No association between triple-negative breast cancer and prognosis of patients receiving breast-conserving treatment

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Abstract. The role of triple-negative breast cancer (TNBC) in breast-conserving treatment is controversial. The present study aimed at evaluating the prognosis of patients with TNBC following breast-conserving treatment (BCT) within 5 years. The present study investigated a cohort of 757 patients with early stage breast cancer, diagnosed and treated with BCT between January 2002 and March 2010 at Tianjin Medical University Cancer Institute and Hospital. The patients were divided into three groups according to receptor expression: Estrogen receptor (ER) or progesterone receptor (PR)-positive; epidermal growth factor receptor 2 (HER2)-enriched: ER and PR negative but HER2-positive; TNBC: ER, PR and HER2 receptor-negative. The primary endpoint was recurrence or mortality within 5 years after breast cancer diagnosis. Multivariable Cox analysis was used to determine the risk of locoregional relapse, distant metastases, total relapse and mortality associated with the intrinsic subtypes. Of the 757 patients with status of all receptors available, 541 (71.5%) were luminal, 66 (8.7%) were HER2-enriched and 150 (19.8%) were TNBC. Patients with TNBC were more likely to have histological grade III tumors (27.3%) compared with luminal (8.3%) and HER2-enriched (16.7%) subtypes (P<0.001). Within 5 years, locoregional recurrence rate was 2.4, 7.6 and 7.3% for luminal, HER2-enriched and TNBC, respectively (P=0.005). Mortality rate was 2.2, 9.1 and 4.7% for luminal, HER2-enriched and TNBC, respectively (P=0.007). There was no significant difference in rates of distant metastases (P=0.164) and total relapse (P=0.138). TNBC was not an independent prognostic predictor for women treated with BCT within 5 years after breast cancer diagnosis on multi-variate analysis. Patients with TNBC were not at significantly increased 5-year risks of locoregional recurrence, distant metastasis, total relapse or mortality at so remain appropriate candidates for BCT.

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Introduction

Breast cancer is a heterogeneous disease and divided into different subtypes according to estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status (1,2). Triple-negative breast cancer (TNBC), which is characterized by the lack of ER, PR and HER2 expression, has attracted substantial attention (3,4). There is a significant overlap between TNBC and basal-like breast cancer. Therefore, TNBC and basal-like breast cancer are frequently regarded as synonymous (5,6). TNBC is assessed by immunohistochemistry, and basal-like breast cancer is identified using gene expression profiling (7). TNBCs are fast-growing tumors and tend to metastasize compared with other types of breast cancer (8). TNBC has consistently been associated with poor clinical outcomes in radical mastectomy due to its invasive characteristics, and poor response to hormone therapy and HER2-targeted therapy (9-11).

Similar survival rates of women following breast-conserving treatment (BCT) and radical mastectomy have been

demonstrated (12,13). Consequently, BCT has become a preferable option for early stage breast cancer patients (14). However, due to the aggressive characteristics of TNBC, whether patients with TNBC are suitable for BCT remains controversial. A number of studies have reported that following BCT women with TNBC had a higher rate of local failure compared with women with other breast cancer subtypes (15,16). Investigators reported that TNBC was associated with an increased risk of distant metastasis, but it was not associated with increased locoregional recurrence (LRR) (17). However, Millar *et al* (18) reported that there was no increase in distant metastasis risk following BCT in patients with TNBC compared with patients with other breast cancer phenotypes. Additionally, Gangi *et al* (19) demonstrated that patients with TNBC were not associated with increased local relapse compared with patients with non-TNBC subtypes following BCT; however, they found that the TNBC phenotype was associated with shorter overall survival (OS).

Taken together, the role of TNBC in BCT remains unclear. The outcomes of patients with TNBC following BCT have not been well described. Therefore, an investigation was conducted to retrospectively compare the 5-year outcomes of women with TNBC to women with other subtypes breast cancer following BCT and to evaluate the prognostic value of TNBC in patients with BCT.

