Breast surgery for young women with early-stage breast cancer

Medicine

Mastectomy or breast-conserving therapy?

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Abstract

Whether breast-conserving therapy (BCT) should be chosen as a local treatment for young women with early-stage breast cancer is controversial. This study compared the survival benefits of BCT or mastectomy in young women under 40 with early-stage breast cancer and further explored age-stratified outcomes. This study investigated whether there is a survival benefit when young women undergo BCT compared with mastectomy.

The characteristics and prognosis of white women under 40 with stage I–II breast cancer from 1988 to 2016 were analyzed using the Surveillance, Epidemiology, and End Results (SEER) database. These women were either treated with BCT or mastectomy. The log-rank test of the Kaplan–Meier survival curve and Cox proportional risk regression model were used to analyze the data and survival. The analysis was stratified by age (18–35 and 36–40 years).

A total of 23,810 breast cancer patients were included, of whom 44.9% received BCT and 55.1% underwent mastectomy, with a median follow-up of 116 months. Patients undergoing mastectomy had a higher tumor burden and younger age. By the end of the 20th century, the proportion of BCT had grown from nearly 35% to approximately 60%, and then gradually fell to 35% into the 21st century. Compared with the mastectomy group, the BCT group had improved breast cancer-specific survival (BCSS) (hazard ratio [HR] 0.917; 95% CI, 0.846–0.995, P = .037) and overall survival (OS) (HR 0.925; 95% CI, 0.859–0.997, P = .041). In stratified analysis according to the different ages, the survival benefit of BCT was more pronounced in the slightly older (36–40 years) group while there was no significant survival difference in the younger group (18–35 years).

In young women with early-stage breast cancer, BCT showed survival benefits that were at least no worse than mastectomy, and these benefits were even better in the 36 to 40 years age group. Young age may not be a contraindication for BCT.

Abbreviations: 95% CIs = 95% confidence intervals, AJCC = American Joint Committee on Cancer, BCSS = breast cancerspecific survival, BCT = breast-conserving therapy, ER = estrogen receptor, HER2 = human epidermal growth receptor 2, HR = hazard ratio, LR = logistic regression, NCCN = the National Comprehensive Cancer Network, OS = overall survival, SEER = Surveillance, Epidemiology, and End Results.

Keywords: breast carcinoma, breast-conserving surgery, early, mastectomy, survival, young age

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Informed consent: The data came from the SEER database. Informed consent was obtained from all individual participants included in the study.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Breast-conserving therapy (BCT) consisting of breast-conserving surgery plus adjuvant radiotherapy has become one of the standards for local breast cancer treatment compared with mastectomy.^[1–4] BCT allows for sparing of the normal breast tissue and has advantages such as being more aesthetic and less invasive. Therefore, BCT results in better physical and mental health and has been shown to improve patients' quality of life.^[5–8]

However, the use of BCT in young women under 40 with earlystage breast cancer has been questioned. Previous studies have shown that BCT and mastectomy achieve the same survival benefit for young patients with early-stage breast cancer.^[9–12] However, in recent years, several studies have found that patients treated with BCT have better outcomes than patients treated with mastectomy.^[13–16] This may be due to improvements in radiotherapy and systemic treatment. However, whether this finding is effective in young people, who display more aggressive features and a higher likelihood of local recurrence,^[17–21] is controversial. Due to young breast cancer patients' rarity, only a small percentage of patients in major randomized trials have been younger than 40.^[10,22]

Unlike most previous studies of early stage breast cancer, this study will focus on young breast cancer patients under 40. Here, this study conducted a retrospective analysis to compare the efficacy of BCT and mastectomy in young patients with earlystage breast cancer in the real world. Using the data from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, this study evaluated the trends and survival of mastectomy or BCT in young women with early-stage breast cancer. Further survival analysis was stratified by age.

2. Patients and methods

2.1. Study population and data sources

The SEER database includes population-based cancer registries, covering approximately 28% of the US population, including basic demographics and clinical characteristics. The SEER data used were released in April 2019, and the data cover 1975 to 2016.

