Comparisons of Oncologic Outcomes between Triple-Negative Breast Cancer (TNBC) and Non-TNBC among Patients Treated with Breast-Conserving Therapy

Sanghwa Kim, Hyung Seok Park, Jee Ye Kim, Jegyu Ryu, Seho Park, and Seung Il Kim

Department of Surgery, Yonsei University College of Medicine, Seoul, Korea.

Purpose: The optimum local surgical strategy regarding breast-conserving therapy (BCT) for triple-negative breast cancer (TNBC) is controversial. To investigate whether BCT is appropriate for patients with TNBC, we evaluated the clinical outcomes of BCT in women with TNBC compared to those of women without TNBC, using a large, single-center cohort.

Materials and Methods: We performed a retrospective analysis of 1533 women (TNBC n=321; non-TNBC n=1212) who underwent BCT for primary breast cancer between 2000 and 2010. Clinicopathological characteristics, locoregional recurrence-free survival (LRFS), and overall survival (OS) were analyzed.

Results: Tumors from the TNBC group had a higher T stage (T2 37.4% vs. 21.0%, $p<0.001$), a lower N stage (N0 86.9% vs. 75.5%, $p<0.001$), and a higher histologic grade (Grade III 66.8% vs. 15.4%, $p<0.001$) than the non-TNBC group. There were no differences in 5-year LRFS rates between the TNBC and non-TNBC groups (98.7% vs. 97.8%, $p=0.63$). The non-TNBC group showed a slightly better 5-year OS than the TNBC group; however, the difference was not significant (96.2% vs. 97.3%, $p=0.72$). In multivariate analyses, TNBC was not associated with poor clinical outcomes in terms of LRFS and OS [hazard ratio (HR) for LRFS=0.37, 95% confidence interval (CI): 0.10−1.31; HR for OS=1.03, 95% CI: 0.31−3.39].

Conclusion: TNBC patients who underwent BCT showed non-inferior locoregional recurrence compared to non-TNBC patients with BCT. Thus, BCT is an acceptable surgical approach in patients with TNBC.

Key Words: Breast neoplasms; mastectomy, segmental; triple negative breast neoplasms

INTRODUCTION

The use of breast-conserving therapy (BCT) has increased as a definitive surgical treatment for early breast cancer patients, and BCT is performed in about 70% of breast cancer operations in Korea.[1] The wide use of BCT is based on previous randomized trials showing favorable survival outcomes of BCT compared to mastectomy.[2-5] For this reason, in 1990, the National Institutes of Health (NIH) Consensus Development Conference on Treatment of Early-Stage Breast Cancer recommended BCT for the majority of women with early-stage breast cancer.[6]

In 2000, Perou, et al.[7] determined the molecular subtypes of breast cancer, which were distinguished by differences in gene expression patterns. Breast cancer subtypes, classified according to molecular phenotype, show different clinicopathological features and influence the prognosis and response to treatment.[8-13] Currently, immunohistochemistry (IHC)-based molecular classification is used as a surrogate for gene expression profiling.[9-11] Molecular subtyping based on IHC could provide a standard method for determining treatment and surveillance strategies in breast cancer patients.[10,12,13]

Among breast cancer subtypes, triple-negative breast cancer (TNBC), in which tumors are negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, has drawn substantial attention due to its aggressive behavior, high risk of early relapse,

and poor overall survival (OS).[12,13] There are no proven effective target therapies for the TNBC subtype of breast cancer, making it a clinical challenge for optimal patient management.[14,15] Multiple studies showed a high risk of local recurrence after BCT in patients who had several clinical risk factors including specific molecular markers or gene expression patterns, such as those exhibited by the TNBC or HER2-enriched subtypes.[16-20] Conversely, other studies have argued that BCT could safely replace mastectomy regardless of the breast cancer subtype.[20-25] Thus, the use of BCT for TNBC is an ongoing concern for surgeons in this era of molecular subtyping for breast cancer. For this reason, we compared the clinical outcomes between patients with TNBC and those with non-TNBC, both of whom underwent BCT, to evaluate the oncologic safety of BCT.

