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Breast-conserving surgery vs. total mastectomy in patients with triple negative breast cancer in early stages: A propensity score analysis

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Abstract.
BACKGROUND: Breast-conserving surgery (BCS) as an alternative to total mastectomy (TM) in patients with early-stage triple-negative breast cancer (TNBC) is not widely spread.
OBJECTIVE: We aimed to compare the overall survival (OS) and disease-free survival (DFS) between both surgical approaches in early-stage TNBC patients at 10 years.
METHODS: We conducted a retrospective cohort study in TNBC female patients with stage I-IIa, treated at a single-center during the period of 2000–2014. We estimated and compared the survival rates with the Kaplan Meier and Long-rank test. Propensity scores were calculated with the generalized boosted regression model and were used in the multivariate Cox regression analysis with the covariate adjustment method.
RESULTS: We included 288 patients, 111 in the BCS vs. 177 in the TM group. The median follow-up was 102 months. Moreover, the patients in the BCS group had superior OS (85% vs. 81%, $p = 0.56$) and DFS (83% vs. 80%, $p = 0.42$) at 10 years. In the multivariate Cox analysis, BCS decreased the mortality risk (HR: 0.79, 95% CI: 0.37–1.67, $p = 0.538$), and the locoregional or distant recurrence risk (HR: 0.67, 95% CI: 0.32–1.41, $p = 0.294$), albeit with no statistical significance.
CONCLUSION: BCS is a safe alternative to TM in Latin-American patients with early-stage TNBC.

Keywords: Triple negative breast cancer neoplasm, breast-conserving surgery; overall survival, distant disease-free survival, adjuvant chemotherapy

1. Background

Breast cancer is the leading neoplastic disease among females, with polyvalent molecular characteristics [1]. The difference in the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) classifies this tumor into four subtypes. One of them, the triple-negative breast cancer (TNBC) – defined as the minimal or non-expression of ER, PR, and HER-2 – is a heterogeneous subtype with an erratic and aggressive behavior [2,3]. Moreover, the overall survival (OS) of Peruvian patients with TNBC at five years is 67% [4,5].

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The surgical treatment of early-stage TNBC is with either breast-conservative surgery (BCS) or total mastectomy (TM). Nonetheless, this evidence-based recommendation comes from studies that included the four breast cancer subtypes in their analysis, rather than focusing on the survival outcomes of patients with TNBC [6–9]. Because of the aggressiveness of the TNBC, it would be reasonable to perform a radical surgical approach to reduce the recurrence and mortality risk [10]; however, research reports are contradictory. While some studies show that TM increases the locoregional recurrence risk [11,12], others state that locoregional and distant recurrence, disease-free survival (DFS), and OS of patients that underwent BCS have no difference from TM [13,14]. We aimed to compare the OS and DFS between BCS and TM in early-stage TNBC patients.

2. Methods

2.1. Study design

This is a retrospective cohort study, carried out and approved by the institutional review board of the National Institute of Neoplastic Diseases (INEN, "Instituto Nacional de Enfermedades Neoplásicas") in Peru. We selected the medical records of patients with the International Code for Disease (ICD)-10: "C50: Malignant neoplasm of breast". Thereafter, we included: (1) female patients with TNBC treated with either BCS or TM from 2000 to 2014; (2) patients with unilateral tumor stage I-IIa; (3) patients with adjuvant radiotherapy after BCS. We identified 401 medical records; nevertheless, we excluded patients without adjuvant chemotherapy after BCS or TM and loss of follow-up after surgery, which yielded a total of 288 medical records.

2.2. Clinicopathological variables

Patients were classified according to the 7th edition of the American Joint Committee on Cancer pathologic staging system [15]. Breast cancer immunophenotype was assessed by conventional immunochemistry, and TNBC was defined as the lack of expression of ER, PR, and HER-2. Patients received paclitaxel (4.5%), doxorubicin and cyclophosphamide (41%), or doxorubicin and cyclophosphamide plus paclitaxel (54.5%) as adjuvant chemotherapy.

