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ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast-Conserving Surgery is Oncologically Safe for Well-Selected, Centrally Located Breast Cancer

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ABSTRACT

Objective. The aim of this study was to evaluate the long-term survival outcomes of breast-conserving surgery (BCS) in centrally located breast cancer (CLBC) compared with mastectomy in CLBC and BCS in non-CLBC, based on the Surveillance, Epidemiology, and End Results (SEER) database.

Methods. Female patients aged < 80 years with unilateral T1-T2 invasive ductal or lobular breast cancer undergoing BCS or mastectomy were enrolled. The differences in clinical-pathological characteristics were evaluated using Chi square tests. Multivariate logistic regression was used to measure the relationship between predictive variables and performing BCS in CLBC. Survival outcomes were estimated using the Kaplan–Meier method and compared using Cox proportional hazards models. To overcome the effects of baseline differences on survival outcome in patients treated with BCS in the central and upper-outer locations, a 1:1 ratio propensity score matching method was performed.

Results. Overall, among 16,522 CLBC patients, 7982 cases (48.3%) underwent BCS between 1998 and 2015. Factors such as older age, Black race, invasive ductal carcinoma (IDC), grade I, small tumor size, none or limited lymph node metastasis, positive progesterone receptor status, and receiving chemotherapy were independently correlated with BCS. BCS was an independent favorable prognostic factor among CLBC patients, based on multivariate Cox analysis. It was also shown that CLBC had similar survival outcomes compared with tumors in the upper-outer quadrant, and had a better breast cancer-specific survival compared with tumors in the lower quadrants, based on multivariate Cox analysis.

Conclusions. BCS should be an acceptable and preferable alternative to mastectomy for well-selected, early-stage T1 or T2 CLBC.

Breast-conserving surgery (BCS) is now the standard treatment for most early-stage breast cancers. It has been proven to be at least equivalent to mastectomy with respect to survival outcomes, and sometimes BCS has even better long-term prognosis.[1,2] With the improvement of systemic therapy, both relative and absolute contraindications to BCS are being challenged.

Approximately 11–26% of all primary breast cancers are located in the central part of the breast.[3,4] Although centrally located breast cancer (CLBC) is no longer an absolute contraindication to BCS, surgeons traditionally prefer to perform mastectomy rather than BCS for these patients. Oncological safety and cosmetic outcomes are the main concerns. On the one hand, published data regarding BCS in CLBC are scarce. There are only limited studies with a small sample size supporting the safety of BCS in CLBC.[5–7] Furthermore, there is scare information on the survival difference between BCS in CLBC and non-CLBC.[3,8] As a result, the oncological safety of such an approach in regard to local or distant recurrence and long-term survival outcome has not yet been sufficiently evaluated. On the other hand, it is perceived that a central lumpectomy with or without nipple-areolar complex removed will lead to unaccepted aesthetic results.

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As limited data support BCS as an oncologically safe alternative to mastectomy in CLBC, we conducted a retrospective study based on the Surveillance, Epidemiology, and End Results (SEER) 18 database to evaluate the long-term survival outcomes of BCS in CLBC compared with mastectomy in CLBC and BCS in non-CLBC.

MATERIALS AND METHODS

Patient Population

This retrospective study employed data derived from the National Cancer Institute's limited-use SEER 18 registry databases released in November 2018. We identified unilateral T1-T2 invasive ductal or lobular breast cancer in female patients aged < 80 years undergoing BCS or mastectomy. Patients with more than one primary cancer; having metastatic disease at diagnosis; without (or unknown) surgery; Tis or T1mic; unknown information on race, location, laterality, histologic grade, tumor size, N category, estrogen receptor (ER) or progesterone receptor (PR) status; or diagnosed at death or autopsy only were excluded from the study. Patients with Paget's disease or breast cancer with nipple areolar complex involved were also excluded (Fig. 1). Because a surgery code was first established in the SEER database in 1998, we selected cases diagnosed between 1 January 1998 and 31 December 2015. Borderline ER or PR status was considered as unknown status. Poorly differentiated and anaplastic histologic grades were considered as grade III disease.

We obtained permission to access the SEER program custom data files with additional treatment fields such as radiation therapy (RT) and chemotherapy. Informed consent was not required because personal identifying information was not accessed. Institutional Review Board (IRB) approval was waived because the SEER is a de-identified national database.

Statistical Analysis

Differences in patient and tumor characteristics were evaluated using Chi square tests. Multivariate logistic regression was used to measure the relationship between various predictive variables and performing BCS in CLBC while adjusting for potentially confounding variables. The follow-up cut-off date was 31 December 2016. Overall survival (OS) was computed from the time of diagnosis until the time of death from any cause, or the last follow-up for patients still alive, while breast cancer-specific survival (BCSS) was computed from the time of diagnosis of breast cancer to the time of death from breast cancer, or the last follow-up for patients still alive. Survival outcomes were estimated using the Kaplan–Meier plot and compared across groups using the log-rank test. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model to fit demographic and disease characteristics for BCSS and OS. To overcome the effects of baseline differences on survival outcome in patients treated with BCS in the central area and upper-outer quadrant, a 1:1 ratio propensity score matching method with a caliper of 0.00001 was performed for each CLBC using 11 covariates: year of diagnosis (± 2 years), age at diagnosis, race, laterality, histology type, histologic grade, tumor size (T1a, T1b, T1c, 2–3 cm, 3–4 cm, and 4–5 cm), N stage, and ER, PR and human epidermal growth factor receptor 2 (HER2) status. A p value < 0.05 was considered statistically significant. The statistical analysis was performed using the SPSS 22.0 software package (IBM Corporation, Armonk, NY, USA).