Young patients with breast cancer are defined as patients \leq 40 years old.^[23,24] Since the SEER database has collected stage information since 1988, this study extracted young (18–40 years old) white women with early-stage (stage I–II) (American Joint Committee on Cancer [AJCC] Cancer Staging, 6th Edition) breast cancer as the first or only tumor between 1988 and 2016 from the SEER database. The unilateral breast cancer with definite mastectomy or BCT was selected. Paget disease and inflammatory breast cancer were not taken into account in the analysis. Patients diagnosed by autopsy or death certificates were excluded. The outcomes of interest were breast cancer-specific survival (BCSS) and overall survival (OS). BCSS was calculated from the date of diagnosis to death from breast cancer, and OS was defined as the interval from diagnosis to death from any cause.

2.2. Statistical analysis

Descriptive statistical methods were used to analyze the demographic characteristics of breast cancer patients. A chisquare test was performed to compare the demographic and clinicopathological characteristics of patients with different surgical patterns. Cumulative survival was calculated by Kaplan–Meier survival analysis and compared between BCT and mastectomy cohorts using log-rank tests. Multivariate Cox regression models were built to assess the independent association of all the variables with BCSS and OS in the cohorts (forward: logistic regression [LR]). Hazard ratios (HRs) and their 95% confidence intervals (95% CIs) were estimated using Cox models. Statistical analyses were performed using SPSS 22.0 (Chicago, IL). Two-sided P < .05 was considered statistically significant.

3. Results

3.1. Patient characteristics

From 1988 to 2016, a total of 23,810 patients \leq 40 years old were included in this study based on the SEER data. The patient selection process was illustrated in Fig. 1. The median age of all patients was 37 (range, 18–40) years, and 8449 patients (35.5%) were under 35 years. The median follow-up was 116 (range, 0– 347) months. Among all the patients, 10,681 (44.9%) received BCT, while 13,129 (55.1%) patients had mastectomy. Compared with BCT, younger patients (18–35 years old) were more likely to undergo mastectomy (P < .001). Meanwhile, the mastectomy group was more likely to have larger tumors (P < .001), positive lymph nodes (P < .001), and higher histological grade (P < .001). There were also significant differences in estrogen receptor (ER) status and human epidermal growth receptor 2 (HER2) status between the 2 cohorts (P = .001) (Table 1).

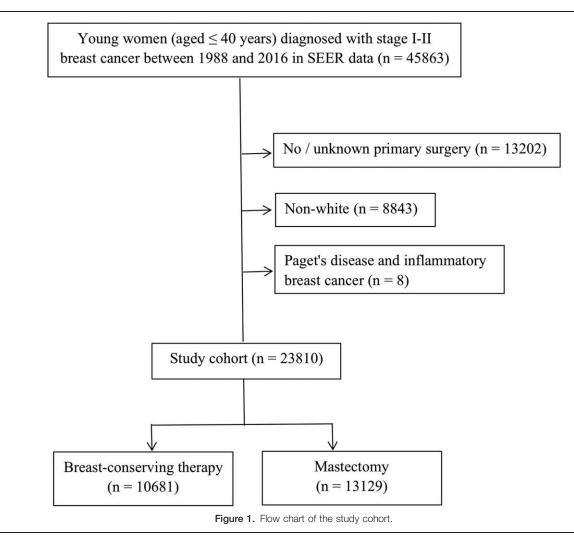
3.2. Trends of crucial breast cancer characteristics over the year

Both the proportions of stage I patients and patients with positive lymph nodes in the study cohort were relatively stable over the years (Fig. 2A and B), even after being divided into 2 age groups. Similarly, the ratios between the 2 age groups were stable over the year (Fig. 2C).

In contrast, the proportion of BCT for young patients with early-stage breast cancer fluctuated over the past 3 decades. The proportion of BCT increased early and then decreased afterward. By the end of the 20th century, the proportion of BCT had grown from nearly 35% to approximately 60% and then gradually fell to 35% into the 21st century. The gaps in the proportion of BCT between the 18 to 35 and 36 to 40 years age groups had enlarged since the beginning of the 21st century. Compared with the 36 to 40 years age group, the younger group was significantly less likely to receive BCT (P < .001) (Fig. 2D).

