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Triple-Negative Breast Cancer Is Not a Contraindication for Breast Conservation

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ABSTRACT

Background. Triple-negative breast cancer (TNBC) is an aggressive subtype shown to have a high risk of locoregional recurrence (LRR). The purpose of this study was to determine the impact of operation type on LRR in TNBC patients.

Methods. A total of 1325 patients with TNBC who underwent breast-conserving therapy (BCT) or mastectomy from 1980 to the present were identified. Clinical and pathological factors were compared by the chi-square test. LRR-free survival (LRRFS), distant metastasis-free survival, and overall survival were estimated by the Kaplan–Meier method. Multivariate analysis was performed by the Cox proportional hazard models.

Results. BCT was performed in 651 patients (49%) and mastectomy in 674 (51%). The mastectomy group had larger tumors, a higher incidence of lymphovascular invasion, and higher pathologic N stage (all $P < 0.001$). At 62-month median follow-up, LRR was seen in 170 (26%) in the BCT group and 203 (30%) in the mastectomy group. Five-year LRRFS rates were higher in the BCT group (76% vs. 71%, $P = 0.032$), as was distant metastasis-free survival (68% vs. 54%, $P < 0.0001$) and overall survival (74% vs. 63%, $P < 0.0001$). On multivariate analysis, T stage (hazard ratio [HR] 1.37, $P = 0.006$), high nuclear grade (HR 1.92, $P = 0.002$), lymphovascular invasion (HR 1.93, $P < 0.0001$), close/positive margins (HR 1.89, $P < 0.0001$), and use of non–anthracycline or taxane-based adjuvant chemotherapy (HR 2.01, $P < 0.0001$) increased the LRR risk, while age >50 years was protective (HR 0.73, $P = 0.007$). Operation type (mastectomy vs. BCT, HR 1.07, $P = 0.55$) was not statistically significant.

Conclusions. BCT is not associated with increased LRR rates compared to mastectomy. TNBC should not be considered a contraindication for breast conservation.

Molecular profiling has expanded our knowledge regarding the heterogeneity of breast cancer and has identified several distinct breast cancer subgroups: those that overexpress luminal A, luminal B, and HER2; and basal-like disease.[1,2] Clinically, however, breast cancers are more frequently grouped according to the expression of three commonly tested markers: estrogen receptor (ER), progesterone receptor (PR); and human epidermal growth factor receptor 2 (HER2). Triple-negative breast cancers (TNBC) are breast tumors that lack the expression of these common tumor markers; they make up approximately 15% of breast cancers.[3,4] When combined with expression profiling data, TNBC most frequently represent basal-like tumors, but they can also characterize claudin-low tumors, which express low levels of tight and adherens junction proteins and frequently have an epithelial-mesenchymal transition-like signature.[5]

Although targeted therapies have been developed for tumors that express ER, PR, or HER2, treatment for tumors that lack these markers remains challenging. Compounding this is the observation that TNBC demonstrate more aggressive clinical features than other subtypes. These tumors are frequently found to have a higher tumor grade, higher proliferation with increased Ki-67 staining, higher

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expression of basal cytokeratins and p53, and a higher association with *BRCA1* mutations.[4,6–9] After treatment, rates of locoregional recurrence (LRR), distant metastasis, and overall survival (OS) are negatively affected by the triple-negative phenotype.[10–15]

Given the aggressive nature of these tumors, it is reasonable to question whether a more aggressive surgical approach is warranted to improve patient outcomes. Reports are conflicting with some suggesting that breast-conserving therapy (BCT) confers an increased risk of LRR, while other reports suggest that the risk of LRR is not greatly increased by this therapy.[10,11,16,17] The purpose of this study was to evaluate the impact of operation type (BCT vs. mastectomy) on LRR in TNBC. We hypothesized that, in appropriately selected patients, BCT would not be associated with an increase in LRR.

METHODS

Patient Selection

The Breast Cancer Management System database at the University of Texas M. D. Anderson Cancer Center is a retrospectively initiated, prospectively maintained database of patients evaluated and treated for breast cancer. We used this database to identify all patients with ER-negative, PR-negative, HER2-negative primary breast cancers diagnosed at M. D. Anderson between December 1980 and December 2007 who underwent primary surgery with either BCT or mastectomy and received adjuvant chemotherapy. Patients receiving neoadjuvant chemotherapy were excluded from analysis as were patients with incomplete information regarding tumor size or receptor status. A total of 1329 patients were identified; 4 patients who had less than 6 months follow-up time were excluded from analysis. Patients were categorized according to the type of surgical intervention received (BCT or mastectomy) for further analysis.