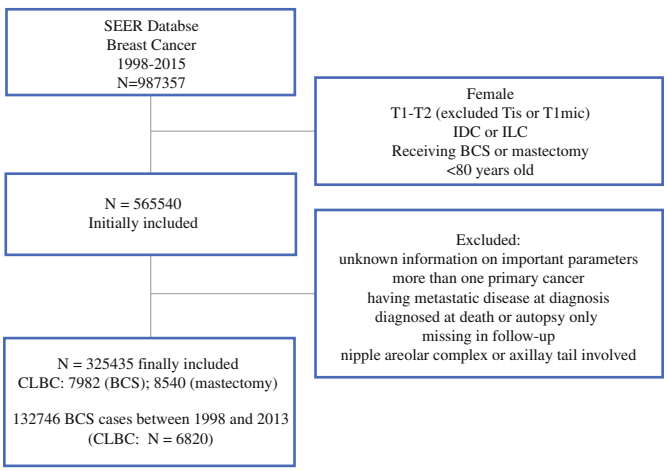

FIG. 1 Patient screening. *SEER* Surveillance, Epidemiology, and End Results, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *BCS* breast-conserving surgery, *CLBC* centrally located breast cancer

RESULTS

Baseline Characteristics among Centrally Located Breast Cancer (CLBC) Patients Treated with Breast-Conserving Surgery (BCS) and Mastectomy

According to the inclusion criteria, 16,522 CLBC cases were enrolled between 1998 and 2015, among which 7982 CLBC cases (48.3%) underwent BCS and 8540 cases (51.7%) underwent mastectomy. The clinical characteristics of CLBC cases undergoing BCS and mastectomy are summarized in Table 1. Older patients, patients with invasive ductal carcinoma (IDC) histology, and patients of White race were more likely to receive BCS. In addition, CLBC patients with less aggressive characteristics such as lower histologic grade, smaller tumor size, none or limited lymph node metastasis, or positive ER or PR status tended to be treated with BCS. CLBC patients treated with BCS were less likely to receive chemotherapy.

Predictive Factors of BCS Among CLBC

Variables associated with BCS in univariate analysis at a threshold of $p < 0.05$ were enrolled in the multivariate logistic regression analysis. Multivariate logistic regressions confirmed that factors such as older age, Black race, IDC, grade I, small tumor size, none or limited lymph node metastasis, positive PR status, and receiving chemotherapy were independently correlated with BCS when compared with mastectomy. Significantly higher odds of BCS were found in T1a (odds ratio [OR] 4.732, 95% CI 3.793–5.903), T1b (OR 5.897, 95% CI 4.813–7.225), T1c (OR 4.082, 95% CI 3.375–4.936), and N0 disease (OR 3.242, 95% CI 2.551–4.122; Hosmer–Lemeshow $p = 0.349$) (Table 2).

Survival Analysis Between BCS and Mastectomy Among CLBC Cases and Subgroup Analysis

In order to precisely evaluate the prognosis and to perform adequate follow-up, CLBC cases that were diagnosed between 1998 and 2013 were enrolled in the analysis. The median follow-up time was 95 months (range 0–227). CLBC cases that underwent BCS had improved BCSS ($p < 0.001$) and OS ($p < 0.001$) compared with those who underwent mastectomy (Fig. 2). According to the multivariate Cox analysis, BCS was an independent favorable prognostic factor for BCSS (HR 0.852, 95% CI 0.748–0.971; $p = 0.017$) and OS (HR 0.895, 95% CI 0.815–0.983; $p = 0.021$) (Table 3).

Furthermore, CLBC patients who underwent BCS had significantly improved BCSS and OS compared with those who underwent mastectomy, in almost all subgroups except for larger tumor and N3 stage (Fig. 3).

TABLE 1 Baseline characteristics of CLBC patients undergoing BCS or mastectomy

	Mastectomy		BCS		*p*-Value
	N	%	*N*	%	
Year					0.025
1998–2003	2300	26.9	2010	25.2	
2004–2009	2950	34.5	2873	36.0	
2010–2015	3290	38.5	3099	38.8	
Age, years					< 0.001
< 60	4593	53.8	3811	47.7	
≥ 60	3947	46.2	4171	52.3	
Race					< 0.001
White	6766	79.2	6636	83.1	
Black	708	8.3	680	8.5	
Others	1066	12.5	666	8.3	
Histologic type					< 0.001
IDC	7671	89.8	7397	92.7	
ILC	869	10.2	585	7.3	
Laterality					0.258
Left	4357	51.0	4002	50.1	
Right	4183	49.0	3980	49.9	
Grade					< 0.001
I	1255	14.7	1896	23.8	
II	4012	47.0	3868	48.5	
III	3273	38.3	2218	27.8	
Tumor size					
T1a	469	5.5	774	9.7	< 0.001
T1b	923	10.8	1857	23.3	
T1c	2769	32.4	3393	42.5	
2–3 cm	2481	29.1	1439	18.0	
3–4 cm	1219	14.3	371	4.6	
4–5 cm	679	8.0	148	1.9	
N stage					< 0.001
N0	4424	51.8	5767	72.3	
N1	2840	33.3	1882	23.6	
N2	880	10.3	240	3.0	
N3	396	4.6	93	1.2	
ER					< 0.001
Negative	1496	17.5	1068	13.4	
Positive	7044	82.5	6914	86.6	
PR					< 0.001
Negative	2584	30.3	1935	24.2	
Positive	5956	69.7	6047	75.8	
Radiation					< 0.001
No or unknown	6731	78.8	1633	20.5	
Yes	1809	21.2	6349	79.5	
Chemotherapy					< 0.001
No or unknown	4008	46.9	4842	60.7	
Yes	4532	53.1	3140	39.3	

CLBC centrally located breast cancer, *BCS* breast-conserving surgery, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *ER* estrogen receptor, *PR* progesterone receptor

TABLE 2 Multivariate analysis of factors associated with BCS compared with mastectomy among CLBC

	OR	95% CI	*p*-Value
Year			0.097
1998–2003 vs. 2010–2015	0.951	0.875–1.034	0.239
2004–2009 vs. 2010–2015	1.044	0.967–1.126	0.270
Age, years			
≥ 60 vs. < 60	1.164	1.087–1.247	< 0.001
Race			< 0.001
Black vs. White	1.183	1.050–1.333	0.006
Others vs. White	0.666	0.597–0.743	< 0.001
Histologic type			
IDC vs. ILC	1.377	1.222–1.552	< 0.001
Histologic grade			< 0.001
I vs. III	1.310	1.180–1.455	< 0.001
II vs. III	1.075	0.992–1.166	0.078
Tumor size			< 0.001
T1a vs. 4–5 cm	4.732	3.793–5.903	< 0.001
T1b vs. 4–5 cm	5.897	4.813–7.225	< 0.001
T1c vs. 4–5 cm	4.082	3.375–4.936	< 0.001
2–3 cm vs. 4–5 cm	2.232	1.840–2.708	< 0.001
3–4 cm vs. 4–5 cm	1.287	1.037–1.597	0.022
N stage			< 0.001
N0 vs. N3	3.242	2.551–4.122	< 0.001
N1 vs. N3	2.074	1.630–2.638	< 0.001
N2 vs. N3	1.047	0.796–1.379	0.741
ER			
Positive vs. negative	1.016	0.900–1.147	0.796
PR			
Positive vs. negative	1.197	1.088–1.316	< 0.001
Chemotherapy			
Yes vs. no or unknown	1.109	1.025–1.200	0.010