MATERIALS AND METHODS

Patient cohort

We used the Breast Cancer Registry database of Severance Hospital, Yonsei University Health System to perform a retrospective analysis. The patient cohort consisted of 1533 women who underwent BCT due to primary breast cancer between 2000 and 2010. Patients were excluded from the analysis if they received neoadjuvant chemotherapy, presented with initial distant metastases, or had large-size tumors, non-epithelial-origin or special-type tumors (e.g., phyllodes tumor, lymphoma, sarcoma, Paget's disease, and inflammatory breast cancer), unavailable data on the type of surgery or radiotherapy, or unavailable data on the molecular subtype of a tumor distinguished as luminal type, HER2-enriched type, or TNBC.

Patients with breast cancer received either BCT or mastectomy according to the operator's decision, which involved the size, location, and multiplicity of the tumor and the patient's preference. Along with breast surgery, sentinel lymph node biopsy or standard level I/II axillary lymph node dissection was performed. After surgery, all enrolled patients received adjuvant radiotherapy with a median boost dose of 10 Gy that covered the whole breast with or without the regional nodal area.[26] Adjuvant endocrine therapy or chemotherapy was administered, if indicated. Criteria according to the sixth edition of the American Joint Committee on Cancer's Cancer Staging Manual were used for TNM staging.[27] Most HER2-positive tumors were not treated with neoadjuvant or adjuvant trastuzumab, as the use of trastuzumab was not sanctioned by the Korean National Health Insurance Service before 2009.

Patient characteristics including age, T stage, N stage, pathologic type, histologic grade, adjuvant hormone therapy, and adjuvant chemotherapy were reviewed. This study was reviewed and approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (IRB No. 4-2015-0132).

Tumor classification

Tumors with <10% ER/PR staining on IHC were considered to be ER/PR negative. We defined HER2-positive tumors as those with 3+ overexpression via immunohistochemical testing (IHC) or HER2 amplification via fluorescence *in situ* hybridization (FISH). Cases with HER2 expression levels of 0–1+ and 2+ with non-amplification via FISH were considered as HER2-negative. We categorized breast cancer based on ER, PR, and HER2 status, using the presence or absence of tumor markers via IHC or FISH as follows: TNBC (ER-, PR-, and HER2-negative) or non-TNBC [either luminal type (ER- and/or PR-positive and any HER2 status) or HER2-enriched type (ER- and PR-negative and HER2-positive)]. Tumors that were ER- and PR-negative and HER2-unknown were excluded. Histological grade was assessed using the modified Bloom-Richardson classification.

Statistical analysis

Categorical variables were analyzed using the chi-square test or Fisher's exact test, and continuous variables were analyzed using Student's t-test. Locoregional recurrence-free survival (LRFS) was measured from the date of the definitive surgery to the date of the first documented locoregional recurrence. The OS was calculated from the date of the definitive surgery to the date of death. Death without any other identifiable cause was considered in the OS analysis. LRFS and OS were plotted using the Kaplan-Meier method and compared using the log-rank test.

Cox proportional hazard models were used for multivariate analyses to determine the association of the TNBC subtype with survival outcomes, after adjusting for potentially confounding variables.

p-values of <0.05 were considered statistically significant; all tests were two-sided. Statistical analyses were carried out using commercially available statistical software (SPSS Statistics 20, IBM, Chicago, IL, USA).

RESULTS

Clinicopathological characteristics of the patient groups

The number of breast cancer patients who received BCT at our institution increased between 2000 and 2010 (Supplementary Fig. 1, only online). BCT has been performed in half of all breast cancer operations since 2006.

Fig. 1 shows the proportion of molecular subtypes in BCT patients during the study period. From 2000, the proportions of TNBC and non-TNBC breast cancer patients who underwent BCT (≈20%) were similar.