At our institution, neoadjuvant chemotherapy is generally offered to patients whose primary tumor at initial presentation is large enough to preclude breast conservation, but has the potential to be downsized by neoadjuvant therapy and the woman desires breast conservation over mastectomy. In addition, patients with clinically positive nodes and tumor size >2 cm are offered neoadjuvant chemotherapy as an option.

Decisions regarding adjuvant chemotherapy are also made on an individualized basis and determined by the patient's nodal status and tumor size. Patient age and comorbidities are also considered. Generally, patients with favorable features (subcentimeter tumors with no nodal involvement) did not receive adjuvant chemotherapy. In most cases, patients receiving anthracycline-based chemotherapy regimens were treated with FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) or FEC (5-fluorouracil, epirubicin, and cyclophosphamide). Patients receiving taxane-based chemotherapy regimens were treated with paclitaxel or docetaxel as single-agents, or more commonly as combinational therapy with FAC or FEC. Patients who were treated with neither anthracyclines nor taxanes most frequently received CMF (cyclophosphamide, methotrexate, and 5-fluorouracil).

Patients presenting with locally advanced disease or with axillary node involvement were evaluated with a metastatic examination, including bone scan, chest X-ray, and abdominal computed tomographic scan. During follow-up, patients underwent a metastatic examination as indicated by symptoms, or at the diagnosis of LRR.

Pathologic Analysis

Primary tumors were staged according to the American Joint Committee on Cancer criteria. Immunohistochemical (IHC) analysis of ER and PR status as well as evaluation of HER2 status by IHC or fluorescence in situ hybridization were performed as previously reported.[18] Patients with ≤10% ER/PR staining on IHC were considered to be ER/PR negative. Surgical margins <2-mm were considered close, tumor at margins (tumor on ink) was considered positive. Patients with margins of <2 mm underwent reexcision to achieve widely negative result when cosmetically feasible.

Statistical Analysis

Patients were categorized according to the type of surgical intervention received. Patient characteristics including age, race, menopausal status, tumor size, nodal status, pathologic stage, nuclear grade, presence of lymphovascular invasion (LVI), resection margins, type of recurrence (locoregional or distant), adjuvant radiation, date of surgery (1980–2000 vs. 2001–2007), and adjuvant chemotherapy type were assessed in both groups and compared by Chi-square test, or t-test as appropriate.

Locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), and OS were measured from the date of definitive surgery to the date of the first documented LRR, distant metastasis, or death, respectively; patients not experiencing the relevant end point were censored at last follow-up. As a result of heterogeneity between groups, 5-year LRRFS, DMFS, and OS were calculated by stage of disease by the Kaplan–Meier product limit method by groups; groups were compared with the log-rank statistic. Five-year LRRFS rates were separately

estimated within BCT and mastectomy groups. Cox proportional hazard models were fit to determine the association of the operative treatment with survival outcomes after adjustment for other patient and disease characteristics. Factors that had significant univariate associations with survival outcomes were included in the models. Final models included operative treatment, age, tumor size, nodal status, grade, LVI, resection margins, and adjuvant chemotherapy type. Test for proportional hazard assumption were carried out by using product terms between operative treatment and time in Cox regression models, and assumptions were met. Results are expressed as hazard ratio (HR) and 95% confidence interval (CI). *P*-values of <0.05 were considered statistically significant; all tests were two-sided. Statistical analyses were carried out by SAS software, version 9.1 (SAS Institute, Cary, NC) and S-Plus 7.0 (Insightful, Seattle, WA).

RESULTS

A total of 1325 patients with TNBC who underwent primary surgery were identified. Patient and clinical characteristics are described in Table 1. Overall, the mean age at diagnosis was 48 years. Overall mean tumor size was 2.5 cm with a median of 2.1 cm. The majority (89%) of patients had high nuclear grade (grade III) tumors, and 93% had negative resection margins.

A total of 651 (49%) underwent BCT while 674 (51%) underwent mastectomy. Age at diagnosis, menopausal status, tumor grade, resection margins, and type of adjuvant chemotherapy received were not statistically significantly different between the two groups. Compared to the BCT group, the mastectomy group had a significantly greater mean tumor size (2.9 cm vs. 2.1 cm; $P < 0.0001$), higher T-stage (T3/4 = 11% vs. 2%; $P < 0.0001$), higher N-stage tumors (N1–3 = 57% vs. 39%; $P < 0.0001$), more stage III disease (14% vs. 3%; $P < 0.0001$), higher proportion of LVI (40% vs. 25%; $P < 0.0001$). Ninety-seven percent of the patients in the BCT group received adjuvant radiation compared to 33% of patients in the mastectomy group ($P < 0.0001$). Of the 20 patients (3%) in the BCT group who did not receive adjuvant radiation, 5 patients refused adjuvant radiation, 2 patients had unknown reasons, 1 had received previous radiation for Hodgkin's lymphoma, and 13 developed a LRR or distant metastasis before beginning planned adjuvant radiation.