Patients and methods

Patients. Between January 2002 and March 2010, a total of 757 patients with early-stage breast cancer treated with BCT at Tianjin Medical University Cancer Institute and Hospital were identified to meet the inclusion criteria. The inclusion criteria were as follows: i) Full details of ER, PR and HER2 status and ii) patients had with stage I/II/III breast cancer and treated by lumpectomy. Exclusion criteria included: i) males with breast cancer; ii) T4 disease; iii) stage IV disease; iv) previously underwent mastectomy and v) unknown ER, PR or HER2 status. Data collected included standard prognostic factors, such as age, menopausal status, tumor size, lymph node, ER, PR, and HER2 status, histological grade, date of surgery, adjuvant treatment received, time of LRR and metastatic progression, date of last follow-up (March 2015) and mortality. In the present study, the age of breast cancer patients ranged between 19 and 83 years, and the median age was 45 years. The pathological samples were taken as part of routine examination and biopsy, and the specimens were obtained on the day of operation performed, the number of specimens obtained varied between 6 and 20, according to different circumstances. The patients were staged using the sixth edition of the American Joint Committee on Cancer (AJCC) staging manual (20). The Elston-Ellis modification of Scarff-Bloom-Richardson (SBR) grading system was used for histological grade of breast cancer (21). Negative pathological margins were defined as no invasive carcinoma or ductal carcinoma *in situ* (DCIS) present at the margins; positive margins were defined as the presence of invasive carcinoma or DCIS at the margin. Ethical approval was obtained from the Tianjin Medical University Hospital (grant no. bc2017008), and written informed consent was obtained from all patients.

Formalin-fixed paraffin-embedded tissues. Samples obtained from each patient were formalin-fixed and paraffin-embedded as part of routine examination. In the study, a 4-mm-thick tissue specimen was cut from breast tumor for formalin fixation processes. Each sample was placed into standard tissue cassettes and completely submerged in a container filled with 4% neutral buffered formaldehyde for 24 h at room temperature. The formaldehyde-fixed samples were embedded in paraffin after stepwise dehydration in 70, 80, 90 and 99% ethanol, followed by isopropanol and xylene.

Immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH). IHC and FISH analysis were conducted on tissue sections (3-4 μm) and tissue microarray slides. IHC (Benchmark XT; Ventana Medical Systems, Inc., Tucson, AZ, USA) was performed on formalin-fixed and paraffin-embedded tissues of 757 patients using the avidin-biotin-immunoperoxidase technique (22). Tissue sections were deparaffinized in xylene and rehydrated in a graded series of ethanol. Antigen-retrieval was performed in citrate buffer (pH 6.0) at 120°C for 2.5 min. Subsequently, the slides were exposed to 3% hydrogen peroxide for 20 min and washed with PBS for 5 min 3 times. The further blocking of tissues was performed with normal goat serum (Abcam Inc., Cambridge, UK) for 30 min at room temperature. The sections were then incubated overnight at 4°C with the following primary antibodies: ER (cat no. NCL-L-PGR-312; dilution, 1:100), PR (cat no. NCL-L-ER-6F11; dilution, 1:80) (both Novocastra; Leica Biosystems GmbH, Wetzlar, Germany), HER2 (cat no. 800-2996; dilution 1:300; Ventana Medical Systems, Inc.). Following 5 washes with PBS, the slides were incubated with biotin-conjugated secondary antibody (cat no. ZB-2010; dilution, 1:200; OriGene Technologies, Inc., Beijing, China) for 30 min at room temperature. The sections with positive expression level was used as the positive control, the negative control was established with the primary antibody replaced by PBS. Detection was done by utilizing iView DAB Detection kit (Ventana Medical Systems, Inc.).

FISH analysis was conducted in line with the protocol of Abbott/Vysis PathVysion HER2 DNA Probe kit (cat no. 30161060/02J01-030; Abbott Molecular, Inc., Des Plaines, IL, USA), the Spectrum Orange fluorophore-labeled DNA probe and Spectrum Green fluorophore-labeled α-satellite DNA probes from this kit were used to assess the HER2 gene locus and chromosome 17, respectively. In total, 2 separate fields of ≥20 cells were counted and the average of the results of the selected tumor areas were used to calculate mean gene and chromosome 17 counts, which were used to calculate the ratio of HER2:CEP17 signal. Tumor cells from matching sites of IHC were scored for the number of red (HER2) and green (chromosome 17) signals. The slides were evaluated using an Olympus BX51 microscope (Olympus Corporation, Tokyo, Japan) with an oil-immersion objective lens and an appropriate filter set at a magnification of x100. Immunoreactivity was assessed independently by ≥2 pathologists.

Subtype definitions. The patients were divided into three subtypes according to receptor expression: i) Luminal: ER or PR-positive, ii) HER2-enriched: ER and PR-negative but HER2 receptor-positive and iii) TNBC:ER, PR and

HER2-negative. ER, PR and HER2 data were obtained through routine clinical testing. The samples were defined as ER or PR-positive if >1% of the cells were positive for immunohistostaining. HER2 immunoreactivity was assessed using a standardized score from 0-3, based on the intensity of staining of the cell membrane and the proportion of tumor cells stained. The no staining or <10% of tumor cells was estimated as negative (score, 0), the weak and incomplete staining of the membrane in >10% of tumor cells was considered negative (score, 1+), the weak to moderate complete staining of the membrane in >10% tumor cells was evaluated as 2+, and strong complete staining of the membrane in >10% of tumor cells was determined to be positive (score, 3+). Samples with 2+ were needed to be detected by FISH test, and the HER2 gene was considered to be amplified when the ratio of HER2:CEP17 in tumor cells was >2.0. Patients with negative ER and PR status and HER2 immunohistostaining score of 2+ but no fluorescence *in situ* hybridization results were excluded in the present analysis.