CLBC centrally located breast cancer, *BCS* breast-conserving surgery, *OR* odds ratio, *CI* confidence interval, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *ER* estrogen receptor, *PR* progesterone receptor

Survival Outcomes Among Patients Undergoing BCS with Tumor Located in the Central Area and the Four Quadrants

Overall, 132,746 patients underwent BCS between 1998 and 2013, among whom 6820 cases had tumor located in the central area, 74,072 cases had tumor located in the upper-outer quadrant, 25,857 cases had tumor located in the upper-inner quadrant, 14,184 cases had tumor located in the lower-outer quadrant, and 11,813 cases had tumor located in the lower-inner quadrant.

Compared with tumors located in the upper-outer quadrant, CLBC had a similar BCSS (log-rank $p = 0.608$) but a worse OS (log-rank $p = 0.001$) (Figs. 4a, b). According to the multivariate analysis, CLBC was still an independent unfavorable prognostic factor for OS (HR 0.904, 95% CI 0.850–0.962) (Table 4; electronic supplementary Table 1).

However, due to the large differences in case numbers and clinical characteristics between patients undergoing BCS with tumor located in the central area or upper-outer quadrant, a 1:1 matched case–control analysis was conducted with a caliper of 0.00001, in which 6652 cases in each cohort were enrolled. The matching analysis was considered successful as no significant difference was observed in any characteristic (electronic supplementary Table 2). We then showed that CLBC had a similar BCSS (log-rank $p = 0.736$) and OS (log-rank $p = 0.284$) compared with tumors in the upper-outer quadrant (Fig. 5; Table 4; electronic supplementary Table 3). Furthermore, the CLBC cohort had a similar BCSS and OS compared with the upper-outer quadrant cohort in each subgroup regardless of age, histologic grade, tumor size, N stage, ER or PR status, etc. Compared with tumors located in the upper-inner quadrant, CLBC had a similar BCSS and OS based on the multivariate analysis (Fig. 4c, d; Table 4; electronic supplementary Table 4). However, when compared with tumors located in the lower quadrants, CLBC had a similar OS but a significantly improved BCSS (lower-outer vs. central: HR 1.133, 95% CI 1.015–1.264; lower-inner vs. central: HR 1.369, 95% CI 1.223–1.532) based on the multivariate analysis (Fig. 4e, h; Table 4; electronic supplementary Tables 5 and 6].

In the subgroup analysis, the CLBC cohort had an improved BCSS in N0 and N1 stage compared with tumor located in the lower-inner quadrant (log-rank $p < 0.001$), as well as an improved BCSS in the N0 stage compared with tumor in the lower-outer quadrant (log-rank $p = 0.002$) (Fig. 6).

DISCUSSION

To the best of our knowledge, this is the first population-based study demonstrating at least equivalent BCSS and OS for BCS and mastectomy in T1-T2 CLBC, and for BCS in T1-T2 CLBC and non-CLBC.

There is abundant high-level evidence supporting BCS in early-stage breast cancer; however, only limited data are available to support the use of BCS for central and retroareolar breast cancers. For example, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial did not include central breast cancer patients specifically.[9] Some studies suggested that tumors in the central and nipple portion had worse survival outcomes compared with tumors in the peripheral quadrant due to presentation with a higher stage.[10] The special anatomic

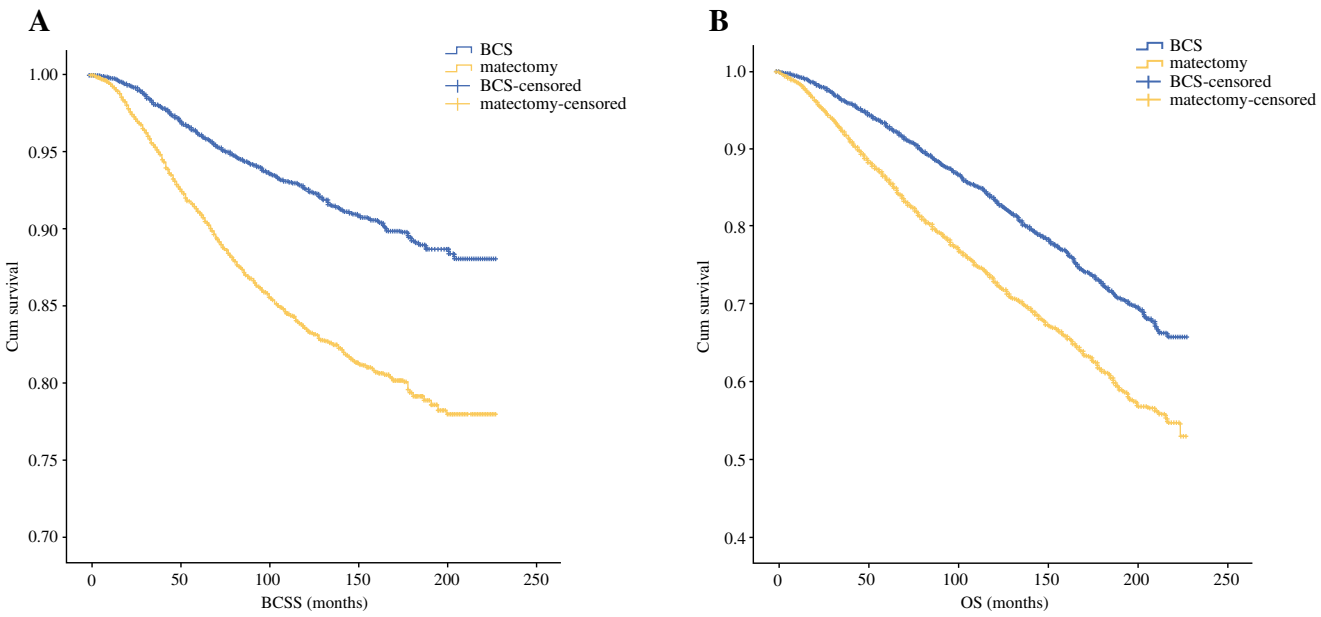

FIG. 2 Kaplan–Meier survival curves of (**a**) BCSS and (**b**) OS, stratified by BCS or mastectomy in CLBC. *BCSS* breast cancer-specific survival, *OS* overall survival, *BCS* breast-conserving surgery, *CLBC* centrally located breast cancer