2.3. Outcomes

Our primary outcome was the difference in mortality risk between BCS and TM at 10 years; we also measured the difference in the recurrence (locoregional or distant) risk. We defined OS from the date of surgery until death or end of the study (December 31, 2016), while DFS from the date of surgery until the diagnosis of locoregional or distant recurrence, death, or end of the study [15]. OS and DFS rates were reported at 5 and 10 years.

2.4. Statistical analysis

We used the program R version 3.5.3 with the packages survival, "survminer", "twang", and "survey" for the analysis. Demographic, clinicopathological, surgical, and adjuvant therapy characteristics were compared and described between both groups with the Chi-square test for qualitative variables and the Student's *t*-test for the quantitative variables. The variable "histologic grade" had 25 (8.9%) missing cases; hence, we performed a diagnostic analysis with logistic regression, which did not evidence a missing pattern. Therefore, we assumed the model "missing completely at random" and used the listwise deletion technique.

For the survival analysis, we included 263 patients (162 in the TM group and 101 in the BCS group). The survival curves and differences for both outcomes (OS and DFS) were estimated with the Kaplan–Meier method and the Log-rank test. Furthermore, we calculated the propensity scores with the generalized boosted regression model and employed the covariate adjustment method in the analysis. We used the average treatment effect (ATE) technique and followed the assumption that patients in our cohort had the same probability to underwent BCS or TM. The propensity score model included the following variables: age, menopausal state, histologic grade, tumor size, and lymph node status; because previous literature identified these variables as risk factors for mortality or recurrence risk [6,16–18]. To verify the balance of the propensity score, we employed the standardized effect size (SES). All the variables in the model had SES < 0.20. Multivariate Cox Regression analysis was employed – with the weighted propensity score as covariate – to identify the mortality and recurrence risk between both groups (BCS vs. TM). We calculated the adjusted proportional Hazard Ratio (HR) with a 95% confidence interval (CI) and considered a p-value <0.05 as statistically significant.

3. Results

3.1. Demographic and oncologic characteristics

We reviewed 288 medical records (111 in the BCS group and 177 in the TM group). Table 1 describes the demographic and clinicopathological characteristics of the study population according to both surgical modalities. Patients in the BCS cohort were younger, more likely to be premenopausal, had lower tumor size, and lower pathologic tumor stage. However, the lymph node status and histologic grade had a similar distribution between both cohorts. The most common histological subtype was invasive ductal carcinoma, followed by invasive lobular carcinoma and medullary carcinoma, with no statistical difference (Table 1).

3.2. Surgery characteristics

Compare to TM, BCS was more frequently performed during the periods of 2006–2010 and 2011–2014; however, TM was more common in the 2000–2005 period (Table 1). A total of 34 (11.8%) patients had positive margins, 31 (27.9%) cases in BCS and 3 (1.7%) cases in TM group ($p < 0.001$). In addition, positive surgical margins were more common in the periods of 2005–2010 (38.2%) and 2011–2014 (41.2%), than the 2000–2004 period (20.6%, $p = 0.080$). Of the patients with this outcome, 28 underwent re-excision plus radiotherapy; however, the remaining 6 cases (5 from BCS and 1 from TM) only received whole breast radiation.

3.3. Impact of surgery type on survival outcomes

We excluded 25 cases with missing values in the histologic grade variable. Of the remaining 263 patients, the locoregional (21 patients, 7.4% in the BCS vs. 8.9% in the TM group, $p = 0.839$) and distant (48 patients, 18.5% in the BCS vs. 17.8% in the TM group, $p = 1.000$) recurrence rates had a similar distribution among both groups, without a statistical difference. Overall, the lungs (31.3%), bones (14.6%), brain (14.6%), and liver (14.6%) were the most common places for metastasis.