Overall 28% of patients had LRR, 43% had distant metastasis, and 45% had both LRR and distant metastasis. Compared to patients in the BCT group, patients in the mastectomy group had a comparable LRR (30% vs. 26%, $P = 0.10$) but a higher rate of distant recurrence (51% vs. 35%, $P < 0.0001$).

Locoregional Recurrence

The median follow-up among all patients was 62 months (range 1–285 months). A total of 373 women had LRR, 26% ($n = 170$) of patients undergoing BCT, and 30% ($n = 203$) undergoing mastectomy (Table 2). Among patients which developed LRR, the median time to LRR was 2.0 years in the BCT group and 1.7 years in the mastectomy group. Kaplan–Meier analysis of LRRFS stratified by stage is shown in Fig. 1a.

Univariate log-rank testing demonstrated that older age, small tumor size, negative nodal status, lower grade, negative/unknown LVI, and negative margins were associated with better LRRFS (all $P \leq 0.001$) (Table 2). Multivariate Cox proportional hazard modeling (Table 3) indicates that operative treatment was not an independent predictor of LRRFS (HR 1.07; 95% CI 0.86 to 1.34; $P = 0.55$). Other factors remained significant after adjustment except for nodal status ($P = 0.11$). Patients receiving adjuvant chemotherapy omitting both anthracyclines and taxanes demonstrated a worse LRRFS compared to anthracycline or taxane-based chemotherapy regimens ($P < 0.0001$).

Among BCT patients, similarly significant univariate association existed between LRRFS and factors examined among all patients although those by tumor size ($P = 0.005$) and grade ($P = 0.029$) became weaker. Consequently, after multivariate adjustment, tumor size ($P = 0.07$) and grade ($P = 0.05$) were not significant. Among mastectomy patients, age and nodal status were not predictive of LRRFS from either univariate or multivariate analyses. When adjuvant radiation was included in multivariate analysis of the mastectomy group, radiation treatment was not found to significantly impact LRRFS ($P = 0.19$), while significance of other factors remained unchanged (data not shown).

Distant Metastases

A total of 572 women had distant metastases, 35% ($n = 230$) of patients in the BCT group, and 51% ($n = 342$) of patients undergoing mastectomy (Table 4). Among patients which developed DM, the median time to distant recurrence was 2.1 years in the BCT group and 2.0 years in the mastectomy group. Kaplan–Meier analysis of DMFS as stratified by stage is shown in Fig. 1b. After multivariate adjustment, BCT was significantly associated with better DMFS (mastectomy HR 1.32; 95% CI 1.10 to 1.59; $P = 0.003$) (Table 5). Similarly, older age, small tumor size, negative nodal status, negative/unknown LVI, negative margins, anthracycline and/or taxane-based adjuvant chemotherapy were predictive of better DMFS in both univariate and multivariate analysis.

TABLE 1 Patient and clinical characteristics by operative treatment

Characteristic	All patients ($n = 1325$) n (%)	BCT ($n = 651$)		Mastectomy ($n = 674$)		P-value
		n	%	n	%	
Age at diagnosis, y						
Mean	48	48		47		0.33[a]
Race						
Nonblack	1140 (86%)	547	84.0	593	88.0	
Black	185 (14%)	104	16.0	81	12.0	0.04
Menopausal status						
Pre	630 (47.5%)	299	45.9	331	49.1	
Post	695 (52.5%)	352	54.1	343	50.9	0.25
Tumor size						
Mean	2.5	2.1		2.9		<0.0001[a]
Median	2.1	2.0		2.5		
Range	0.1–19	0.1–12		0.2,19		
T1	642 (48.5%)	385	59.1	257	38.1	
T2	597 (45.1%)	254	39.0	343	50.9	
T3/4	86 (6.5%)	12	1.8	74	11.0	<0.0001
N stage						
N0	687 (51.8%)	400	61.4	287	42.6	
N1	430 (32.5%)	191	29.3	239	35.5	
N2	127 (9.6%)	38	5.8	89	13.2	
N3	81 (6.1%)	22	3.4	59	8.8	<0.0001
Pathologic stage						
I	422 (31.8%)	268	41.2	154	22.8	
II	793 (59.8%)	365	56.1	428	63.5	
III	110 (8.3%)	18	2.8	92	13.6	<0.0001
Nuclear grade						
I or II	144 (11.5%)	67	10.8	77	12.1	
III	1111 (88.5%)	554	89.2	557	87.9	0.45
LVI						
Negative/unknown	888 (67.6%)	488	75.3	400	60.1	
Positive	426 (32.4%)	160	24.7	266	39.9	<0.0001
Resection margins						
Free	1210 (92.8%)	585	91.5	625	94.0	
Positive	34 (2.6%)	19	3.0	15	2.3	
Close	60 (4.6%)	35	5.5	25	3.8	0.23
Surgical date						
1980–2000	715 (54%)	325	49.9	390	57.9	
2000–2007	610 (46%)	326	50.1	284	42.1	0.004
LRR						
No	952 (71.8%)	481	73.9	471	69.9	
Yes	373 (28.2%)	170	26.1	203	30.1	0.11
Distant recurrences						
No	753 (56.8%)	421	64.7	332	49.3	
Yes	572 (43.2%)	230	35.3	342	50.7	<0.0001
Adjuvant radiation						
No	471 (35.6%)	20	3.1	451	66.9	
Yes	852 (64.4%)	629	96.9	223	33.1	<0.0001