Baseline characteristics of the patients and tumor classification according to subtype are described in Table 1. Of 1533 tumors, 1212 were non-TNBC, and 321 were of the TNBC subtype. The mean age of all patients was 48.7±9.5 years at diagnosis; however, the age distribution was different between the two
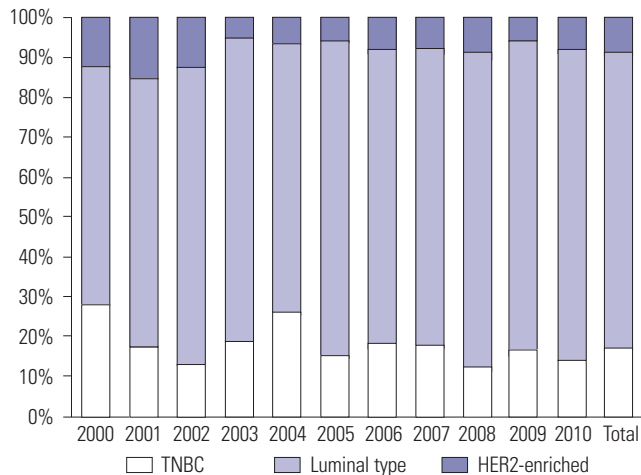
Fig. 1. Molecular subtype proportions according to breast cancer subtype with breast-conserving therapy. TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2.

groups: the TNBC group had more young patients than the non-TNBC group. There were 51 patients (15.9%) younger than 35 years of age in the TNBC group and 56 patients (4.6%) younger than 35 years of age in the non-TNBC group, respectively ($p<0.001$). The TNBC group had larger tumors (T2 37.4% vs. 21.0%, $p<0.001$), fewer nodal metastases (N0 86.9% vs. 75.5%, $p<0.001$), and more tumors with a higher histological grade (Grade III 66.8% vs. 15.4%, $p<0.001$) than the non-TNBC group. The patients with TNBC had more tumors with other histological types than the patients with non-TNBC (13.4% vs. 7.4%, $p=0.001$). In the non-TNBC group, approximately one in ten patients (10.7%) had ER-negative tumors, and one quarter of the patients (23.5%) had PR-negative ($p<0.001$) tumors. In addition, tumors from 216 non-TNBC cases were positive for amplification of HER2 (19.5%).

Adjuvant hormone therapy was administered to 1131 patients (93.3%) in the non-TNBC group compared to only 2.8% of patients in the TNBC group. More patients with TNBC received adjuvant chemotherapy than patients with non-TNBC, and this difference was significant (87.9% vs. 60.0%, $p<0.001$).

Clinical outcomes

The median follow-up period of all patients was 57 months (range 0–156). Figs. 2 and 3 illustrate the Kaplan-Meier plots of LRFS and OS comparing the two groups. Locoregional recurrence developed in seven cases (2.2%) with TNBC and in 28 cases (2.3%) with non-TNBC, and this was not significantly different. LRFS for the TNBC group was comparable to the non-TNBC group based on log-rank test results (5-year LRFS of TNBC vs. non-TNBC: 98.7% vs. 97.8%, $p=0.63$) (Fig. 2). Thirteen patients (4.0%) in the TNBC group and 39 patients (3.2%) in the non-TNBC group died during the follow-up period. The non-TNBC group tended to show slightly better survival than the TNBC group; however, the difference was not statistically significant (96.2% vs. 97.3%, $p=0.72$) (Fig. 3).

On multivariable analyses, the TNBC group did not show a significantly increased risk of locoregional recurrence and death compared to the non-TNBC group [hazard ratio (HR) for LRFS=0.37, 95% confidence interval (CI): 0.10–1.31; HR for OS=1.03, 95% CI: 0.31–3.39] (Table 2). Only the nodal stage independently affected OS, though it was not predictive of the prognosis of LRFS.