Treatment delivery. All patients in the present study were treated surgically with breast-conserving surgery. A total of 675 patients had completed breast radiation therapy. Breast plus supraclavicular fossa radiation therapy was performed on 61 patients. A total of 21 patients did not undergo radiation treatment. Adjuvant systemic chemotherapy and hormone therapy were performed according to standard practices during that time interval. The majority of patients in the present study received anthracycline/taxane-based or cyclophosphamide, methotrexate and 5-fluorouracil chemotherapy regimens, and a minority of patients chose other chemotherapy regimens. It was recommended that patients with ER- and/or PR-positive disease who were premenopausal received tamoxifen treatment; postmenopausal patients chose aromatase inhibitors. Of the 757 patients with breast cancer, 717 received adjuvant systemic chemotherapy and 493 received hormone therapy. In total, 3 patients in the present study received trastuzumab therapy (data not shown).

Follow-up and outcomes. Follow-up has been maintained by reviewing clinical charts and by contacting patients by telephone or mail. Factors analyzed included clinical (age, menopause status, tumor-node-metastasis stage, tumor size), pathological (lymph node status, histological grade, pathological subtype and final margin status) and treatment (systemic therapy). The end-point of the present study was 5-year LRR, distant metastasis or mortality, and the study was ended when breast cancer mortality occurred. Total recurrence referred to LRR or distant metastasis. LRR-free survival (LRFS) was defined as the time from diagnosis to development of LRR (recurrence within the breast and regional relapse, including ipsilateral supraclavicular fossa, axilla or internal mammary lymph nodes). Distant metastasis-free survival (DMFS) was defined as the time from pathological diagnosis to the time from first evidence of distant metastasis. Disease-free survival (DFS) defined as the time of diagnosis to development of first evidence of metastasis or LRR. OS was defined as from the time of diagnosis to last follow-up or time of mortality from breast

cancer (patients who succumbed to other causes were considered censored from the time of mortality).

Statistical analysis. All statistical analyses were carried out using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). The Kaplan-Meier method was used for univariate analysis and calculating LRFS, DMFS, DFS and OS, and the significance was assessed using the log-rank test. Cox proportional hazards regression analysis was used for multivariate analysis. Factors with a significance of P<0.10 in univariate analysis were included in the multivariate Cox model. Differences between categorical variables were calculated using the χ^2 test. P<0.05 was considered to indicate a statistically significant difference.

Results

Patients. Of the 757 patients diagnosed with early breast cancer and treated with BCT in whom the status of all three markers (ER, PR, and HER2) were available, 541 (71.5%) were sorted as luminal subtype, 66 (8.7%) were defined as HER2-enriched subtype and 150 (19.8%) were classified as TNBC subtype (Table I). The follow-up time ranged from 13 to 157 months, and the median follow-up time was 83 months. The 5-year LRFS, DMFS, DFS and OS for the whole cohort were 96.2, 94.3, 92.9 and 96.7%, respectively.

Clinicopathological characteristics according to different subtypes. Patient characteristics and results of statistical comparisons according to different breast cancer subtypes were summarized in Table I. The distribution of young patients (≤35 years) was significantly different between luminal (13.1%), HER2-enriched (27.3%) and TNBC (19.3%) subtypes, (P=0.016; Table I). Patients with TNBC were more likely to have histological grade III tumors (27.3%) compared with the luminal (8.3%) and HER2 (16.7%) subtypes (P<0.001; Table I). Selection of chemotherapy treatment was also different among the 3 groups (P=0.021; Table I).

5-year outcomes of breast cancer patients following BCT according to different subtypes. The 5-year outcomes of the three different breast cancer subtypes following BCT were different. The rate of 5-year LRR was significantly different between luminal (2.4%), HER2-enriched (7.6%) and TNBC (7.3%) groups (P=0.005; Table II). The rate of 5-year mortality was 2.2, 9.1 and 4.7% for luminal, HER2-enriched and TNBC, respectively (P=0.007; Table II). There was no significant difference in the rates of distant metastases (P=0.164) and total relapse (P=0.138; Table II). The 5-year LRFS was 97.6, 92.4 and 92.7% for luminal, HER2-enriched and TNBC groups, respectively (P=0.005; Fig. 1A). The 5-year DMFS was 95.0, 89.4 and 94.0% for luminal, HER2-enriched and TNBC groups, respectively (P=0.164; Fig. 1B). The 5-year DFS was 93.9, 87.9 and 91.3% for luminal, HER2-enriched and TNBC groups, respectively (P=0.138; Fig. 1C). The 5-year OS was 97.8, 90.9 and 95.3% for luminal, HER2-enriched and TNBC groups, respectively (P=0.007; Fig. 1D).