3.3. Survival analysis

The 10-year BCSS rates for patients receiving BCT and mastectomy were 89.1% and 87.7% (P=.002), while the 10-year overall survival rates were 87.8% and 85.9% (P=.002), respectively. This study analyzed the prognostic factors, including year of diagnosis, age at diagnosis, histological grade, stage T, lymph node status, ER status, HER-2 status, surgery, and chemotherapy. Multivariate analysis showed that certain clinical pathological features were independent factors and were associated with worse BCSS and OS, including younger patients, higher histological grade, higher T stage, lymph node-positive, ER, and HER-2 negative status. Notably, the surgery was also an independent prognostic factor. Compared with the mastectomy



group, the BCT group achieved significantly higher BCSS (HR: 0.917; 95% CI: 0.846–0.995, *P*=.037) and OS (HR: 0.925; 95% CI: 0.859–0.997, *P*=.041) (Table 2).

Then this study further investigated the effects of surgery on survival in the 2 age groups. The 10-year BCSS and OS in the 36 to 40 years age group achieved significantly different, but not in the 18 to 35 group (Fig. 3). Further multivariate analysis of survival in different subgroups of age was also performed. The results showed that the surgery was still an independent prognostic factor in the 36 to 40 group, but not in the 18 to 35 group. In other words, the BCSS and OS survival of BCT were similar with mastectomy in the 18 to 35 group, while were better than mastectomy in the 36 to 40 group (HR: 0.886; 95% CI: 0.798–0.984, P=.024) and OS (HR: 0.897; 95% CI: 0.816–0.986, P=.024) (Table 3).

4. Discussion

BCT is a local treatment that can preserve noncancerous breast tissue, achieve better cosmetic results, reduce tissue damage, and reduce complications. It is generally agreed that patients treated with BCT have better physical and psychological health, superior social function, and higher quality of life than patients receiving a mastectomy.^[5–7] This is particularly crucial in young women

with early-stage breast cancer, as most people expect to live a long time after diagnosis.^[25–28] However, the survival benefit of BCT has been controversial in recent years with long-term follow-up and improved local radiation therapy, especially for young women with early-stage breast cancer. This study analyzed cases (obtained from the SEER database) of breast surgery performed on young women with early-stage breast cancer in a cohort of women representing the United States' general population.

In this study, among young women with breast cancer, patients with a higher tumor burden, such as larger tumor size, higher pathological grade, and hormone receptor-negative diseases, were prone to receive mastectomy. Meanwhile, younger patients were more likely to undergo mastectomy. This is likely because breast cancer in young patients tends to have more aggressive features and occurs at a more advanced stage. Historically, young breast cancer patients have been previously shown to have a higher risk of local recurrence than older breast cancer patients.^[17–20,22,29] Notably, in 2005, the National Comprehensive Cancer Network's (NCCN) guidelines for breast cancer recommended an age below 35 as an indication for mastectomy. Therefore, young patients during that era may have undergone mastectomy rather than BCT based on the findings from these studies. Additionally, young patients are more likely to