TABLE 1 continued

Characteristic	All patients ($n = 1325$) n (%)	BCT ($n = 651$)		Mastectomy ($n = 674$)		P-value
		n	%	n	%	
Adjuvant chemotherapy						
Anthracycline based	611 (46.1%)	310	47.6	301	44.7	
Taxane based	27 (2%)	14	2.2	13	1.9	
Anthracycline + taxane based	521 (39.3%)	245	37.6	276	40.9	
Non-anthracycline/taxane based	166 (12.5%)	82	12.6	84	12.5	0.65

[a] Two-sample t-test

TABLE 2 Five-year LRRFS estimates by patient and clinical characteristics

Characteristic	All patients			BCT ($n = 651$)			Mastectomy ($n = 674$)		
	n	5-Year estimate (95% CI)	P-value	n	5-Year estimate (95% CI)	P-value	n	5-Year estimates (95% CI)	P-value
All	1325	0.73 (0.7, 0.76)		651	0.76 (0.72, 0.79)		674	0.71 (0.67, 0.74)	0.032
Age									
≤50 years	813	0.71 (0.67, 0.74)		393	0.72 (0.67, 0.76)		420	0.69 (0.64, 0.74)	
>50 years	512	0.77 (0.73, 0.81)	0.001	258	0.81 (0.75, 0.86)	0.003	254	0.73 (0.66, 0.78)	0.14
Race									
Nonblack	1140	0.73 (0.7, 0.76)		547	0.76 (0.72, 0.79)		593	0.71 (0.66, 0.74)	
Black	185	0.73 (0.65, 0.79)	0.65	104	0.75 (0.64, 0.83)	0.70	81	0.71 (0.59, 0.8)	0.69
Tumor size									
T1	642	0.78 (0.74, 0.81)		385	0.79 (0.74, 0.83)		257	0.77 (0.71, 0.82)	
T2–4	683	0.69 (0.65, 0.72)	<0.0001	266	0.71 (0.65, 0.77)	0.005	417	0.67 (0.61, 0.71)	0.002
Lymph nodes									
N0	687	0.77 (0.74, 0.8)		400	0.8 (0.75, 0.84)		287	0.73 (0.67, 0.78)	
N1–3	638	0.69 (0.65, 0.72)	<0.0001	251	0.69 (0.62, 0.74)	<0.0001	387	0.69 (0.63, 0.73)	0.10
Nuclear grade									
I or II	144	0.86 (0.79, 0.91)		67	0.88 (0.77, 0.94)		77	0.85 (0.74, 0.92)	
III	1111	0.71 (0.68, 0.74)	0.001	554	0.74 (0.70, 0.77)	0.029	557	0.68 (0.64, 0.72)	0.012
LVI									
Negative/unknown	888	0.8 (0.77, 0.82)		488	0.81 (0.77, 0.84)		400	0.78 (0.74, 0.82)	
Positive	426	0.58 (0.53, 0.63)	<0.0001	160	0.59 (0.5, 0.66)	<0.0001	266	0.59 (0.52, 0.65)	<0.0001
Resection margins									
Free	1210	0.75 (0.72, 0.77)		585	0.78 (0.74, 0.81)		625	0.72 (0.68, 0.75)	
Positive/close	94	0.54 (0.43, 0.64)	<0.0001	54	0.55 (0.40, 0.68)	<0.0001	40	0.54 (0.37, 0.68)	0.007
Surgical date									
1980–2000	715	0.74 (0.7, 0.77)		325	0.75 (0.69, 0.79)		390	0.73 (0.68, 0.78)	
2000–2007	610	0.72 (0.68, 0.76)	0.58	326	0.77 (0.71, 0.81)	0.52	284	0.66 (0.6, 0.72)	0.10
Adjuvant radiation									
No	471	0.7 (0.65, 0.74)		20	0.24 (0.08, 0.44)		451	0.72 (0.67, 0.76)	
Yes	852	0.75 (0.72, 0.78)	0.009	629	0.77 (0.74, 0.80)	<0.0001	223	0.68 (0.61, 0.74)	0.58
Adjuvant chemotherapy									
Anthracycline + taxane based	521	0.72 (0.68, 0.76)		245	0.75 (0.69, 0.8)		276	0.69 (0.63, 0.75)	
Anthracycline or taxane based	638	0.76 (0.72, 0.79)		324	0.77 (0.72, 0.81)		314	0.75 (0.70, 0.80)	
Non-anthracycline/taxane based	166	0.65 (0.57, 0.72)	0.01	82	0.72 (0.6, 0.81)	0.70	84	0.58 (0.46, 0.69)	0.002