Univariate analysis of the prognostic factors associated with 5-year outcomes of patients following BCT. The prognostic factors associated with 5-year LRFS, DMFS, DFS and OS in

Table I. Distribution of clinical and treatment characteristics among different types patients with breast-conserving treatment.

Parameters	Luminal, n (%)	HER2-enriched, n (%)	TNBC, n (%)	P-value
Total	541 (71.5)	66 (8.7)	150 (19.8)	
Age at diagnosis, years				0.016
≤35	71 (13.1)	18 (27.3)	29 (19.3)	
36-55	368 (68.0)	39 (59.1)	100 (66.7)	
>55	102 (18.9)	9 (13.6)	21 (14.0)	
Menopausal status				0.676
Premenopausal	369 (68.2)	48 (72.7)	100 (66.7)	
Postmenopausal	172 (31.8)	18 (27.3)	50 (33.3)	
Number of positive LNs				0.937
0	421 (77.8)	54 (81.8)	119 (79.3)	
1-3	97 (17.9)	10 (15.2)	26 (17.3)	
≥4	23 (4.3)	2 (3.0)	5 (3.3)	
Tumor size, cm				0.316
T1 (≤2)	378 (69.9)	41 (62.1)	93 (62.0)	
T2 (>2, ≤5)	145 (26.8)	22 (33.3)	49 (32.7)	
T3 (>5)	18 (3.3)	3 (4.6)	8 (5.3)	
TNM stage				0.601
I	321 (59.3)	35 (53.1)	81 (54.0)	
II	196 (36.2)	29 (43.9)	61 (40.7)	
III	24 (4.5)	2 (3.0)	8 (5.3)	
Pathological subtype				0.566
IDC	396 (73.2)	50 (75.8)	116 (77.3)	
Other	145 (26.8)	16 (24.2)	34 (22.7)	
Histological grade				<0.001
I	106 (19.6)	5 (7.6)	16 (10.7)	
II	344 (63.6)	41 (62.1)	81 (54.0)	
III	45 (8.3)	11 (16.7)	41 (27.3)	
Unknown	46 (8.5)	9 (13.6)	12 (8.0)	
Margin status				0.230
Positive	12 (2.2)	0 (0.0)	1 (0.7)	
Negative	529 (97.8)	66 (100.0)	149 (99.3)	
Chemotherapy				0.021
CMF	89 (16.4)	21 (31.8)	23 (15.3)	
A/T	404 (74.7)	39 (59.1)	119 (79.4)	
Other	15 (2.8)	2 (3.0)	5 (3.3)	
No	33 (6.1)	4 (6.1)	3 (2.0)	
Radiation				0.138
Breast	477 (88.2)	58 (87.8)	140 (93.3)	
Breast and SCF	48 (8.9)	4 (6.1)	9 (6.0)	
No	16 (2.9)	4 (6.1)	1 (0.7)	
Hormone therapy				<0.001
Yes	484 (89.5)	3 (4.5)	6 (4.0)	
No	18 (3.3)	63 (95.5)	144 (96.0)	
Unknown	39 (7.2)	0 (0.0)	0 (0.0)	

HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2; LNs, lymph nodes; IDC, invasive ductal cancer; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; A/T, anthracyclines/taxane; SCF, supraclavicular fossa; TNM, tumor-node-metastasis.

Table II. 5-year outcomes of different subtype breast cancer patients with breast-conserving treatment.

Parameters	Luminal, n (%)	HER2 type, n (%)	TNBC, n (%)	P-value
Total	541 (71.5)	66 (8.7)	150 (19.8)	
LRR				0.005
Yes	13 (2.4)	5 (7.6)	11 (7.3)	
No	528 (97.6)	61 (92.4)	139 (92.7)	
Distant metastases				0.164
Yes	27 (5.0)	7 (10.6)	9 (6.0)	
No	514 (95.0)	59 (89.4)	141 (94.0)	
Total relapse				0.138
Yes	33 (6.1)	8 (12.1)	13 (8.7)	
No	508 (93.9)	58 (87.9)	137 (91.3)	
Mortality				0.007
Yes	12 (2.2)	6 (9.1)	7 (4.7)	
No	529 (97.8)	60 (90.9)	143 (95.3)	

HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; LRR, locoregional recurrence.
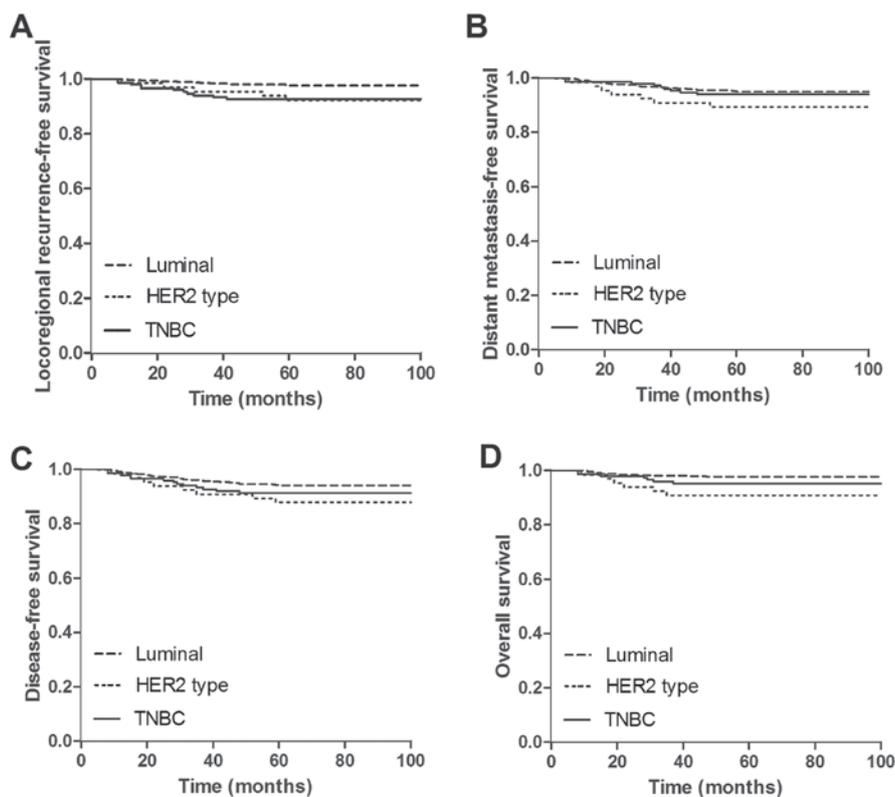

Figure 1. Kaplan-Meier analysis of 5-year survival outcomes of patients with BCT according to different breast cancer subtypes: (A) Locoregional recurrence-free survival; (B) distant metastasis-free survival; (C) disease-free survival and (D) overall survival probabilities. Statistically significant differences between the groups were determined using the log-rank test.

the whole cohort of patients following BCT were evaluated by univariate analysis. The results indicated that margin status (P=0.021), radiation therapy (P=0.031) and hormone therapy (P=0.008) may be associated with LRFS (Table III). Menopausal status (P=0.032), histological grade (P=0.049), margin status (P=0.004), chemotherapy treatment (P=0.001)

and radiotherapy (P<0.001) may be prognostic factors for DMFS. Age at breast cancer diagnosis (P=0.029), histological grade (P=0.018), margin status (P<0.001), chemotherapy treatment (P=0.015), radiation therapy (P<0.001) and hormone therapy (P=0.046) may be associated with DFS. Factors associated with OS may be chemotherapy treatment (P=0.011),

Table III. Univariate analysis of clinicopathological parameters for 5-year LRFS, DMFS, DFS and OS of patients with BCT.

Characteristics	n	LRFS %	LRFS P-value	DMFS %	DMFS P-value	DFS %	DFS P-value	OS %	OS P-value
Age at diagnosis, years			0.054		0.142		0.029		0.256
≤35	118	92.4		92.4		88.1		94.9	
36-55	507	97.0		95.5		94.5		97.4	
>55	132	96.2		91.7		90.9		95.5	
Menopausal status			0.458		0.032		0.075		0.362
Premenopausal	517	96.5		95.6		94.0		97.1	
Postmenopausal	240	95.4		91.7		90.4		95.8	
Number of positive LNs			0.176		0.169		0.071		0.177
0	594	96.5		95.1		93.9		97.3	
1-3	133	96.2		91.0		89.5		94.7	
≥4	30	90.0		93.3		86.7		93.3	
Tumor size, cm			0.120		0.191		0.163		0.225
T1 (≤2)	512	96.1		93.4		92.4		96.3	
T2 (>2, ≤5)	216	97.2		96.8		94.9		98.1	
T3 (>5)	29	89.7		93.1		86.2		93.1	
TNM stage			0.246		0.995		0.502		0.667
I	437	96.1		94.3		93.4		96.8	
II	286	96.9		94.4		92.7		96.9	
III	34	91.2		94.1		88.2		94.1	
Pathological subtype			0.814		0.282		0.553		0.807
IDC	562	96.3		93.8		92.5		96.8	
Other	195	95.9		95.9		93.8		96.4	
Histological grade			0.061		0.049		0.018		0.193
I	127	98.4		98.4		96.9		99.2	
II	466	96.4		93.6		92.7		96.1	
III	97	91.8		90.7		86.6		94.8	
Unknown	67	97.0		97.0		95.5		98.5	
Margin			0.021		0.004		<0.001		0.338
Positive	13	84.6		76.9		61.5		92.3	
Negative	744	96.4		94.6		93.4		96.8	
Chemotherapy			0.558		0.001		0.015		0.011
CMF	133	95.5		92.5		91.0		96.2	
A/T	562	96.6		95.9		94.3		97.5	
Other	22	95.5		81.8		85.0		92.5	
None	40	92.5		85.0		81.8		86.4	
Radiation			0.031		<0.001		<0.001		<0.001
Breast	675	96.4		95.3		94.1		97.2	
Breast and SCF	61	96.7		91.8		88.5		96.7	
No	21	85.7		71.4		66.7		81.0	
Hormone therapy			0.008		0.200		0.046		0.026
Yes	493	97.6		95.3		94.3		98.0	
No	225	92.9		92.0		89.3		94.2	
Unknown	39	97.4		94.9		94.9		94.9	

LRFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival; DFS, disease-free survival; OS, overall survival; BCT, breast-conserving treatment; IDC, invasive ductal cancer; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; A/T, anthracyclines/taxane; SCF, supraclavicular fossa; TNM, tumor-node-metastasis.

Table IV. Multivariate analysis of 5-year risks of LRR and distant metastases of patients with breast-conserving treatment.

	LRR			Distant metastases		
Characteristics	HR	95% CI	P-value	HR	95% CI	P-value
Molecular subtypes						
TNBC	1.000			1.000		
Luminal	0.316	0.043-2.317	0.257	0.767	0.344-1.712	0.517
HER2-enriched	0.937	0.318-2.757	0.906	1.492	0.540-4.126	0.441
Age at diagnosis, years						
≤35	1.000			NA		
36-55	0.407	0.174-0.949	0.037			
>55	0.459	0.143-1.470	0.190			
Menopausal status						
Premenopausal	NA			1.000		
Postmenopausal				1.536	0.770-3.063	0.223
Histological grade						
I	1.000			1.000		
II	2.345	0.534-10.291	0.259	5.064	1.198-21.407	0.027
III	3.595	0.731-17.675	0.115	6.408	1.351-30.397	0.019
Unknown	1.274	0.172-9.440	0.813	1.487	0.202-10.939	0.697
Margin						
Positive	1.000			1.000		
Negative	0.135	0.028-0.647	0.012	0.210	0.059-0.746	0.016
Chemotherapy						
None	NA			1.000		
CMF				1.007	0.295-3.434	0.992
A/T				0.473	0.159-1.403	0.177
Other				1.826	0.479-6.965	0.378
Radiation therapy						
None	1.000			1.000		
Breast	0.178	0.050-0.638	0.008	0.206	0.077-0.554	0.002
Breast and SCF	0.123	0.019-0.805	0.029	0.338	0.090-1.266	0.107
Hormone therapy						
No	1.000			NA		
Yes	1.081	0.152-7.697	0.938			
Unknown	1.119	0.069-18.065	0.937			

LRR, locoregional recurrence; HR, hazard ratio; CI, confidence interval; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2; NA, not applicable; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; A/T, anthracyclines/taxane; SCF, supraclavicular fossa.

radiation therapy (P<0.001) and hormone therapy (P=0.026; Table III).

Multivariate analysis of prognosis of TNBC for patients following BCT within 5 years. Multivariate Cox regression analysis included molecular subtype, age at diagnosis, menopausal status, lymph node status, histological grade, margin status, chemotherapy treatment, radiation and hormone therapy. Compared with patients with TNBC, the luminal subtype was not associated with a significant lower risks in LRR [hazard ratio (HR), 0.316; 95% confidence interval (CI), 0.043-2.317; P=0.257; Table IV)], distant metastasis (HR,

0.767; 95% CI, 0.344-1.712; P=0.517; Table IV), total relapse (HR, 1.623; 95% CI, 0.475-5.539; P=0.440; Table V) or breast cancer mortality (HR, 0.478; 95% CI, 0.080-2.869; P=0.419; Table V). HER2-enriched subtype was also not associated with reduced risks in LRR (HR, 0.937; 95% CI, 0.318-2.757; P=0.906; Table IV), distant metastasis (HR, 1.492; 95% CI, 0.540-4.126; P=0.441; Table IV), total relapse (HR, 1.277; 95% CI, 0.512-3.186; P=0.600; Table V) or breast cancer mortality (HR, 1.602; 95% CI, 0.511-5.023; P=0.419; Table V) when contrasted to that of TNBC group. As a result, TNBC was not an independent prognostic predictor for patients with BCT in the present study.