Table 1

Characteristics	ALL (%)	Mastectomy (%)	BCT (%)	P value
Year of diagnosis				<.001
1988–1997	3491 (14.7)	1711 (13.0)	1780 (16.7)	
1998–2007	10,007 (42.0)	4805 (36.6)	5202 (48.7)	
2008–2016	10,312 (43.3)	6613 (50.4)	3699 (34.6)	
Age at diagnosis	10,012 (10.0)	0010 (00.1)	0000 (01.0)	<.001
≤35	8449 (35.5)	5025 (38.3)	3424 (32.1)	2.001
36–40	15,361 (64.5)	8104 (61.7)	7257 (67.9)	
Laterality	10,001 (01.0)			.751
Left	11,957 (50.1)	6581 (50.1)	5376 (50.3)	.701
Right	11,853 (49.9)	6548 (49.9)	5305 (49.7)	
Grade	11,000 (40.0)	00-0 (+0.0)	3303 (43.7)	<.001
	2476 (11.2)	1182 (9.7)	1294 (13.0)	<.001
	8005 (36.2)	4485 (36.9)	3520 (35.3)	
II III/IV	11,636 (52.6)	6475 (53.3)	5161 (51.7)	
Unknown	1693	987	706	
	1095	907	700	<.001
Stage	10 705 (45 0)		E2E0 (40 2)	<.001
	10,725 (45.0)	5475 (41.7)	5250 (49.2)	
Т	13,085 (55.0)	7654 (58.3)	5431 (50.8)	. 001
	14,000 (50.0)	7050 (50.0)	0740 (00.0)	<.001
T0-1	14,098 (59.2)	7350 (56.0)	6748 (63.2)	
T2-3	9712 (40.8)	5779 (44.0)	3933 (36.8)	001
N			=== (/= o	<.001
NO	16,797 (70.5)	9073 (69.1)	7724 (72.3)	
N1	7013 (29.5)	4056 (30.9)	2957 (27.7)	
Breast subtype				.001
HR+/HER2-	4482 (58.6)	2854 (57.3)	1628 (61.0)	
HR+/HER2+	1338 (17.5)	898 (18.0)	440 (16.5)	
HR-/HER2+	436 (5.7)	314 (6.3)	122 (4.6)	
HR-/HER2-	1394 (18.2)	914 (18.4)	480 (18.0)	
Unknown	16,160	8149	8011	
ER status				.001
Positive	14,858 (68.7)	8229 (69.7)	6629 (67.6)	
Negative	6760 (31.3)	3583 (30.3)	3177 (32.4)	
Borderline/Unknown	2192	1317	875	
PR status				.417
Positive	13,362 (62.5)	7278 (62.3)	6084 (62.8)	
Negative	8018 (37.5)	4413 (37.7)	3605 (37.2)	
Borderline/Unknown	2430	1438	992	
HER-2 status				.001
Positive	1775 (23.2)	1213 (24.3)	562 (21.0)	
Negative	5882 (76.8)	3771 (75.7)	2111 (79.0)	
Borderline/Unknown	16,153	8145	8008	
Chemotherapy				<.001
Yes	16,278 (64.9)	8519 (64.9)	7759 (72.6)	
No/Unknown	7532 (35.1)	4610 (35.1)	2922 (27.4)	

BCT = breast-conserving therapy, ER = estrogen receptor, HER-2 = human epidermal growth receptor 2, PR = progesterone receptor,

participate vigorously in medical decisions. Moreover, fear of relapse, anxiety related to long-term monitoring, and the fact that long-term radiotherapy will interfere with daily activities may lead them to choose mastectomy, which is considered a more aggressive treatment.^[30,31]

Over the past several decades, an increasing number of patients with early-stage breast cancer have been diagnosed with the improvement of optimal screening strategies, especially for older patients. However, in young patients, sensitive methods for screening early-stage breast cancer still need to be investigated. This study included young women with stage I and II breast cancer. The trends of key characteristic ratios have been stable over the past 3 decades in young women. This finding is consistent with previous studies.^[32,33] To reduce the incidence and mortality of early-stage breast cancer in young patients, new methods for screening, early detection, and prevention should be considered.

In contrast, the proportions of breast conservation over the years appear to fluctuate. In this study, the proportion of breast conservation increased earlier and then decreased over time, consistent with many other studies.^[34-38] The gaps in the proportion of BCT between the 18 to 35 and 36 to 40 years age groups had enlarged since the beginning of the 21st century. Younger patients appeared to be more cautious about BCT. These changes are likely related to the publication of findings from landmark randomized controlled trials, improvements in detection technology, and advances in breast reconstruction methods. In the 1990s, the rates of BCT rose rapidly because of

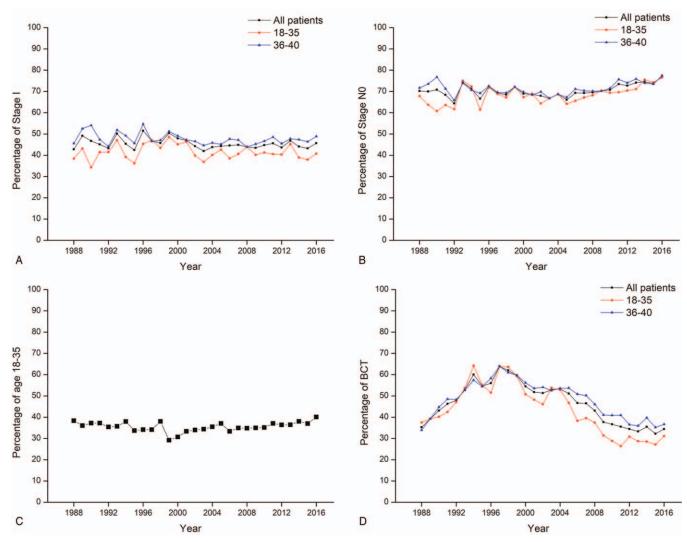


Figure 2. Trends of key breast cancer characteristics over the year. A. Percentage of stage I by age at diagnosis; B. Percentage of N0 by age at diagnosis; C. Percentage of age 18 to 35 years; D. BCT rates by age at diagnosis. BCT=breast-conserving therapy.

