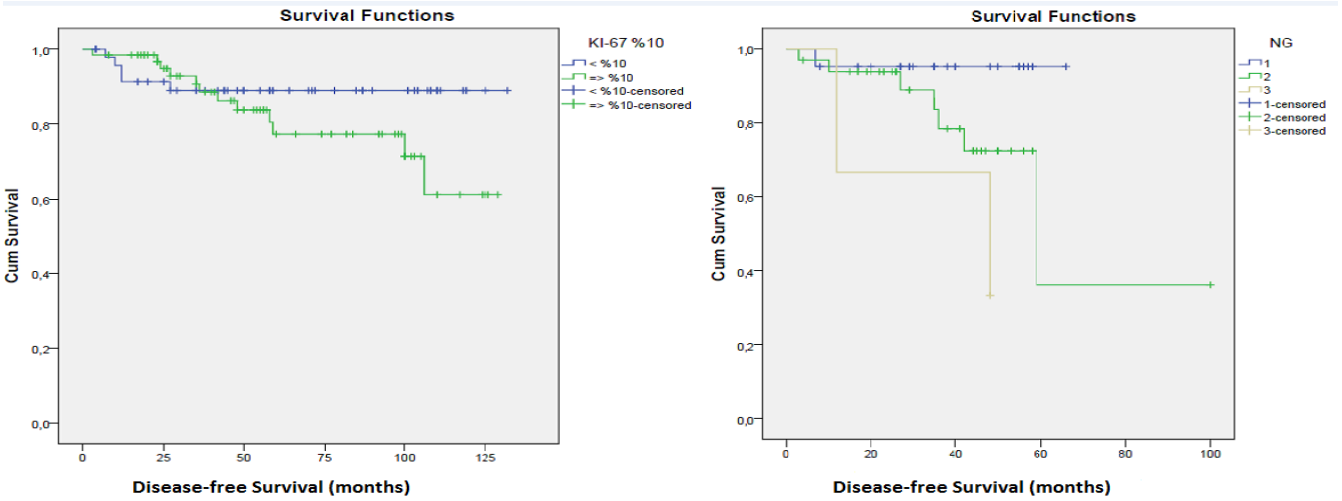


Figure 3. The Relationship Between Tumor Stage and Disease-Free Survival

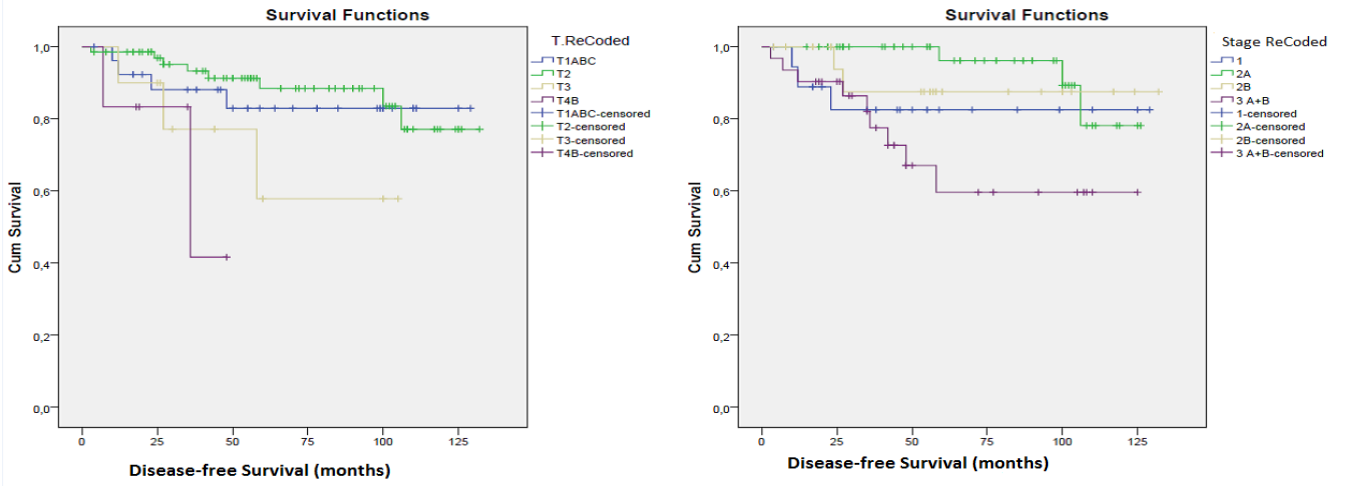