structure in the central portion lay in the lymphatics of the breast collected in a subareolar plexus and then drained towards the axilla, which were first indicated by Sappey early in 1870. Similar to Sappey, Suami et al. also found that the lymphatics deep to the nipple and areola were a dense network of lymph capillaries.[11] Consequently, surgeons generally hesitate to perform BCS for CLBC for fear of oncological safety. Although several studies with limited cases showed promising overall and disease-free survival in favor of BCS in CLBC,[5–7,12] reliable long-term evidence of BCS in a large number of patients with central breast cancer does not exist.

According to this study, only 48.3% of CLBC patients underwent BCS. CLBC patients who were presented with less aggressive characteristics tended to undergo BCS, especially those with smaller tumor mass. For BCS in CLBC, oncological safety and aesthetic results were both important. It could be more likely to achieve a negative surgical margin and cosmetic effect also in cases of smaller tumor mass. Cases with more aggressive characteristics such as younger age, higher histologic grade, more lymph nodes metastasis, and negative hormone receptors were more likely to be treated with mastectomy. Although these factors were not contradictions for BCS, mastectomy was preferred, probably due to the concern regarding oncological safety for BCS in these CLBC cases. However, based on the results of this study, BCS in CLBC led to significantly improved BCSS and OS compared with mastectomy in almost all subgroups.

Some studies on the comparisons between BCS and mastectomy for CLBC, in spite of no more than 100 CLBC cases being enrolled, have been published. Gajdos et al. showed that BCS in CLBC had comparable local and distant recurrence-free survival rates compared with mastectomy.[13] Simmons et al. also declared no significant differences in local or distant relapse for central or retroareolar tumors treated with BCS compared with mastectomy.[14] However, according to the results of our study, CLBC patients who received BCS had even better BCSS and OS compared with those undergoing mastectomy, after a median follow-up of 95 months. Recently, two large population-based studies from The Netherlands demonstrated improved long-term overall and metastasis-free survival for BCS compared with mastectomy in early-stage breast cancer, adjusting for confounding variables.[1,2] Furthermore, BCS resulted in noninferior outcomes, even in N2-N3 disease.[15] In our study, BCS in CLBC still showed improved BCSS and OS compared with mastectomy in all N subgroups, expect for N3 due to limited cases in this subgroup. The improved survival outcomes for BCS have likely attributed to the improvements in diagnosis, surgery, and RT over the last 30 years.

The basic principles of BCS should not be compromised in patients with central breast cancer; that is to say, BCS can be performed safely if negative margins are achieved and appropriate adjuvant RT or systemic therapy is administered.[16] Gajdos et al. indicated that without RT, the involvement of the nipple-areola complex (NAC) was related to a higher risk of local recurrence for BCS in central breast cancer.[13] Cabioglu et al. showed that the

TABLE 3 Multivariate analysis of prognostic factors among CLBC patients who underwent BCS or mastectomy

	BCSS			OS		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Year of diagnosis	0.963	0.950–0.976	< 0.001	0.966	0.957–0.976	< 0.001
Age, years						
≥ 60 vs. < 60	1.377	1.238–1.532	< 0.001	2.615	2.415–2.832	< 0.001
Race			< 0.001			< 0.001
Black vs. White	1.307	1.114–1.535	0.001	1.298	1.150–1.466	< 0.001
Others vs. White	0.769	0.641–0.924	0.005	0.727	0.634–0.834	< 0.001
Histologic type						
ILC vs. IDC	0.960	0.797–1.156	0.669	1.007	0.889–1.142	0.909
Laterality						
Left vs. right	1.136	1.026–1.258	0.014	1.075	1.001–1.155	0.046
Histologic grade			< 0.001			< 0.001
II vs. I	2.316	1.826–2.939	< 0.001	1.166	1.043–1.303	0.007
III vs. I	2.965	2.322–3.787	< 0.001	1.381	1.223–1.560	< 0.001
N stage			< 0.001			< 0.001
N1 vs. N0	1.873	1.644–2.133	< 0.001	1.431	1.310–1.564	< 0.001
N2 vs. N0	3.575	3.029–4.220	< 0.001	2.529	2.230–2.868	< 0.001
N3 vs. N0	6.555	5.461–7.867	< 0.001	4.030	3.462–4.691	< 0.001
Tumor size			< 0.001			< 0.001
T1b vs. T1a	0.904	0.627–1.304	0.589	1.061	0.863–1.304	0.574
T1c vs. T1a	1.267	0.914–1.757	0.155	1.406	1.163–1.701	< 0.001
2–3 cm vs. T1a	2.011	1.448–2.794	< 0.001	1.898	1.560–2.310	< 0.001
3–4 cm vs. T1a	2.610	1.859–3.664	< 0.001	2.404	1.950–2.964	< 0.001
4–5 cm vs. T1a	2.867	2.013–4.084	< 0.001	2.616	2.084–3.283	< 0.001
Surgery						
BCS versus mastectomy	0.852	0.748–0.971	0.017	0.895	0.815–0.983	0.021
ER						
Negative versus positive	1.199	1.029–1.397	0.020	1.198	1.066–1.346	0.002
PR						
Negative versus positive	1.494	1.307–1.709	< 0.001	1.222	1.109–1.346	< 0.001
Radiation						
Yes versus no or unknown	0.848	0.752–0.957	< 0.001	0.834	0.762–0.912	< 0.001
Chemotherapy						
Yes versus no or unknown	0.918	0.812–1.038	0.170	0.668	0.613–0.728	< 0.001

CLBC centrally located breast cancer, *BCS* breast-conserving surgery, *HR* hazard ratio, *CI* confidence interval, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *ER* estrogen receptor, *PR* progesterone receptor

absence of adjuvant RT was associated with a higher risk of local recurrence for CLBC treated with BCS,[16] and Marshall et al. further confirmed excellent long-term local recurrence-free survival, disease-free survival, and OS even for Paget's disease of the breast when receiving BCS and RT.[17] In our study, nearly 80% of CLBC patients treated with BCS received RT, and BCS plus RT showed much improved BCSS and OS.