The median follow-up was 102 months, the overall mortality rate was 14.8% (16% for BCS and 12.9% for TM, $p = 0.598$), and the overall recurrence rate (locoregional or distant) was 15.6% (17.3% for BCS and 12.9% for TM, $p = 0.433$) at 10 years. The OS rate was superior in the BCS cohort at 5 (88% vs. 86%) and 10 (85% vs. 81%) years, see Fig. 1. Moreover, the DFS rate in the BCS cohort was superior at 5 (88% vs. 84%) and 10 (83% vs. 80%) years, see Fig. 2. Both outcomes without statistical significance (OS: $p = 0.56$, and DFS: $p = 0.42$). Table 2 shows the unweighted and weighted mean of the variables, and the well-balanced standardized effect size to perform the regression analysis. Therefore, the multivariate Cox regression analysis with the weighted covariate adjustment identifies that BCS decreased the mortality risk (HR: 0.79, 95% CI: 0.37–1.67, $p = 0.538$) and the recurrence risk (HR: 0.67, 95% CI: 0.32–1.41, $P = 0.294$) of early-stage TNBC patients. However, no statistical significance was reached (Table 3).

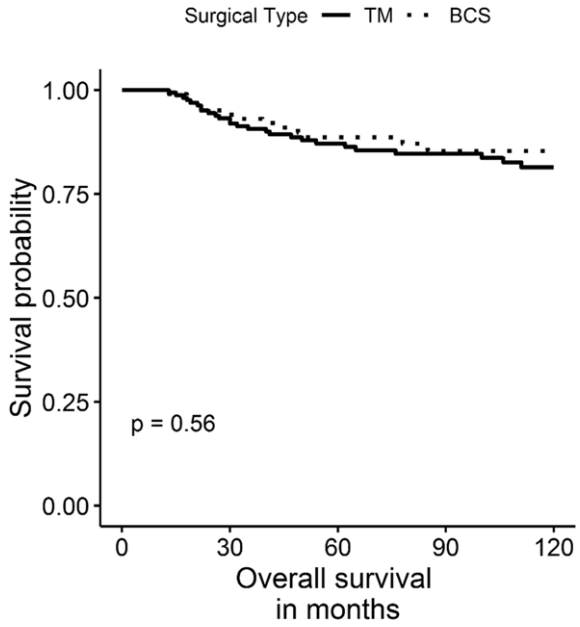


Fig. 1. Overall survival of early-stage triple-negative breast cancer patients according to surgical treatment (BCS: breast-conserving surgery and TM: total mastectomy). *P*-values by the log-rank test.

4. Discussion

The surgical treatment for patients with early-stage TNBC is with either BCS or TM [6,19]. Our study identified that both surgical approaches had equivalent survival outcomes (OS and DFS); therefore, BCS is a safe alternative to TM in this population. Similar to previous studies, we support the practice of BCS. For example, Chen et al. [17] found that BCS reduced

Table 1
Demographic and Clinicopathological characteristics of patients according to breast surgery management