Figure 4. Relationship Between Lymph Node Status and Disease-Free Survival

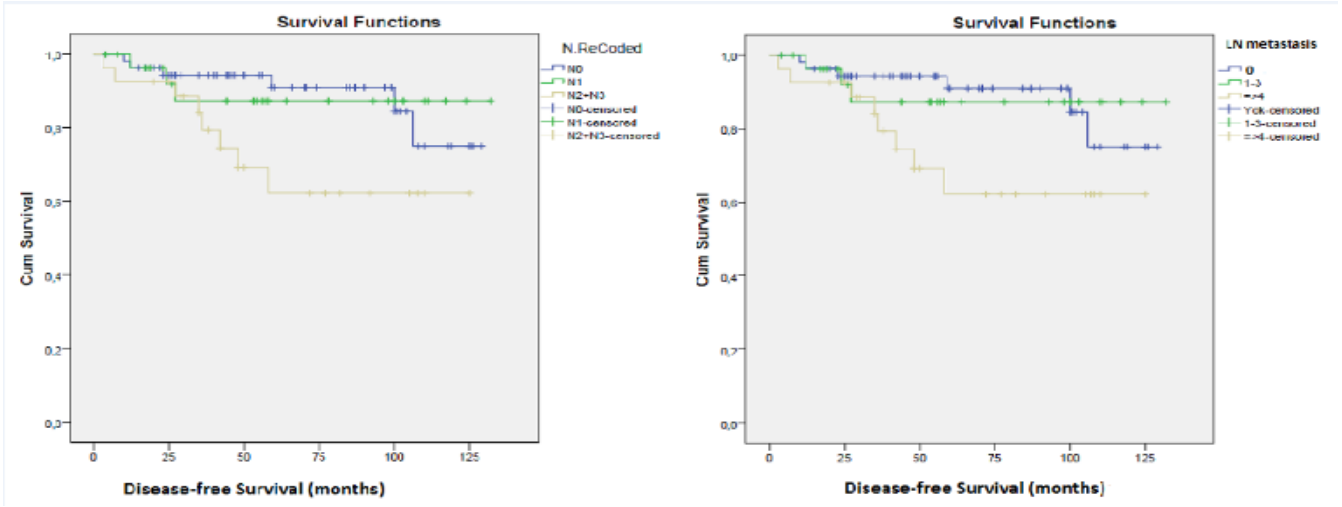
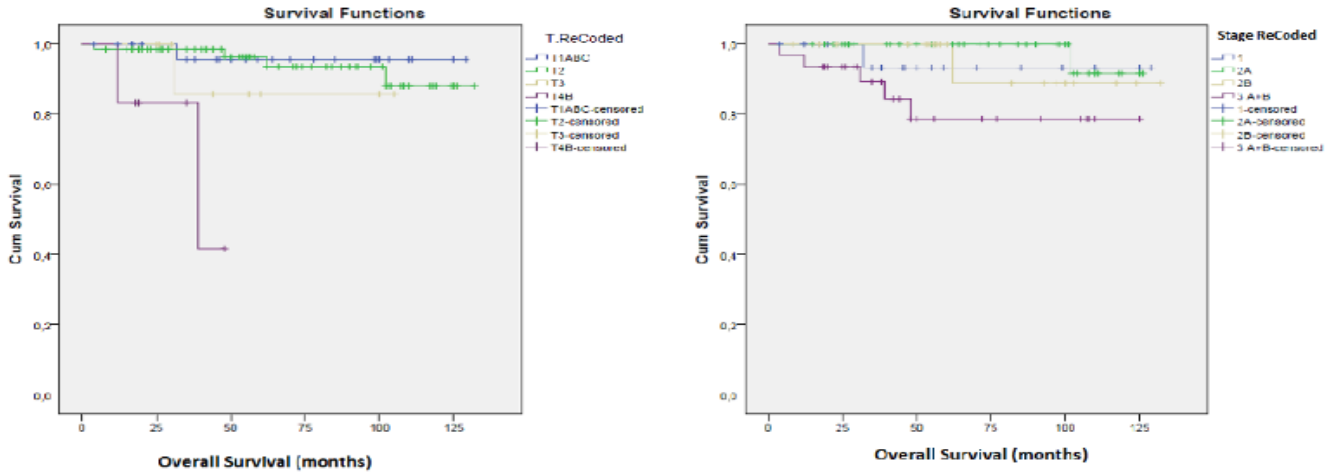