The main limitation of this study was the lack of information regarding cosmetic results after BCS in CLBC, and information regarding the proportion of NAC resections. Because the risk of NAC involvement was four times greater for breast cancer in the central area than in peripheral counterparts,[18,19] resection of the NAC is commonly recommended. It is generally accepted that preservation of the NAC is of great importance for the aesthetic appearance of the breast as a whole. A fishmouth-shaped incision with resection of the NAC was revealed as the main risk factor for poor aesthetic outcomes;[20,21] however, in many cases, removal of the NAC extended the indications for BCS without compromising cosmetic effects.[22] Loss of the NAC was mainly evaluated to be

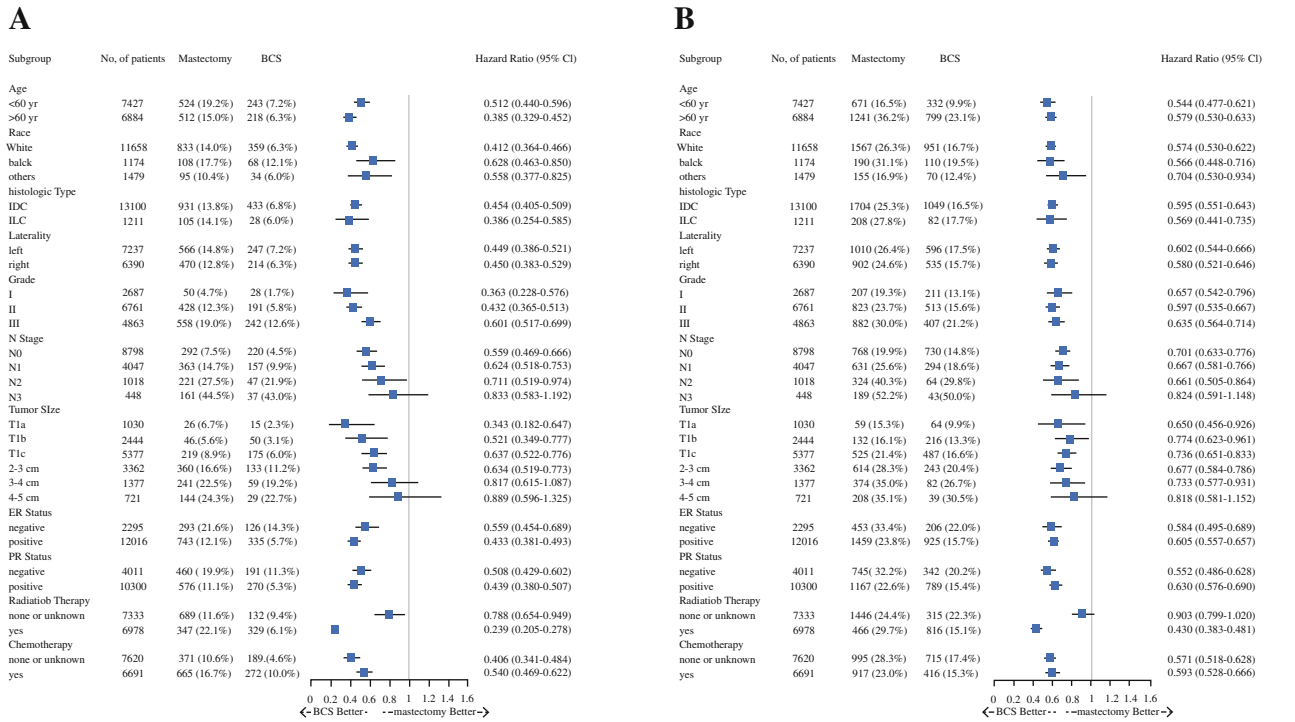

FIG. 3 Subgroup survival outcome comparisons between CLBC patients undergoing BCS or mastectomy. (**a**) BCSS; (**b**) OS. *CLBC* centrally located breast cancer, *BCS* breast-conserving surgery, *BCSS* breast cancer-specific survival, *OS* overall survival, *CI* confidence interval, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *ER* estrogen receptor, *PR* progesterone receptor