the main guidelines for early-stage (stage I or II) breast cancer^[39] based on several randomized controlled trials.^[1,4,9,40,41] With the widespread application of MRI and the development of breast reconstruction technology since the beginning of the 21st century, the rate of BCT has declined.^[34,42,43]

Nevertheless, in recent years, a growing number of studies have shown better survival outcomes of BCT than mastectomy for early-stage breast cancer in the real world.^[13–16,44–47] The reasons are not yet clear or may be related to a better quality of life for patients with BCT^[48,49] and advancement of radiotherapy and systematic therapy.^[50–52] Current studies indicate that local radiotherapy may induce the activation of the immune system to benefit from whole-body immunotherapeutic effects.^[53,54] In recent years, the improvement of surgical methods (such as control of the pathology of resection margins) and the development of radiotherapy technology have further reduced the recurrence rate of breast cancers. Significant progress has been made in various systemic therapies, including improvements in chemotherapeutics, endocrine therapy, targeted therapy, and immunotherapy.^[55] These advances are particularly important for young women, since women under 40 are more likely to present a high-risk tumor phenotype.^[17,19]

The survival differences between BCT and mastectomy in young women still need to be investigated. Like Lazow et al^[56] and Yu et al,^[57] this study focused on young patients with earlystage breast cancer and conducted a population-based survival assessment for breast surgery. The overall 10-year BCSS rate was 89.1% in the BCT group versus 87.7% in the mastectomy group. These BCSS rates and the difference between BCT and mastectomy are similar to other long-term outcomes from retrospective studies. In an analysis among stage I young breast cancer patients, BCSS at 10 years was 91% in the BCT group versus 86% after mastectomy.^[58] The results also showed higher OS in young women who received BCT than in those who underwent mastectomy. After various confounding factors were excluded for multivariate analysis, such as histological grade, T stage, lymph node status, ER status, HER-2 status, BCT still showed survival benefits for BCSS (HR: 0.917; 95% CI: 0.846-0.995, P=.037) and OS (HR: 0.925; 95% CI: 0.859-0.997, P = .041). Subgroup analysis showed that the results also held for

Table 2

Multivariate analysis of risk factors for BCSS and OS in the population.

Variables	BCSS		0\$	
	HR (95% CI)	P value	HR (95% CI)	P value
Year of diagnosis				
1988–1997	Reference		Reference	
1998–2007	0.669 (0.607-0.737)	<.001	0.703 (0.643-0.768)	.001
2008-2016	0.447 (0.373–0.537)	<.001	0.478 (0.403–0.567)	<.001
Age at diagnosis				
<35	Reference		Reference	
36–40	0.857 (0.790–0.929)	<.001	0.912 (0.847–0.983)	.015
Grade				
	Reference		Reference	
	2.242 (1.775–2.832)	<.001	1.735 (1.434–2.099)	<.001
 III/IV	2.528 (2.003–3.191)	<.001	1.970 (1.629–2.382)	<.001
Unknown	2.003 (1.542–2.601)	<.001	1.584 (1.275–1.967)	<.001
Stage T	2.000 ((1001
T0-1	Reference		Reference	
T2-3	1.549 (1.427–1.680)	<.001	1.534 (1.424–1.653)	<.001
Stage N	1.040 (1.427 1.000)	<	1.004 (1.424 1.000)	<.001
NO	Reference		Reference	
N1	1.885 (1.737–2.045)	<.001	1.766 (1.638–1.904)	<.001
ER status	1.000 (1.101 2.010)	<	1.700 (1.000 1.004)	<.001
Positive	Reference		Reference	
Negative	1.151 (1.046–1.267)	.004	1.171 (1.072–1.278)	<.001
Borderline/Unknown	1.082 (0.956–1.225)	.210	1.083 (0.968–1.212)	.164
PR status	1.002 (0.000 1.220)	.210	1.000 (0.000 1.212)	.104
Positive				
Negative	Not included		Not included	
Borderline/Unknown	Not included			
HER-2 status				
Positive	Reference		Reference	
Negative	3.002 (1.844–4.886)	<.001	2.755 (1.770–4.287)	<.001
Borderline/Unknown	2.420 (1.482–3.952)	<.001	2.249 (1.441–3.509)	<.001
Surgery	2.420 (1.402 0.002)	<	2.245 (1.441 0.000)	<.001
Mastectomy	Reference		Reference	
BCS+RT	0.917 (0.846–0.995)	.037	0.925 (0.859–0.997)	.041
Chemotherapy	0.017 (0.010 0.000)	.001	0.020 (0.000 0.007)	.1+0.
Yes	Reference		Reference	
No/Unknown	0.718 (0.649–0.795)	<.001	0.773 (0.707–0.846)	<.001
	0.110 (0.049-0.190)	<.001	0.113 (0.101-0.040)	<.001