Figure 5. Relationship Between Cancer Stage and Overall Survival



DISCUSSION

Multifocality, multicentricity and bilaterality rates are high in invasive lobular carcinomas. Therefore, surgeons are cautious about performing breast-conserving surgery in these patients (7-8). In this study, it was detected that mastectomy was more preferred for patients with larger tumor sizes, N2-N3 lymph node metastases and more advanced cancer stages while breast-conserving surgery was preferred for patients with early-stage breast cancer with smaller tumor sizes and no lymph node metastases or N1 metastases. In this study, there was no statistically significant difference detected in disease-free survival and overall survival between patients who had total mastectomy and breast-conserving surgery. BCS provides patients with a higher quality of life in the postoperative period due to superior physical and psychological outcomes (14). In early-stage invasive breast cancer, disease-free survival and overall survival rates have been reported to be superior after BCS+radiotherapy compared to total mastectomy (15,16).

The reasons for this may be the development of surgical techniques, radiotherapy and other adjuvant treatment protocols over time (17,18). If the breast/tumor ratio is suitable for resection, BCS can be safely performed in patients with invasive breast cancer with a large tumor size (10,12,13). The specific growth pattern of ILC may complicate surgical excision with clean margins (19). However, BCS can be performed safely in large-sized ILCs with negative surgical margins. There was no significant difference in disease-free survival in these patients when compared to patients with total mastectomy (20). In our study, most of the patients who underwent BCS had tumors smaller than 5 cm. Only one patient with T4 tumor underwent BCS. In this study, most of the patients with tumors larger than 5 cm underwent total mastectomy. In this study, there were three reasons why we preferred total mastectomy to larger tumors: aesthetic concern, breast/tumor ratio and difficulty in providing negative surgical margins. Adjuvant radiotherapy was applied to all patients in our study who underwent BCS.

In the literature, it has been reported that the mean age of patients underwent breast-conserving surgery is higher than who have undergone total mastectomy (21). The reasons for this may be that breast cancer diagnosed at a young age is more aggressive, detected at more advanced stages, and the risk of local recurrence after surgery is higher (22,23). In this study, the mean age of all patients was over 50 years. The mean age of the patients in BCS group was younger than total mastectomy group. However, no statistically significant difference was detected between groups according to disease-free and overall survival. Lymphovascular invasion and Ki-67 are prognostic factors associated with survival in invasive breast cancer (24,25). In our study, lympho-vascular invasion and Ki-67 were detected as poor prognostic factors that adversely affected disease-free survival and overall survival regardless of the surgical technique.

The limitations of our study are its retrospective design and the small number of patients. Due to the retrospective design of the study, it could not be evaluated why BCS or total mastectomy was recommended for each patient separately. In addition, the fact that the breast/tumor ratio was not calculated for each patient is an important shortcoming. Prospective randomized studies with larger numbers of patients are needed to confirm the results reported in our study.

CONCLUSION

We suggest that breast-conserving surgery with negative surgical margins combined with adjuvant radiotherapy can be safely applied in patients with ILC.

Ethics Committee Approval: 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 conformed to the provisions of the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the University's Ethics Committee (23-11.2T/43).

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