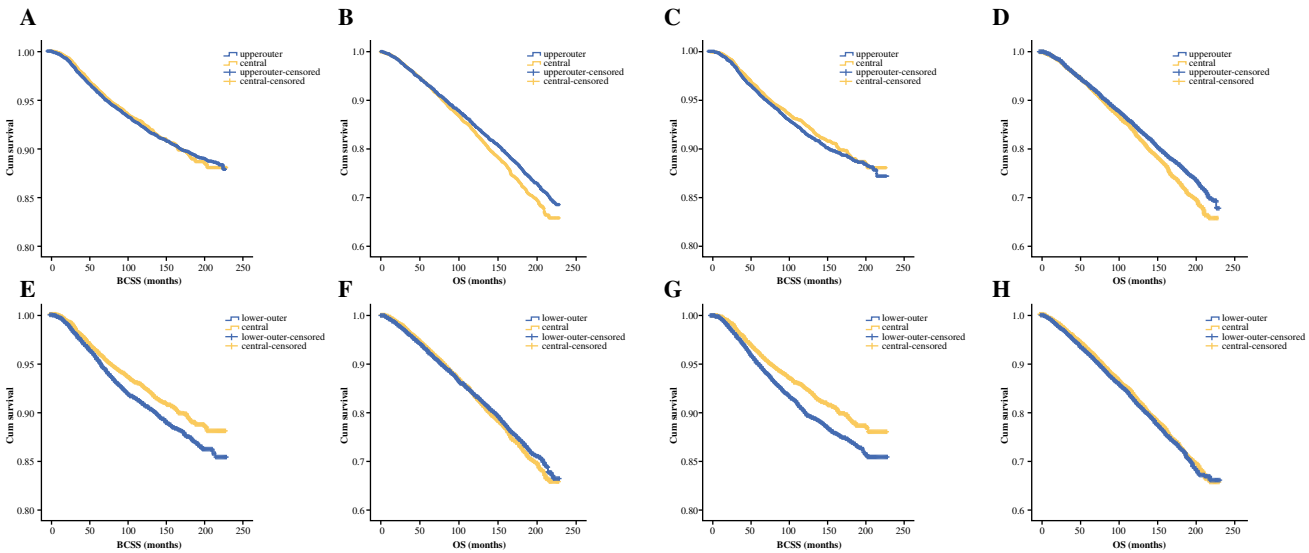

FIG. 4 Kaplan–Meier survival curves of BCSS and OS for patients undergoing BCS comparisons among the central area and the four quadrants (**a**) BCSS between CLBC and the upper-outer quadrant; (**b**) OS between CLBC and the upper-outer quadrant; (**c**) BCSS between CLBC and the upper-inner quadrant; (**d**) OS between CLBC and the upper-inner quadrant; (**e**) BCSS between CLBC and the lower-outer quadrant; (**f**) OS between CLBC and the lower-outer quadrant; (**g**) BCSS between CLBC and the lower-inner quadrant; (**h**) OS between CLBC and the lower-inner quadrant. *BCSS* breast cancer-specific survival, *OS* overall survival, *BCS* breast-conserving surgery, *CLBC* centrally located breast cancer, *Cum* cumulative

cosmetically unacceptable by surgeons; however, after removal of the NAC, patients judged their cosmetic results to be better than their surgeons did.[5–7,22] Additionally, restoration of the central defects achieved by multiple oncoplastic procedures with or without immediate reconstruction of the NAC have been shown to be oncologically

TABLE 4 Survival analyses of breast cancer patients undergoing BCS with tumor located in the central area and four quadrants

	BCSS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Upper-outer versus central	1.025	0.932–1.128			0.899	0.846–0.956	0.904	0.850–0.962
Upper-outer versus central (matched)	0.977	0.854–1.118			0.955	0.877–1.039		
Upper-inner versus central	1.081	0.976–1.198			0.891	0.833–0.953	0.980	0.916–1.050
Lower-outer versus central	1.235	1.108–1.377	1.133	1.015–1.264	0.980	0.912–1.053		
Lower-inner versus central	1.291	1.156–1.443	1.369	1.223–1.532	1.052	0.978–1.132		

BCS breast-conserving surgery, *BCSS* breast cancer-specific survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

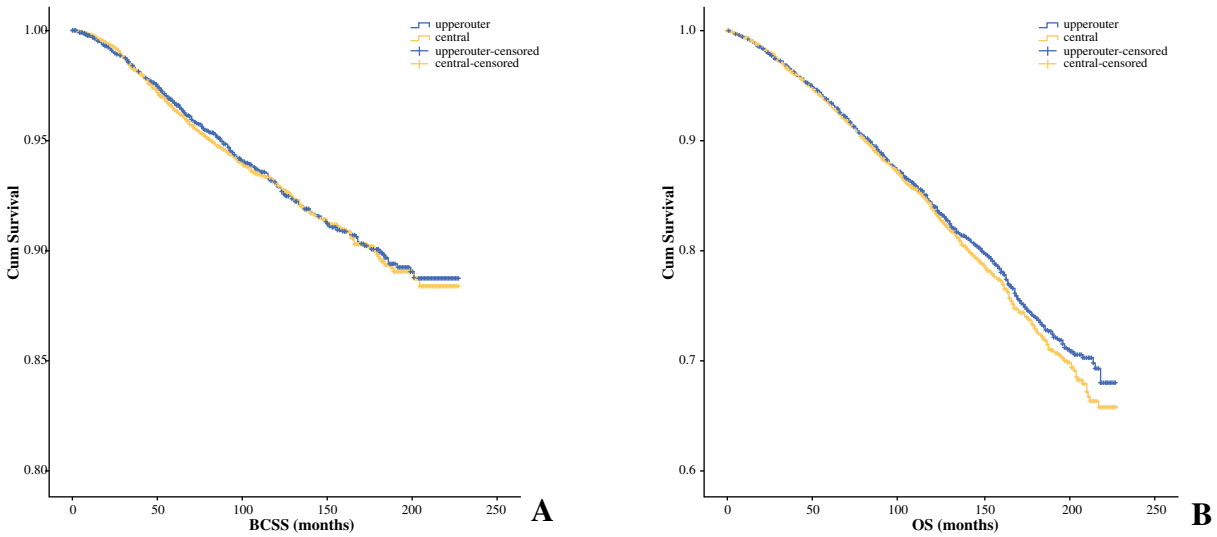

FIG. 5 Kaplan–Meier survival curves of BCSS and OS for patients undergoing BCS, stratified by central area and the upper-outer quadrant in the matched cohorts. (**a**) BCSS; (**b**) OS. *BCSS* breast cancer-specific survival, *OS* overall survival, *BCS* breast-conserving surgery, *Cum* cumulative

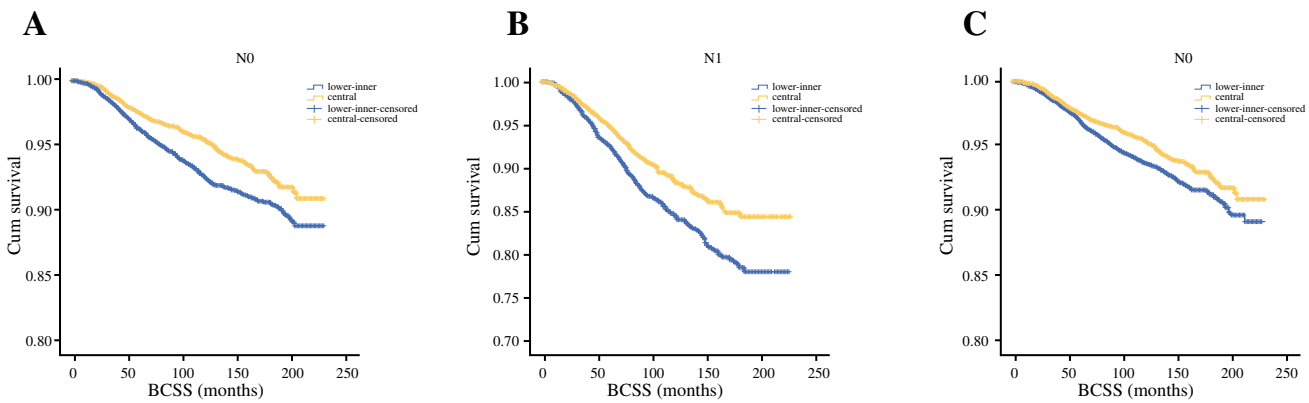

FIG. 6 Subgroup analyses of Kaplan–Meier survival curves of BCSS and OS for patients undergoing BCS, stratified by central area and the lower quadrants. (**a**) BCSS in N0 between CLBC and the lower-inner quadrant; (**b**) BCSS in N1 between CLBC and the lower-inner quadrant; (**c**) BCSS in N0 between CLBC and the lower-outer quadrant. *BCSS* breast cancer-specific survival, *OS* overall survival, *BCS* breast-conserving surgery, *CLBC* centrally located breast cancer