BCSS = breast cancer specific survival, CI = confidence interval, ER = estrogen receptor, HER-2 = human epidermal growth receptor 2, HR = hazard ratio, OS = overall survival, PR = progesterone receptor.

patients aged 36 to 40 years. While there was separate analysis for the younger than 36 subset, the results do not seem to justify the trend of favoring BCT over mastectomy. Some studies have claimed that BCT and mastectomy are equivalent,^[59-62] while others have shown that BCT improves survival.^[13,63-66] For example, Cao et al^[61] examined 15-year outcomes among 616 women under 40 with early-stage breast cancer treated with BCT, compared with 349 patients treated with mastectomy. The OS, local relapse-free survival, and distant relapse-free survival were similar between the BCT and mastectomy cohorts. Nevertheless, in an analysis of 11,859 patients under 40 from the National Cancer Database between 2004 and 2014, Lazow et al^[56] demonstrated that BCT was associated with significantly increased 10-year survival versus unilateral and bilateral mastectomy. Another study^[57] of 8656 patients under 40 showed that patients in the BCT group demonstrated better OS and BCSS than those in the mastectomy group. Indeed, Quan et al^[63] identified 1381 patients under 35 and demonstrated no survival advantage to mastectomy over BCT in very young breast cancer patients. Therefore, it should be cautious in interpreting the improvement in BCSS and OS after BCT based on the data in the current analysis. For young patients with early stage breast cancer, BCT should be determined by the patients' wills and the surgical techniques. Because BCT may provide a survival advantage that is not inferior to mastectomy, especially in the relatively older (36–40) population. And age alone should not be a contraindication to BCT.

Multivariate analysis also demonstrated decreased survival rates associated with diagnosed in earlier years, younger patients, higher histological grade, higher T stage, lymph node positive, ER, and HER-2 negative status. The fact that our model identified poor survival associated with these factors is not unexpected. It was consistent with previous perceptions and it might serve as validation of our model. The improved survival among patients who received BCT might be due to differences related to adjuvant therapy, such as chemotherapy administration. Nevertheless, in this study, multivariate analysis showed that chemotherapy had no effect on survival between the 2 groups. Meanwhile, these should not bias the results when comparing BCT to mastectomy because the National Comprehensive Cancer Network guidelines do not differentiate between BCT and mastectomy when determining adjuvant systemic therapy. This analysis was unable