Characteristics	Surgical management *n*, (%)		*P*-value
	Breast-conservative surgery (*n* = 111)	Total Mastectomy (*n* = 177)	
Age at diagnosis mean (SD)	47.96 (12.68)	51.76 (11.10)	0.008
Age at diagnosis			0.009
≤35	19 (17.1)	12 (6.8)	
36–64	83 (74.8)	139 (78.5)	
≥65	9 (8.1)	26 (14.7)	
Year of surgery			<0.001
2000–2005	11 (9.9)	89 (50.3)	
2006–2010	64 (57.7)	46 (26.0)	
2011–2014	36 (32.4)	42 (23.7)	
Menopausal status			0.033
Postmenopausal	54 (48.6)	110 (62.1)	
Premenopausal	57 (51.4)	67 (37.9)	
Laterality			0.176
Right	55 (49.5)	72 (40.7)	
Left	56 (50.5)	105 (59.3)	
Tumor size (cm)			<0.001
0–2	51 (45.9)	39 (22)	
2–5	60 (54.1)	138 (78.0)	
Lymph node status			1.000
Negative	100 (90.1)	160 (90.4)	
1–3 nodes positive	11 (9.9)	17 (9.6)	
Pathologic tumor stage			<0.001
Stage I	40 (36.0)	25 (14.1)	
Stage II	71 (64.0)	152 (85.9)	
Histologic grade			0.256
I	0 (0.0)	2 (1.1)	
II	17 (15.3)	41 (23.2)	
III	84 (75.7)	119 (67.2)	
Missing	10 (9.0)	15 (8.5)	
Histological subtypes			0.210
Invasive ductal carcinoma	102 (91.9)	168 (95)	
Invasive lobular carcinoma	4 (3.6)	2 (1.1)	
Medullary carcinoma	5 (4.5)	2 (1.1)	
Mucoepidermoid carcinoma	0 (0.0)	2 (1.1)	
Apocrine carcinoma	0 (0.0)	1 (0.6)	
Metaplastic carcinoma	0 (0.0)	1 (0.6)	
Secretory carcinoma	0 (0.0)	1 (0.6)	
Perineural invasion			<0.001
Yes	70 (63.1)	131 (74.0)	
No	9 (8.1)	29 (16.4)	
Missing	32 (28.8)	17 (9.6)	

~40% the mortality risk, and Adkins et al. [18] identified that TM increased the mortality risk by 22%. Nevertheless, both studies analyzed patients with pathologic tumor stages I–III, which negatively affects the survival outcomes due to the inclusion of patients with higher tumor stages. Moreover, Abdulkarim et al. [12] included breast cancer patients with stages I–II, and reported an OS of 87% and 82% at 5 years in the BCS and the TM groups, respectively; although OS was not their primary objective. In contrast, we included

Table 2
Showing the balance of covariates before and after weighting by the propensity score

	Unweighted mean (BCS)	Unweighted mean (TM)	Unweighted standardized effect size	Weighted mean (BCS)	Weighted mean (TM)	Weighted standardized effect size
Age at diagnosis	47.525	51.938	−0.371	49.684	50.471	−0.066
Menopausal status	1.515	1.389	0.253	1.471	1.445	0.052
Tumor size	1.545	1.802	−0.564	1.704	1.734	−0.068
Lymph node status	1.089	1.093	−0.012	1.070	1.085	−0.053
Histologic grade	1.832	1.735	0.231	1.767	1.769	−0.004

Table 3
Multivariate Cox regression analysis of mortality and recurrence risk

	Overall survival			Disease-free survival		
	HR*	95% CI	*P*-value	HR*	95% CI	*P*-value
Age at diagnosis	1.01	0.96-1.06	0.627	1	0.96–1.04	0.932
Menopausal state						
Postmenopausal	1	-	-	1	-	-
Premenopausal	1.1	0.37–3.27	0.867	1.25	0.45–3.44	0.671
Surgery type						
TM	1	-	-	1	-	-
BCS	0.79	0.37–1.67	0.538	0.67	0.32–1.41	0.294
Tumor size (cm)						
0–2	1	-	-	1	-	-
2–5	1.44	0.66–3.12	0.362	1.14	0.55–2.37	0.722
Lymph node status						
Negative	1	-	-	1	-	-
1–3 positive nodes	2.08	0.71–6.13	0.183	1.07	0.3–3.81	0.914
Histologic grade						
Grade I–II	1	-	-	1	-	-
Grade III	0.92	0.42–1.98	0.828	0.88	0.42–1.85	0.734

*Adjusted for propensity score.

patients with pathologic tumor stages I–IIa, and our principal outcome was mortality risk.