safe and cosmetically effective.[23–29] Furthermore, the cosmetic results of NAC preservation have also been studied. In one series, an excellent or good cosmetic result was achieved in most patients, especially those with smaller tumors.[6] Patients with large central tumors might convert to successful NAC preservation after the completion of neoadjuvant chemotherapy.[30] It was reported that BCS resulted in superior quality of life in CLBC patients with a tumor/breast volume ratio below 15.[31] Therefore, the aesthetic factor should not be a main obstacle for the performance of BCS in relevant CLBC patients.

It has been shown that breast cancers with tumors located in upper-outer quadrant had a more favorable survival advantage when compared with tumors in other locations;[32] however, it has not been fully clarified whether BCS in various tumor locations will have any impact on survival outcomes. In this study, the survival outcomes in CLBC were compared with tumors in the four quadrants among patients receiving BCS. First, CLBC has been demonstrated to have comparable BCSS and OS compared with the upper-outer quadrant based on multivariate analysis in the matched cohort. According to the literature, the oncological outcomes for CLBC after BCS were comparable with non-CLBC.[3,5,8] Fowble et al. evaluated 119 central tumors and 70 cases of retroareolar tumors treated with BCS, and showed no difference in overall or relapse-free survival at 5 years between these patients and those with distally located tumors.[3] Fitzal et al. also showed no significant differences in terms of the overall, local, or distant recurrence-free survivals between CLBC and non-CLBC after a median follow-up of 35.3 months.[8] Furthermore, this study demonstrated a significantly improved BCSS in favor of CLBC compared with tumors located in the lower quadrants in cases of BCS. Some studies showed that the lower-inner quadrant was an independent unfavorable prognostic factor even for stage I breast cancer.[33,34] According to the subgroup analysis in this study, CLBC had significantly improved BCSS in cases of no or limited axillary lymph node metastasis compared with tumor in the lower quadrants. It was suggested that the increased drainage of the internal and inferior mammary lymph nodes might play a key role.[35] Shahar et al. found that internal mammary chain drainage was strongly correlated with tumor location, i.e. 31.6% for the lower-outer quadrant and 42.9% for the lower-inner quadrant.[36] Therefore, the proper performance of BCS in CLBC did not impair survival outcomes compared with tumors in other sites.

Although the strength of our study lay in its homogeneous study population with a large sample size, this was a retrospective study and the intrinsic defects existed. Furthermore, the impact of HER2 status and endocrine therapy on surgical choice and survival outcome was unavailable. Information on the cosmetic results after BCS in CLBC was also unavailable, as discussed above, as was information regarding margin width. However, according to the study by Azu et al., a population-based surgeon sample identified from the SEER registries was used to determine the attitudes towards margin width. Even for T1 invasive cancer, 11% of surgeons endorsed margins of tumor not touching ink, 42% endorsed margins of 1–2 mm, 28% endorsed margins of $\geq$ 5 mm, and 19% endorsed margins $>$ 1 cm as precluding the need for re-excision.[37] According to the current guideline, no ink on tumor is the standard for an adequate margin for BCS in invasive cancer;[38] therefore, it could be presumed that a negative margin was achieved for each BCS practice.

CONCLUSIONS

Our study demonstrated the long-term oncological safety of BCS in CLBC compared with mastectomy, and also showed that the central area did not have a negative impact on long-term survival among patients treated with BCS. As a result, BCS should be an acceptable and preferable alternative to mastectomy for well-selected, early-stage T1 or T2 central breast cancer.

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REFERENCES

1. van Maaren MC, de Munck L, de Bock GH, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. *Lancet Oncol.* 2016;17(8):1158–1170.
2. Lagendijk M, van Maaren MC. Breast conserving therapy and mastectomy revisited: Breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. *Int J Cancer.* 2018;142(1):165–175.
3. Fowble B, Solin LJ, Schultz DJ, Weiss MC. Breast recurrence and survival related to primary tumor location in patients undergoing conservative surgery and radiation for early-stage breast cancer. *Int J Radiat Oncol Biol Phys..* 1992;23(5):933–939.
4. Galimberti V, Zurrida S, Zanini V, et al. Central small size breast cancer: how to overcome the problem of nipple and areola involvement. *Eur J Cancer.* 1993;29A(8):1093–1096.
5. Haffty BG, Wilson LD, Smith R, et al. Subareolar breast cancer: long-term results with conservative surgery and radiation therapy. *Int J Radiat Oncol Biol Phys.* 1995;33(1):53–57.