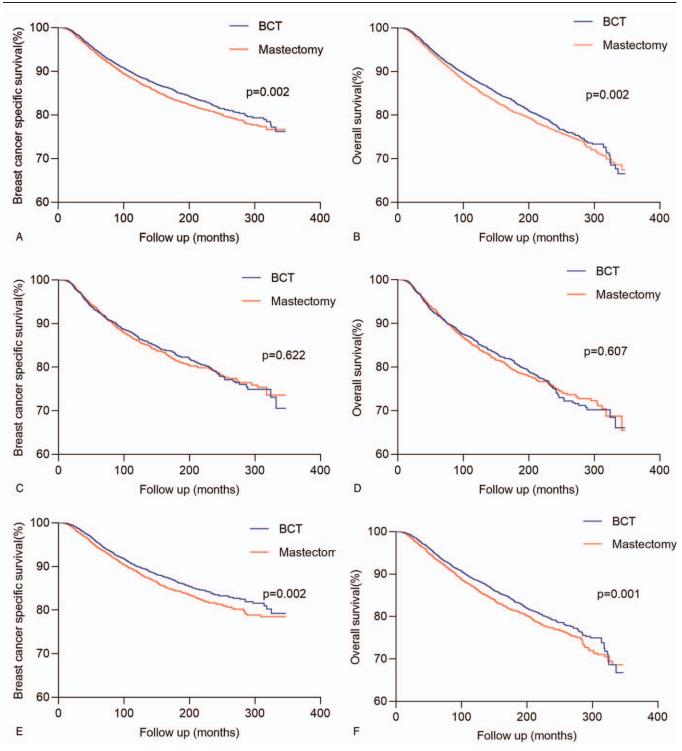


Figure 3. Kaplan–Meier survival curves for BCSS and OS by treatment. A. BCSS for all patients; B. OS for all patients; C. BCSS for 18 to 35 years of age; D. OS for 18 to 35 years of age; E. BCSS for 36 to 40 years of age; F. OS for 36 to 40 years of age. BCSS=breast cancer-specific survival, OS=overall survival.

to account for chemotherapy regimens because this variable is not definitely recorded in the SEER database. However, we acknowledged that it is possible that systemic therapies are used differently for patients who received BCT versus those who underwent a mastectomy. If this is true, it deserves further assessment. We acknowledge several limitations of our study. First, in a retrospective study, bias inevitably occurs due to the possibility of other imbalanced prognostic factors (such as comorbidities, subsequent chemotherapy, and endocrine therapy, etc) and bias in treatment selection. Second, since the data on HER-2 status

Table 3

Multivariate analysis of risk factors for BCSS and OS in the population by age (only surgery is listed).

Variables	BCSS		0\$	
	HR (95% CI)	P value	HR (95% CI)	P value
ALL				
Surgery				
Mastectomy	Reference		Reference	
BCS+RT	0.917 (0.846-0.995)	.037	0.925 (0.859-0.997)	.041
18–35				
Surgery				
Mastectomy	Not included		Not included	
BCS+RT				
36–40				
Surgery				
Mastectomy	Reference		Reference	
BCS+RT	0.886 (0.798-0.984)	.024	0.897 (0.816-0.986)	.024
BCS+RT	0.886 (0.798–0.984)	.024	0.897 (0.816–0.986)	

BCSS = breast cancer specific survival, CI = confidence interval, HR = hazard ratio, OS = overall survival

was not collected in the database until 2010, most of our patients lacked relevant information, and other key information, such as Ki-67, neurovascular invasion, and other aspects, was also lacking. Third, systemic treatments, such as chemotherapy, endocrine therapy, and targeted therapy, were not extracted for analysis. In addition, the SEER database does not contain survival information on relapses, which is undoubtedly essential for patients.

In summary, this large population-based study suggests that for young women with early-stage breast cancer, BCT may provide a survival advantage that is not inferior to mastectomy, especially in the relatively older (36–40) population. This may reduce the problem of over treatment in young women with earlystage breast cancer. Clinicians need to explain the advantages of the 2 choices to patients to make rational judgments. At the same time, relevant prospective studies need to be conducted to evaluate the benefit of BCT for young patients with early-stage breast cancer. Future studies should take into account genetic testing in the analysis of choosing treatments and predicting survival.

Author contributions

Conceptualization: Zhi-Hong Sun, Chuang Chen, Sheng-Rong Sun, Wei-Xing Wang.

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Investigation: Chuang Chen, Xin-Wen Kuang, Sheng-Rong Sun, Wei-Xing Wang.

Methodology: Sheng-Rong Sun, Wei-Xing Wang.

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Validation: Sheng-Rong Sun, Wei-Xing Wang.

- Writing original draft: Zhi-Hong Sun, Chuang Chen.
- Writing review & editing: Zhi-Hong Sun, Chuang Chen, Xin-Wen Kuang, Jun-Long Song, Sheng-Rong Sun, Wei-Xing Wang.

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