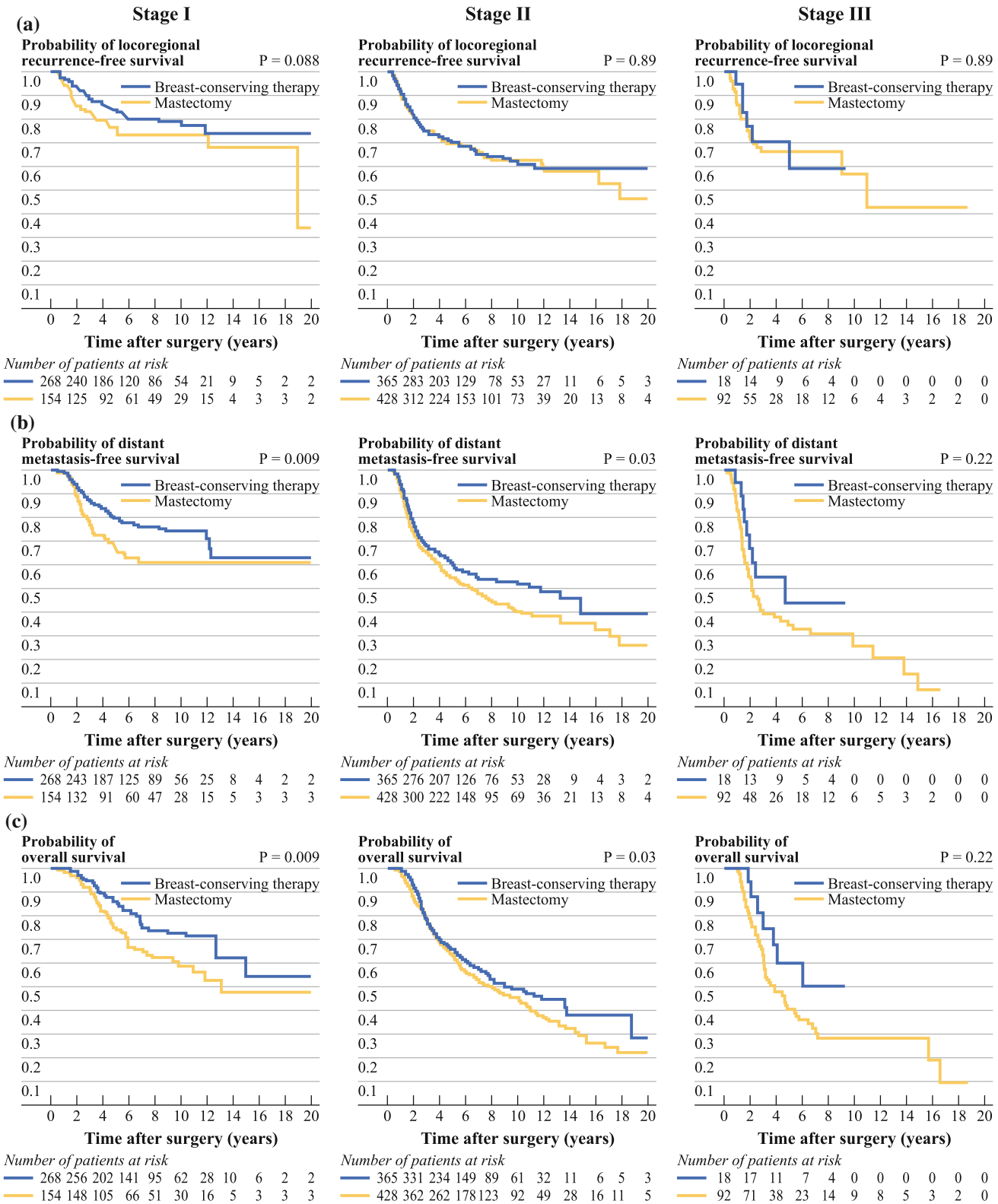

FIG. 1 Kaplan–Meier estimates of LRRFS (**a**), DMFS (**b**), and OS (**c**) by operative treatment (BCT vs. mastectomy) within stage I, II, and III disease