Table V. Multivariate analysis of 5-year risks of total relapse and breast cancer mortality of patients with breast-conserving treatment.

Characteristics	Total relapse			Breast cancer mortality		
	HR	95% CI	P-value	HR	95% CI	P-value
Molecular subtype						
TNBC	1.000			1.000		
Luminal	1.623	0.475-5.539	0.440	0.478	0.080-2.869	0.419
HER2-enriched	1.277	0.512-3.186	0.600	1.602	0.511-5.023	0.419
Age at diagnosis, years						
≤35	1.000			NA		
36-55	0.359	0.173-0.747	0.006			
>55	0.250	0.078-0.807	0.020			
Menopausal status						
Premenopausal	1.000			NA		
Postmenopausal	2.133	0.972-4.682	0.059			
Number of positive LNs						
0	1.000			NA		
1-3	1.741	0.868-3.490	0.118			
≥4	2.077	0.536-8.050	0.290			
Histological grade						
I	1.000			NA		
II	2.532	0.885-7.247	0.083			
III	3.584	1.121-11.457	0.031			
Unknown	0.836	0.175-3.989	0.823			
Margin status						
Positive	1.000			NA		
Negative	0.117	0.041-0.336	<0.001			
Chemotherapy						
None	1.000			1.000		
CMF	1.331	0.382-4.633	0.653	0.611	0.134-2.784	0.525
A/T	0.723	0.236-2.220	0.571	0.496	0.126-1.960	0.318
Other	2.218	0.564-8.720	0.254	1.877	0.355-9.921	0.458
Radiation therapy						
None	1.000			1.000		
Breast	0.179	0.068-0.471	<0.001	0.219	0.066-0.729	0.013
Breast and SCF	0.174	0.041-0.740	0.018	0.278	0.046-1.672	0.162
Hormone therapy						
No	1.000			1.000		
Yes	0.455	0.147-1.407	0.171	0.812	0.149-4.426	0.810
Unknown	0.326	0.056-1.902	0.213	1.961	0.219-17.577	0.547

Total recurrence referred to locoregional recurrence or distant metastasis. TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; CI, confidence interval; NA, not applicable; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; A/T, anthracyclines/taxane; SCF, supraclavicular fossa.

Other prognostic factors associated with 5-year outcomes for patients with BCT. In multivariate analysis, patients who were aged 36-55 years showed a reduced risk in 5-year LRR compared with patients ≤35 years (P=0.037; Table IV), and both patients aged 36-55 years and patients >55 years showed a inferior risk of total relapse compared with patients ≤35 years

(P<0.05; Tables IV and V). Patients with histological grade II or III tumors exhibited higher risk of distant metastasis (P<0.05; Table IV), and patients with histological grade III tumors also showed an increased risk of total relapse (P=0.031; Table V) compared with patients with histological grade I tumors. Negative margin status was associated with reduced risks of

LRR, distant metastasis and total relapse (P<0.05; Tables IV and V) compared with positive margin status. Patients performed radiation therapy presented decreased risks in LRR, distant metastasis, total relapse and breast cancer mortality compared with patients without radiation therapy (Tables IV and V).

Discussion

The associations between breast cancer types with different gene expression profiles and the prognosis of patients have recently been investigated (23). TNBC confers a poor clinical outcome to patients following BCT (24). Basal-like subtype has also been reported to be associated with an increased risk of local relapse and distant metastasis following BCT (15). Although basal-like subtype and TNBC are different breast cancer subtypes, it has been widely accepted that TNBC and basal-like breast tumors are synonymous (7).

In the current study, it was demonstrated that patients with TNBC presented different clinicopathological parameters compared with patients with luminal and HER2-enriched breast cancer. Patients with TNBC tended to have relatively high histological grades of tumor compared with luminal and HER2-enriched breast cancer patients. Consistent with this finding, previous studies have also reported that TNBC was more frequently associated with a higher histological grade (8,24). Selection of chemotherapy treatment also differed between the 3 groups. The proportion of the patients that received chemotherapy was higher in the TNBC group than in other groups, which was consistent with the results of a previous study (25). Besides, patients with TNBC tended to choose anthracycline/taxane based chemotherapy regimens in the present study, although Kim et al (26) did not find similar results among luminal, HER2-enriched and TNBC groups.