Two factors may explain the non-significant mortality risk between BCS and TM in the multivariate Cox regression analysis. First, the frequency of performance between both surgical approaches differed across time. At the beginning of our observation period, surgeons conducted TM more frequently, while BCS was an uncommon procedure, and its use increased during the following years. Therefore, a learning curve within the surgeons was still developing during the first years of the BCS implementation. Second, the proportion of positive surgical margins were higher in the BCS group, which shows a lack of experience from the surgeons in the first interventions of the BCS. Although both factors could have impacted the OS, our results acknowledge BCS as a safe alternative to TM.

On the other hand, previous studies state that BCS compared to TM has an equivalent locoregional and distant recurrence risk at 5 years [6,18,20]. Parker et al. [20] identified that the recurrence risk (locoregional or distant) between both types of surgery was non-significant, while Adkins et al. [18] reported that BCS did not increase the locoregional recurrence risk. Our results are consistent with these previous experiences; the multivariate analysis did not show a higher locoregional or distant recurrence risk in patients that underwent BCS. However, we reported our results at 10 years compared to the previous investigations, which enhance a long-term favorable outcome for BCS.

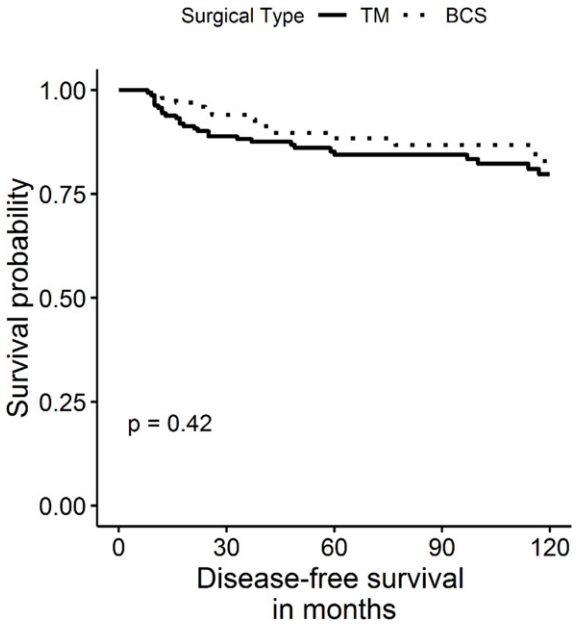


Fig. 2. Disease-free survival of early-stage triple-negative breast cancer patients according to surgical treatment (BCS: breast-conserving surgery and TM: total mastectomy). *P*-values by the log-rank test.

Our study has some limitations. First, we excluded medical records due to missing data on the treatment characteristics and loss of follow-up. Second, BCS became more common after 5 years of the beginning of the study, which implies a lack of experience from the surgeons performing this surgery during that period. This is the most likely reason for the high positive margins in the BCS cohort, however, the majority of patients had a re-excision with radiotherapy. Third, this is a single-center investigation, thereby, the generalization of our results must be taken with caution.

5. Conclusion

In conclusion, we support the use of BCS as a safe alternative to TM in patients with early-stage TNBC. Our results evidence a slight benefit from BCS on OS and DFS (without statistical significance). These results will help physicians and surgeons make evidence-based decisions in their daily practice.

Abbreviations

BCS: Breast-conserving surgery
CI: Confidence interval
DFS: Disease-free survival
ER: Estrogen receptors
HER-2: Human epidermal growth factor receptor 2
HR: Hazard ratio
ICD: International Code for Disease
INEN: Instituto Nacional de Enfermedades Neoplásicas
OS: Overall survival
PR: Progesterone receptors
TM: Total mastectomy
TNBC: Triple-negative breast cancer

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Conflict of interest

The authors do not have any financial relationship with a commercial entity that has interest in the subject carried out in this manuscript or any conflict of interest to declare.