TABLE 3 Multivariate Cox proportional hazard model for LRRFS

Characteristic	All patients			BCT			Mastectomy		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Mastectomy vs. BCT	1.07	0.86 to 1.34	0.55						
Age: >50 vs. ≤ 50 years	0.73	0.58 to 0.92	0.007	0.66	0.46 to 0.92	0.016	0.79	0.58 to 1.07	0.13
Tumor size: T2–4 vs. T1	1.37	1.09 to 1.72	0.006	1.35	0.98 to 1.86	0.07	1.39	1 to 1.92	0.048
Lymph nodes: N1–3 vs. N0	1.21	0.96 to 1.53	0.11	1.48	1.05 to 2.07	0.025	1.02	0.73 to 1.42	0.91
Grade: III vs. I/II	1.92	1.28 to 2.89	0.002	1.89	0.99 to 3.63	0.05	1.94	1.15 to 3.27	0.013
LVI: positive vs. negative/unknown	1.93	1.54 to 2.42	<0.0001	2.00	1.43 to 2.79	<0.0001	1.99	1.46 to 2.71	<0.0001
Resection margin: close/positive vs. free	1.89	1.37 to 2.6	<0.0001	2.02	1.32 to 3.1	0.001	1.86	1.14 to 3.03	0.013
Adjuvant chemotherapy: anthracycline or taxane vs. anthracycline + taxane	1.02	0.80 to 1.30	0.88	1.31	0.91 to 1.87	0.14	0.85	0.61 to 1.18	0.32
Adjuvant chemotherapy: other vs. anthracycline + taxane	2.01	1.46 to 2.77	<0.0001	1.72	1.03 to 2.89	0.038	2.24	1.47 to 3.4	0.0002

Overall Survival

There were a total of 562 deaths, 227 (35%) in the BCT group, and 335 (50%) in the mastectomy group. Kaplan–Meier analysis of OS stratified by stage is shown in Fig. 1c. After multivariate adjustment, the association between operative treatment and OS remained significant (mastectomy HR 1.22; 95% CI 1.02 to 1.47; $P = 0.032$) (Table 5). On multivariate analyses, smaller tumor size, negative nodal status, lower grade, and negative/unknown LVI were also predictive of better OS.

DISCUSSION

BCT with adjuvant radiation has become the standard of care for the treatment of invasive breast cancer in appropriately selected patients with early-stage disease. Within the last 30 years, several randomized-controlled trials have demonstrated that BCT has equivalent long-term outcomes when compared to mastectomy.[19–27] Local recurrence rates for BCT in these studies have ranged 3–20%, compared to 2–14% in those receiving mastectomy. The most common reasons for this LRR are thought to be poor patient selection, inadequate surgery or radiotherapy, or biologically aggressive disease. TNBCs have been shown to be biologically aggressive, and have been demonstrated to have higher LRR rates. In the current study we have shown that despite this aggressive nature, a more aggressive surgical approach is not warranted as the risk of LRR was not greatly affected by type of surgery.

Previous studies have evaluated patterns of recurrence after BCT in patients with TNBC. Nguyen et al. reviewed 793 patients who underwent BCT and determined that 89 patients with TNBC had significantly higher risk of local recurrence (adjusted HR 7.1; $P = 0.009$) than other less aggressive subtypes.[10] They also found that TNBC patients had a greater risk of distant metastasis (adjusted HR 2.3; $P = 0.035$). Similarly, Solin et al. reviewed outcomes after BCT in 519 patients and found that 90 patients with TNBC had a higher 8-year rate of local recurrence (8% vs. 4%; $P = 0.041$) and a lower 8-year rate of freedom from distant metastasis (81% vs. 92%; $P = 0.0066$) than those patients with other breast cancer subtypes.[11]

In contrast, a report by Haffty et al. demonstrated no statistically significant difference in 5-year breast-relapse free survival between TNBC patients and non-TNBC patients (83% vs. 83%, $P = $ NS).[17] In this study, 117 of 482 patients were classified as being negative for TNBC. A marginally significant difference was demonstrated in 5-year nodal-relapse free survival (94% vs. 99%, $P = 0.05$) and a significant difference was shown in 5-year DMFS (68% vs. 83%, $P = 0.002$). A study by Freedman et al. also failed to demonstrate a significant difference in 5-year LRR in a cohort of TNBC patients when compared to hormone-receptor-positive or HER2-positive patients (3.2% vs. 2.3% and 4.6% respectively; $P = 0.36$).[16]