DISCUSSION

Based on several randomized-controlled trials, BCT has been proven to have clinical outcomes equivalent to mastectomy and has become the standard local treatment option for women with early-stage breast cancer.[2-5] Given the aggressive features of TNBC, however, there is a concern that a more aggressive treatment approach should be considered.[15] The current study demonstrated that clinical outcomes in terms of LRFS and OS in patients with TNBC who underwent BCT were not different from those with non-TNBC.

The use of BCT for breast cancer patients has increased significantly at our institution since 2006. According to the Korean Breast Cancer Society (KBCS) registry data, while the proportion of patients who underwent total mastectomy decreased from 71.2% in 2000 to 33.8% in 2011, the proportion of patients who underwent BCT surgery increased from 27.9% in 2000 to 65.7% in 2011.[1] These data are concordant with our results.

TNBC generally comprises 10–20% of breast cancers[28] with a reported prevalence of 12.5% in a large, California population-based study by Bauer, et al.,[29] despite racial differences in the prevalence of TNBC.[11,30] In agreement with these studies, our data showed a 10–20% proportion of TNBC in the breast cancer population, except for two years, 2000 and 2004. The data regarding the rates of locoregional recurrence and distant recurrence for TNBC patients with BCT are incongruent. In our study, the LRFS rates of TNBC and non-TNBC patients were not significantly different; however, the OS rate of TNBC patients was slightly reduced until 6 years after the BCT, which might have been due to the aggressive behavior of TNBC. Interestingly, TNBC patients had a better clinical outcome if they survived longer than 6 years after treatment, compared to non-TNBC patients. After we adjusted for confounding factors in the prognosis, such as age, stage, histologic grade, and systemic therapy, the multivariate analysis revealed that TNBC was unlikely to be an independent prognostic factor affecting the decision to undergo BCT in breast cancer patients. This indicates that tumor subtype (TNBC or non-TNBC) alone does not influence LRFS in breast cancer patients with BCT. Similarly, Haffty, et al.[25] showed no difference in the ipsilateral breast relapse-free survival between the patients with TNBC and other subtypes with conservative management. Patients classified as TNBC were younger and had larger tumors than other subtypes yet had similar LN metastasis rates.[25] The triple-negative subtype was

an independent predictor of distant metastasis.[25] In contrast, Arvold, et al.[31] showed that TNBC patients had a significantly increased risk of local recurrence compared with luminal subtypes. In addition, 91% of the patients in that study received adjuvant systemic therapy; the data were stratified according to the luminal subtype by histologic grade; and the study compared five breast cancer subtypes and age quartiles and demonstrated that young age remained an independent risk factor for locoregional recurrence.[31] A similar study by Nguyen, et al.[19] also reported that the breast cancer subtype, as approximated based on ER, PR, and HER-2 status, was significantly associated with both local and distant recurrence after BCT. In that study,

the luminal B and HER2-enriched subtypes had more instances of lymph node metastasis and lymphovascular invasion than TNBC, although the TNBC group had larger tumors and received more chemotherapy.[19] Meta-analysis of 22 studies by Wang, et al.[20] reported that the TNBC subtype was associated with increased risks of both ipsilateral locoregional recurrence and distant metastasis compared to non-TNBC subtypes. In the TNBC cohort, however, patients who received BCT were less likely to develop ipsilateral locoregional recurrence and distant metastasis than those who underwent a mastectomy.[20]

In a previous study that compared the characteristic features of TNBC and other subtypes, the TNBC group was character-