References

[1] World Health Organization. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 [Internet]. WHO; 2012 [cited 2018 26/1]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx.
[2] Hubalek M, Czech T et al., Biological subtypes of triple-negative breast cancer, *Breast Care*, 12(1): 8–14, 2017.
[3] Pareja F, Geyer FC et al., Triple-negative breast cancer: the importance of molecular and histologic subtyping, and recognition of low-grade variants, *NPJ Breast Cancer*, 2: 16036, 2016.
[4] Yabar A, Melendez R et al., Effect of Ki-67 assessment in the distribution of breast cancer subtypes: evaluation in a cohort of Latin American patients, *Mol Clin Oncol*, 6(4): 503–509, 2017.
[5] Vallejos CS, Gómez HL et al., Breast cancer classification according to immunohistochemistry markers: subtypes and association with clinicopathologic variables in a peruvian hospital database, *Clinical Breast Cancer*, 10(4): 294–300, 2010.
[6] Zumsteg ZS, Morrow M et al., Breast-conserving therapy achieves locoregional outcomes comparable to mastectomy in women with T1-2N0 triple-negative breast cancer, *Ann Surg Oncol*, 20(11): 3469–3476, 2013.
[7] Gradishar WJ, Anderson BO et al., NCCN guidelines insights: breast cancer, version 1.2017, *J Natl Compr Canc Netw*, 15(4): 433–451, 2017.

[8] Gnant M, Harbeck N et al., St. Gallen/Vienna 2017: a brief summary of the consensus discussion about escalation and de-escalation of primary breast cancer treatment, *Breast Care (Basel)*, 12(2): 102–107, 2017.

[9] Vila J, Gandini S et al., Overall survival according to type of surgery in young (*leq*40 years) early breast cancer patients: A systematic meta-analysis comparing breast-conserving surgery versus mastectomy, *Breast*, 24(3): 175–181, 2015.

[10] Bhatti AB, Khan AI et al., Outcomes of triple-negative versus non-triple-negative breast cancers managed with breast-conserving therapy, *Asian Pac J Cancer Prev*, 15(6): 2577–2581, 2014.

[11] Bernier J, Poortmans PM, Surgery and radiation therapy of triple-negative breast cancers: from biology to clinics, *Breast*, 28: 148–155, 2016.

[12] Abdulkarim BS, Cuartero J et al., Increased risk of locoregional recurrence for women with T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy, *J Clin Oncol*, 29(21): 2852–2858, 2011.

[13] Black DM, Mittendorf EA, Landmark trials affecting the surgical management of invasive breast cancer, *Surg Clin North Am*, 93(2): 501–518, 2013.

[14] Cho JH, Park JM et al., Oncologic safety of breast-conserving surgery compared to mastectomy in patients receiving neoadjuvant chemotherapy for locally advanced breast cancer, *J Surg Oncol*, 108(8): 531–536, 2013.

[15] Edge SB, Byrd DR et al.*AJCC Cancer Staging Manual.* . 7 ed. IOS Press; 2010.

[16] Lyman GH, Kuderer NM et al., Menopausal status and the impact of early recurrence on breast cancer survival, *Cancer Control*, 4(4): 335–341, 1997.

[17] Chen QX, Wang XX et al., The different outcomes between breast-conserving surgery and mastectomy in triple-negative breast cancer: a population-based study from the SEER 18 database, *Oncotarget*, 8(3): 4773–4780, 2017.

[18] Adkins FC, Gonzalez-Angulo AM et al., Triple-negative breast cancer is not a contraindication for breast conservation, *Ann Surg Oncol*, 18(11): 3164–3173, 2011.

[19] Kim S, Park HS et al., Comparisons of oncologic outcomes between triple-negative breast cancer (TNBC) and non-TNBC among patients treated with breast-conserving therapy, *Yonsei Med J*, 57(5): 1192–1198, 2016.

[20] Parker CC, Ampil F et al., Is breast conservation therapy a viable option for patients with triple-receptor negative breast cancer?, *Surgery*, 148(2): 386–391, 2010.