Although the above studies directly looked at recurrence in TNBC after BCT, only one recent study has sought to compare outcomes of TNBC patients undergoing BCT or mastectomy. Parker et al. reviewed 202 patients with TNBC who underwent BCT ($n = 61$) or mastectomy ($n = 141$).[28] Five-year disease-free survival for those in the BCT group was estimated at 68% vs. 57% for those in the mastectomy group ($P = 0.14$). Five-year OS estimates, however, were significantly better for the BCT group (89% vs. 69%, $P = 0.018$). Consistent with the current study,

TABLE 4 Five-year survival estimates by patient and clinical characteristics

Characteristic	*n*	DMFS		OS	
		5-Year estimate (95% CI)	*P*-value	5-Year estimate (95% CI)	*P*-value
All	1325	0.61 (0.58, 0.64)		0.68 (0.66, 0.71)	
Operative treatment					
BCT	651	0.68 (0.64, 0.71)		0.74 (0.7, 0.77)	
Mastectomy	674	0.54 (0.50, 0.58)	<0.0001	0.63 (0.59, 0.67)	<0.0001
Age					
≤50 years	813	0.58 (0.55, 0.62)		0.67 (0.63, 0.7)	
>50 years	512	0.66 (0.61, 0.7)	0.001	0.71 (0.66, 0.75)	0.44
Race					
Nonblack	1140	0.61 (0.58, 0.64)		0.69 (0.66, 0.71)	
Black	185	0.61 (0.53, 0.68)	0.79	0.66 (0.58, 0.72)	0.12
Tumor size					
T1	642	0.71 (0.67, 0.75)		0.78 (0.74, 0.81)	
T2–4	683	0.51 (0.47, 0.55)	<0.0001	0.59 (0.56, 0.63)	<0.0001
Lymph nodes					
N0	687	0.7 (0.66, 0.73)		0.78 (0.74, 0.81)	
N1–3	638	0.52 (0.48, 0.56)	<0.0001	0.58 (0.54, 0.62)	<0.0001
Nuclear grade					
I or II	144	0.68 (0.59, 0.75)		0.75 (0.67, 0.82)	
III	1111	0.60 (0.57, 0.63)	0.10	0.67 (0.64, 0.69)	0.02
LVI					
Negative/unknown	888	0.69 (0.66, 0.72)		0.75 (0.71, 0.78)	
Positive	426	0.44 (0.39, 0.49)	<0.0001	0.55 (0.5, 0.6)	<0.0001
Resection margins					
Free	1210	0.62 (0.59, 0.65)		0.69 (0.66, 0.72)	
Positive/close	94	0.48 (0.37, 0.58)	0.001	0.58 (0.47, 0.68)	0.013
Surgical date					
1980–2000	715	0.60 (0.56, 0.63)		0.69 (0.66, 0.73)	
2000–2007	610	0.63 (0.59, 0.67)	0.35	0.67 (0.63, 0.71)	0.10
Adjuvant radiation					
No	471	0.58 (0.54, 0.63)		0.65 (0.6, 0.69)	
Yes	852	0.62 (0.59, 0.66)	0.054	0.70 (0.67, 0.74)	0.048
Adjuvant chemotherapy					
Anthracycline and taxane based	521	0.58 (0.53, 0.62)		0.63 (0.59, 0.67)	
Anthracycline or taxane based	638	0.66 (0.62, 0.7)		0.72 (0.69, 0.76)	
Non-anthracycline/taxane based	166	0.53 (0.45, 0.61)	<0.0001	0.69 (0.61, 0.76)	0.002

multivariate analysis did not identify surgical approach to have a significant effect on disease-free survival (adjusted HR 0.84, $P = 0.60$).

Of interest in the current study is the finding that adjuvant radiotherapy did not have a marked impact on LRRFS in the mastectomy group. This would seem to conflict with consensus within the literature in which postmastectomy radiotherapy was prospectively shown to decrease LRR rates in high-risk patients.[29,30] Recent reports have suggested that this improvement also extends to patients with TNBC.[31,32] The time range included in the current cohort reflects an era during which attitudes about and indications for postmastectomy radiotherapy have been in evolution, including within our institution. As such, the group studied may not accurately reflect the impact of such therapy on LRR as managed by current protocols. It also is possible that high-risk patients were more likely to receive postmastectomy radiation, and multivariate analysis may not be able to control for these biases in patient selection for differing therapy.