**Table 1.** Baseline Patient and Tumor Characteristics

Baseline characteristics	Non-TNBC (n=1212)		TNBC (n=321)		All patients (n=1533)		p value*
	n	%	n	%	n	%	
Age							<0.001
≤35	56	4.6	51	15.9	107	7.0	
>35	1156	95.4	269	84.1	1425	93.0	
T stage							<0.001
T1	957	79.0	201	62.6	1158	75.5	
T2	255	21.0	120	37.4	375	24.5	
N stage							<0.001
N0	915	75.5	279	86.9	1194	77.9	
N1	241	19.9	37	11.5	278	18.1	
N2	42	3.5	5	1.6	47	3.1	
N3	14	1.2	0	0.0	14	0.9	
Histological type							0.001
Ductal	1079	89.0	274	85.4	1353	88.3	
Lobular	43	3.5	4	1.2	47	3.1	
Other	90	7.4	43	13.4	133	8.7	
Histological grade							<0.001
I	351	31.9	16	5.7	367	26.6	
II	580	52.7	77	27.5	657	47.6	
III	169	15.4	187	66.8	356	25.8	
ER							<0.001
Negative	130	10.7	321	100.0	451	29.4	
Positive	1082	89.3	0	0.0	1082	70.6	
PR							<0.001
Negative	285	23.5	321	100.0	606	39.5	
Positive	927	76.5	0	0.0	927	60.5	
HER2							<0.001
Negative	892	80.5	321	100.0	1213	84.9	
Positive	216	19.5	0	0.0	216	15.1	
Hormone therapy							<0.001
No	81	6.7	312	97.2	393	25.6	
Yes	1131	93.3	9	2.8	1140	74.4	
Adjuvant chemotherapy							<0.001
No	485	40.0	39	12.1	524	34.2	
Yes	726	60.0	282	87.9	1008	65.8	

TNBC, triple-negative breast cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.
*Non-TNBC vs. TNBC.

ized by younger patients, larger and higher grade tumors, and more instances of lymph node metastasis.[15] Our results showed that TNBC patients were younger, had larger tumors with a

higher histologic grade than non-TNBC patients, and had clinicopathological features that were similar to TNBC patients in prior studies, except in terms of lymph node metastasis. TNBC
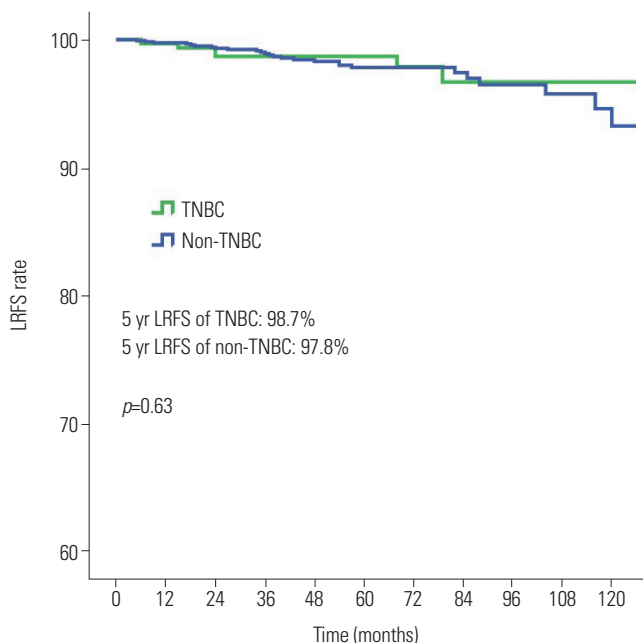
Fig. 2. Univariate analysis of locoregional recurrence-free survival after breast-conserving therapy according to TNBC and non-TNBC subtypes. TNBC, triple-negative breast cancer; LRFS, locoregional recurrence-free survival.
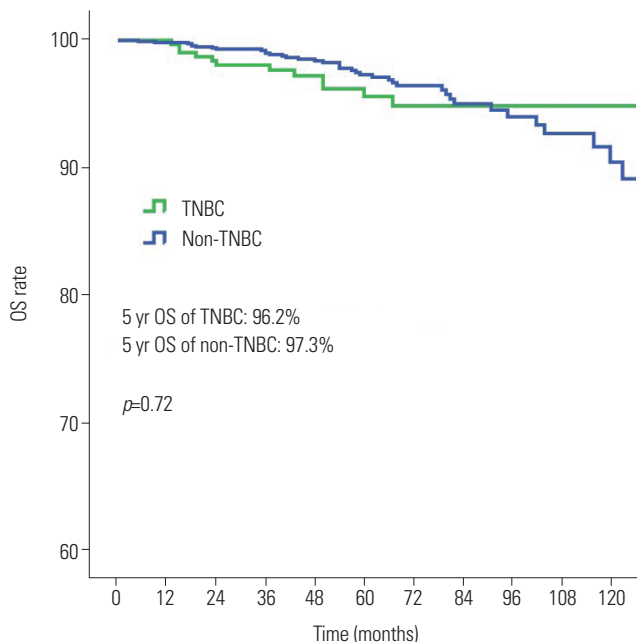
Fig. 3. Univariate analysis of overall survival after breast-conserving therapy according to TNBC and non-TNBC subtypes. OS, overall survival; TNBC, triple-negative breast cancer.