However, there was no significant difference in prognosis between patients with TNBC and patients with luminal and HER2 subtypes following BCT. In the present study, the results of univariate analysis revealed that patients in the HER2-enriched subtype group exhibited reduced 5-year LRFS and OS, and rates of LRR and mortality were relatively high compared with the luminal and TNBC groups (i.e. the prognosis of patients with TNBC was not the poorest). Furthermore, results of multivariate analysis in our study indicated that TNBC was not associated with increased risks of 5-year LRR, distant metastasis, total relapse and mortality for patients with BCT. Similar to the present study, Gangi A et al (19) observed that TNBC was not associated with an increased rate of 5-year local relapse compared with non-TNBC subtypes in a retrospective study of 1851 patients with BCT. Additionally, Freedman et al (27) reported that the isolated 5-year LRR rate for patients with BCT was not different according to different breast cancer subtypes, and it was observed that there was a significantly higher rate of mortality in the HER2-enriched group compared with other subtypes. Findings in the present study indicated that HER2-enriched tumor was not an independent prognostic predictor for patients with BCT. The high rates of LRR and mortality in HER2-enriched subtype may be attributed to a small proportion of patients with positive HER2 status that had received trastuzumab therapy. Another reason for these high

rates might be that young patients (≤35 years) who appeared to have a poorer prognosis (as confirmed in the present study) tended to be assigned to the HER2-enriched group and not the TNBC group. Noh et al (25) also demonstrated that despite the observation that TNBC and HER2-enriched subtypes were associated with younger age and higher histological grade, the rates of LRR and distant recurrence were not significantly different according to different molecular subtypes of breast cancer in patients following BCT.

To the best of our knowledge, the outcomes of TNBC patients with BCT remain contradictory. Solin et al (16) investigated 519 patients treated with BCT, and reported that patients with TNBC had an increased risk of local failure but a reduced risk of distant metastasis compared with other breast cancer subtypes. On the contrary, another investigation demonstrated that the TNBC subtype was associated with a higher risk of distant metastasis and mortality but was not associated with significantly higher rates of local relapse compared with other subtype (17). Kaplan et al (24) reported that patients with TNBC at a low risk of LRR had a significantly higher risk of distant metastasis compared with hormone receptor-positive/HER2-negative patients. Additionally, Braunstein et al (28) observed that TNBC was associated with reduced DFS following BCT in a retrospective study, which included 2,233 women who underwent BCT. In general, the issues regarding the role of TNBC in BCT remain unresolved. Encouragingly, the investigators have reported that TNBC patients with BCT had significantly lower LRR rate compared with patients treated with mastectomy (29). Results from a prospective randomized controlled multi-center trial indicate that for patients with TNBC following BCT, radiotherapy and chemotherapy exhibited significantly improved 5-year DFS and OS compared with those that received chemotherapy alone (30). Together with the findings from the previously mentioned reports and results from our study, patients with TNBC may remain appropriate candidates for BCT.

To date, publications evaluating the prognostic value of TNBC in BCT, demonstrated mixed results. There may be a number of reasons to account of these inconsistencies in findings. The term 'TNBC' has been used interchangeably with 'basal-like tumor'. The majority of TNBC are basal-like breast cancers, and the majority of basal-like tumors are also TNBC, which means that there is a considerable overlap between TNBC and basal-like tumors (31,32). Additionally, TNBC has been subdivided into six distinct subtypes based on expression of various genes, including two basal-like subtypes, one with cell-cycle and DNA-damage-response gene expression signatures and the other enriched in growth factor signaling and myoepithelial markers; one immunomodulatory subtype; two mesenchymal subtypes with high expression of genes involved in differentiation and growth factor pathways; and one luminal androgen receptor subtype driven by androgen signaling (4,33). For certain TNBC subtypes, mastectomy may lead to improved long-term outcomes compared with BCT (34). However, few studies differentiate basal-like subtype tumors from TNBC or clearly define the distinct TNBC subtypes (32,35), which may result in contradictory outcomes following BCT reported in studies investigating patients with TNBC.

There are a number of limitations to the present study. Firstly, similar to other publications, owing to the limitations

of detection techniques, examination instrumentation and cost, TNBC was not distinguished from basal-like tumors, and TNBC was used as a surrogate to represent the basal-like category of breast cancer, which may confound the results of our investigation to some extent. Secondly, the immunostaining data did not classify TNBC into detailed subtypes in the present study. Thirdly, we acknowledge other limitations, including the retrospective study design, small sample size used and short follow-up periods. Finally, other unbalanced confounding factors between groups, including hormone therapy regimen, economic conditions, smoking, alcohol consumption, obesity and chronic disease, were also potential limitations. As a result, the contribution of the present study to the investigation of molecular subtypes in breast cancer may be limited.

In conclusion, the data in the present study suggests that the clinicopathological characteristics of TNBC differ from luminal and HER2-enriched subtypes. TNBC patients treated with BCT did not have a significantly increased risk of recurrence or mortality, and patients with TNBC may remain appropriate candidates for BCT. However, detailed molecular taxonomy and prospective randomized clinical trials are required.

Acknowledgements

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