TABLE 5 Multivariate Cox proportional hazard model for survival

Characteristic	DMFS			OS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Mastectomy vs. BCT	1.32	1.1 to 1.59	0.003	1.22	1.02 to 1.47	0.032
Age: >50 vs. ≤ 50	0.74	0.61 to 0.89	0.001	0.93	0.77 to 1.11	0.40
Tumor size: T2–4 vs. T1	1.63	1.35 to 1.97	<0.0001	1.66	1.38 to 2.01	<0.0001
Lymph nodes: N1–3 vs. N0	1.44	1.19 to 1.75	0.0002	1.45	1.20 to 1.77	0.0002
Grade: III vs. I/II	1.25	0.95 to 1.66	0.11	1.36	1.03 to 1.80	0.031
LVI: positive vs. negative/unknown	1.62	1.35 to 1.94	<0.0001	1.56	1.30 to 1.87	<0.0001
Resection margin: close/positive vs. free	1.49	1.12 to 1.98	0.006	1.29	0.96 to 1.73	0.09
Adjuvant chemotherapy: anthracycline or taxane vs. anthracycline + taxane	0.90	0.74 to 1.09	0.29	0.90	0.74 to 1.10	0.30
Adjuvant chemotherapy: other vs. anthracycline + taxane	1.68	1.29 to 2.19	0.0001	1.40	1.06 to 1.84	0.017

The current study has other limitations. The LRR rates reported here (26% in BCT group; 30% in mastectomy group) are somewhat high relative to both historic and more modern series. In an effort to optimize follow-up, we have included patients treated in the 1980 s and 1990 s; however, there have been several changes in our treatment algorithms over the past few decades. In the mastectomy group, there were a relatively low proportion of patients who received adjuvant radiotherapy (33%) as discussed above. Although TNBC alone has not been validated as an indication for adjuvant radiotherapy in this group, several trials have demonstrated improvement in LRR rates for radiotherapy after mastectomy in the setting of node-positive disease (58% of the current cohort).[33] There have also been changes in systemic therapy, with increasing use of taxanes as well as anthracyclines in the latter part of the series. Further, there has been improvement in breast imaging, with introduction of digital mammography, breast MRI, and routine use of ultrasound. In general, fewer than 10% of breast cancer patients at our institution undergo breast MRI, and this modality is generally reserved for screening in high risk patients (e.g., lifetime breast cancer risk >20%; genetic predisposition such as *BRCA1/2* mutation; prior breast irradiation).[34]

In order to have accurate pathologic variables, we have limited our study to patients who had surgery first. Eliminating patients that received neoadjuvant therapy from the study may have introduced bias into our cohort by limiting our study to lower-risk patients. On the other hand, to minimize variability in systemic therapy, we limited our study to patients who received adjuvant chemotherapy, and therefore our results may not be applicable to TNBC patients with very small tumors, or patients with higher risk tumors that do not receive systemic therapy. Further, HER2 testing was not standard in breast cancer during the earliest years of the present study, and thus we only included patients who had HER2 testing as part of Institutional Review Board-approved retrospective laboratory studies.

Finally, it should be noted that in our study we have defined our TNBC cohort to be patients with ER and PR staining ≤10%. Recently the joint panel of ASCO Clinical Practice Guidelines Committee and CAP Council on Scientific Affairs recommended that ER and PR staining ≥1% by IHC be considered positive.[35] Limiting our study to patients with ER and PR staining less than 1%, we still did not see a statistically significant difference in LRRFS by surgery type (data not shown). However, we cannot exclude the possibility that differences may have emerged if patients with ER/PR staining ≥1% had been treated with endocrine therapy. We recently reported that only 1.3% of patients treated at our institution between 2000 and 2006 underwent genetic testing before surgery; thus, genetic testing is unlikely to have influenced the choice of treatment in this study period.[34] In our previous work genetic testing was associated with utilization of contralateral prophylactic mastectomy, suggesting that increased utilization of genetic testing could potentially impact prevention of future primary lesions. We also recently reported that up to 20% of patients with TNBC have a *BRCA* mutation; thus, we expect that TNBC patients will increasingly be referred for genetic testing.[6] This would increase presurgical diagnosis of *BRCA* mutations, further decreasing ipsilateral breast tumor recurrence rates.

In summary, although it has been suggested that the aggressive nature of TNBC warrants a more aggressive surgical approach (i.e., mastectomy), the current study demonstrates that surgical treatment with BCT does not have a negative impact on the risk of LRR in a large cohort of TNBC patients. However, the high LRR rates observed in our cohort emphasize the need to identify molecular mediators of LRR in TNBC and targeted therapies that can improve local and distant control.

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