Table 2. Multivariate Analysis for Locoregional Recurrence-Free Survival and Overall Survival

Multivariate analysis	Locoregional recurrence-free survival				Overall survival			
	Hazard ratio	95% CI		*p* value	Hazard ratio	95% CI		*p* value
		Lower	Upper			Lower	Upper	
Subtype								
Non-TNBC	Ref.				Ref.			
TNBC	0.37	0.10	1.31	0.12	1.03	0.31	3.39	0.96
Age								
≤35	Ref.				Ref.			
>35	0.73	0.21	2.53	0.62	0.96	0.34	2.76	0.94
T stage								
T1	Ref.				Ref.			
T2	1.45	0.66	3.21	0.36	1.09	0.58	2.05	0.80
N stage								
N0	Ref.				Ref.			
N+	0.82	0.33	2.03	0.67	2.06	1.08	3.92	0.03
Histological grade								
I/II	Ref.				Ref.			
III	1.32	0.55	3.17	0.53	1.51	0.75	3.06	0.25
Hormone therapy								
No	Ref.				Ref.			
Yes	0.45	0.15	1.38	0.16	0.99	0.32	3.06	0.98
Adjuvant chemotherapy								
No	Ref.				Ref.			
Yes	0.72	0.30	1.75	0.47	1.26	0.53	2.99	0.60

TNBC, triple-negative breast cancer; CI, confidence interval.

patients had less metastasis to the lymph nodes and underwent more adjuvant chemotherapy, which might have been responsible for the better outcome of these patients. Dent, et al.[15] also showed that TNBC had a more aggressive clinical course, though this feature was transient. These features of TNBC could support our result, which showed favorable outcomes for TNBC compared to non-TNBC after BCT.

However, there were limitations to the retrospective study design. First, as trastuzumab was approved for use by the Korean National Health Insurance only after the mid-2000s, testing for HER2 expression and prescribing trastuzumab were not routinely performed. Thus, there was a lack of information regarding the administration of trastuzumab and HER2 evaluations in the registry prior to that time. Second, certain TNBC patients received hormone therapy. In the current study, about 2.8% of TNBC patients were treated with hormone therapy, and their tumors were weakly positive for hormone receptor expression (1−9%) on IHC. The tumors with weak hormone receptor positivity were regarded as negative. Whether the hormone receptor positivity of 1−9% in these patients was real or an artifact has been disputed among many physicians.[32] At our institution, hormone receptor expression over 1% was considered as positive according to the guidelines from the American Society of Clinical Oncology and the College of American Pathologists in 2010, which recommended a threshold of 1% or more for classifying breast cancer as ER-positive.[33] Changes in the definition of the threshold of hormone receptor expression can influence clinical outcomes.

The complexity of clinical, biological, and histopathological information on breast cancer creates difficulties for managing locoregional disease. Moreover, there are no specific locoregional treatment guidelines for TNBC.[34] However, this study showed non-inferior locoregional recurrence in patients with early TNBC and comparable outcomes between TNBC and non-TNBC. Our findings support the hypothesis that BCT is an acceptable surgical approach in patients with TNBC.

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