6. Dale PS, Giuliano AE. Nipple-areolar preservation during breast-conserving therapy for subareolar breast carcinomas. *Arch Surg.* 1996;131(4):430–433.
7. Eggemann H, Ignatov A, Elling D, et al. Efficacy and patient satisfaction of breast conserving therapy for central breast cancer by the B technique. *Ann Surg Oncol.* 2013;20(11):3438–3445.
8. Fitzal F, Mittlboeck M, Trischler H, et al. Breast-conserving therapy for centrally located breast cancer. *Ann Surg.* 2008;247(3):470–476.
9. Christian MC, McCabe MS, Korn EL, Abrams JS, Kaplan RS, Friedman MA. The National Cancer Institute audit of the National Surgical Adjuvant Breast and Bowel Project Protocol B-06. *New Engl J Med.* 1995;333(22):1469–1474.
10. Ji F, Xiao WK, Yang CQ, et al. Tumor location of the central and nipple portion is associated with impaired survival for women with breast cancer. *Cancer Manag Res.* 2019;11:2915–2925.
11. Suami H, Pan WR, Mann GB, Taylor GI. The lymphatic anatomy of the breast and its implications for sentinel lymph node biopsy: a human cadaver study. *Ann Surg Oncol.* 2008;15(3):863–871.
12. Bussieres E, Guyon F, Thomas L, Stockle E, Faucher A, Durand M. Conservation treatment in subareolar breast cancers. *Eur J Surg Oncol.* 1996;22(3):267–270.
13. Gajdos C, Tartter PI, Bleiweiss IJ. Subareolar breast cancers. *Am J Surg.* 2000;180(3):167–170.
14. Simmons RM, Brennan MB, Christos P, Sckolnick M, Osborne M. Recurrence rates in patients with central or retroareolar breast cancers treated with mastectomy or lumpectomy. *Am J Surg.* 2001;182(4):325–329.
15. Wang J, Deng JP, Sun JY, et al. Noninferior Outcome After Breast-Conserving Treatment Compared to Mastectomy in Breast Cancer Patients With Four or More Positive Lymph Nodes. *Front Oncol.* 2019;9:143.
16. Cabioglu N, Krishnamurthy S, Kuerer HM, et al. Feasibility of breast-conserving surgery for patients with breast carcinoma associated with nipple discharge. *Cancer.* 2004;101(3):508–517.
17. Marshall JK, Griffith KA, Haffty BG, et al. Conservative management of Paget disease of the breast with radiotherapy: 10- and 15-year results. *Cancer.* 2003;97(9):2142–2149.
18. Banerjee A, Gupta S, Bhattacharya N. Preservation of nipple-areola complex in breast cancer–a clinicopathological assessment. *J Plast Reconst Aesthetic Surg.* 2008;61(10):1195–1198.
19. Lambert PA, Kolm P, Perry RR. Parameters that predict nipple involvement in breast cancer. *J Am College Surg.* 2000;191(4):354–359.
20. Hennigs A, Biehl H, Rauch G, et al. Change of Patient-Reported Aesthetic Outcome Over Time and Identification of Factors Characterizing Poor Aesthetic Outcome After Breast-Conserving Therapy: Long-Term Results of a Prospective Cohort Study. *Ann Surg Oncol.* 2016;23(5):1744–1751.
21. Santos G, Urban C, Edelweiss MI, et al. Long-Term Comparison of Aesthetical Outcomes After Oncoplastic Surgery and Lumpectomy in Breast Cancer Patients. *Ann Surg Oncol.* 2015;22(8):2500–2508.
22. Pezzi CM, Kukora JS, Audet IM, Herbert SH, Horvick D, Richter MP. Breast conservation surgery using nipple-areolar resection for central breast cancers. *Arch Surg.* 2004;139(1):32–37; discussion 38.
23. Farouk O, Attia E, Roshdy S, et al. The outcome of oncoplastic techniques in defect reconstruction after resection of central breast tumors. *World J Surg Oncol.* 2015;13:285.
24. McCulley SJ, Durani P, Macmillan RD. Therapeutic mammaplasty for centrally located breast tumors. *Plast Reconstruct Surg.* 2006;117(2):366–373.
25. Tausch C, Hintringer T, Kugler F, Schmidhammer C, Bauer M, Aufschnaiter M. Breast-conserving surgery with resection of the nipple-areola complex for subareolar breast carcinoma. *British J Surg.* 2005;92(11):1368–1371.
26. Kang J, Wechter D, Grumley J. Neoareolar wise pattern reduction in patients requiring central partial mastectomy. *Ann Surg Oncol.* 2013;20(10):3351.
27. Kimball CC, Nichols CI, Vose JG, Peled AW. Trends in Lumpectomy and Oncoplastic Breast-Conserving Surgery in the US, 2011–2016. *Ann Surg Oncol.* 2018;25(13):3867–3873.
28. Carstensen L, Bigaard J. Management of central breast tumours with immediate reconstruction of the nipple-areola complex; a suggested guide. *Breast.* 2015;24(1):38–45.
29. Faure C, Escalon J, Bremond A, Mignotte H, Perol D, Delay E. [Oncoplastic technics with nipple-areolar complex resection for the treatment of central breast cancers]. *Annales de chirurgie plastique et esthetique.* 2008;53(2):112–123.
30. 30. Jadeja P, Ha R, Rohde C, et al. Expanding the Criteria for Nipple-Sparing Mastectomy in Patients With Poor Prognostic Features. *Clinical Breast Cancer.* 2018;18(3):229–233.
31. Vos E, Koppert L, van Lankeren W, Verhoef C, Koerkamp BG, Hunink M. A preliminary prediction model for potentially guiding patient choices between breast conserving surgery and mastectomy in early breast cancer patients; a Dutch experience. *Quality Life Res.* 2018;27(2):545–553.
32. Sohn VY, Arthurs ZM, Sebesta JA, Brown TA. Primary tumor location impacts breast cancer survival. *Am J Surg.* 2008;195(5):641–644.
33. 33. Sarp S, Fioretta G, Verkooijen HM, et al. Tumor location of the lower-inner quadrant is associated with an impaired survival for women with early-stage breast cancer. *Ann Surg Oncol.* 2007;14(3):1031–1039.
34. Wu S, Zhou J, Ren Y, et al. Tumor location is a prognostic factor for survival of Chinese women with T1-2N0M0 breast cancer. *Int J Surg.* 2014;12(5):394–398.
35. Estourgie SH, Nieweg OE, Olmos RA, Rutgers EJ, Kroon BB. Lymphatic drainage patterns from the breast. *Ann Surg.* 2004;239(2):232–237.
36. Shahar KH, Buchholz TA, Delpassand E, et al. Lower and central tumor location correlates with lymphoscintigraphy drainage to the internal mammary lymph nodes in breast carcinoma. *Cancer.* 2005;103(7):1323–1329.
37. Azu M, Abrahamse P, Katz SJ, Jagsi R, Morrow M. What is an adequate margin for breast-conserving surgery? Surgeon attitudes and correlates. *Ann Surg Oncol.* 2010;17(2):558–563.
38. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Ann Surg Oncol.* 2014;21(3):704–716.