Original Article

A retrospective comparative cohort study of SEER database analysis of the prognostic value of breast-conserving surgery and mastectomy in patients with multifocal multicenter breast cancer

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Background: The prognosis of multifocal multicentric breast cancer (MIBC) was related to many factors, and there are different recommendations for surgical approaches. We compare the effects of breast-conserving surgery (BCS) and mastectomy on the survival of multifocal multicenter breast cancer female patients.

Methods: A total of 38,164 female patients with pathologically confirmed multifocal multicenter invasive breast cancer from 2000 to 2018 in the Surveillance, Epidemiology, and End Results (SEER) database were extracted, and the effects of different factors on the survival of these patients were retrospectively analyzed. The patients were divided into a BCS group and a mastectomy group, and the differences of breast cancer-specific survival (BCSS) and overall survival (OS) were compared between the 2 groups.

Results: Of the 38,164 patients included in the analysis, 14,533 (38.08%) underwent BCS and 23,631 (61.92%) underwent mastectomy. Multivariate analysis showed that age, grading, staging, number of lesions, radiotherapy, and BCS would affect the independent factors of BCSS and OS in patients. The median follow-up time was 108 months [interquartile range (IQR): 64–162 months). Multifactorial Cox proportional model analysis of prognostic risk showed that BCS reduced BCSS in patients older than 70 years [hazard ratio (HR): 1.35; 95% confidence interval (CI): 1.2–1.53; P<0.001], stage I and II, positive hormone receptor (HR), all 2–3 lesions, no radiotherapy (HR: 1.46; 95% CI: 1.33–1.6; P<0.001) and no chemotherapy (HR: 1.42; 95% CI: 1.28–1.57; P<0.001); BCS also reduced OS in patients over 40 years of age, stages I, II, and IIIC, all molecular subtypes, all HR-positive or negative, 2–3 lesions, and no radiotherapy (HR: 1.38; 95% CI: 1.31–1.46; P<0.001) and no chemotherapy (HR: 1.36; 95% CI: 1.29–1.44; P<0.001) patients. Multivariate Cox regression showed that BCS is an adverse factor for BCSS [adjusted HR 1.2 (1.11–1.3), P<0.001] and OS [adjusted HR 1.24 (1.19–1.3), P<0.001].

Conclusions: In early, good prognosis, treatment-sensitive patients, there is no survival advantage for BCS

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and more BCSS and OS benefit for mastectomy patients.

Keywords: Surveillance, Epidemiology, and End Results (SEER) database; multifocal multicenter breast cancer; prognosis; breast-conserving surgery (BCS); mastectomy

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Introduction

The latest data released by the World Health Organization's International Agency for Research on Cancer (IARC) on global cancer in 2020 show that the incidence of female breast cancer has made it the most common cancer in the world in 2020, accounting for 11.7% (2.26 million/19.29 million) of new cancer cases (1). Multifocal multicentric breast cancer (MIBC) is usually defined as 2 or more malignant lesions in the same breast, and with the development and advancement of imaging, more and more MIBCs are being detected (2,3), and there is an incidence of approximately 5–60% of breast cancers (4,5). MIBCs include multifocal breast cancers (MFBC) and multicentric breast cancers (MCBC). It has been suggested that MIBC has a less favorable prognosis than single foci (6,7). MIBC is associated with both local and distant tumor recurrence, has a negative impact on prognosis, and is independent of surgical approaches and adjuvant therapy (6). In terms of treatment, for patients with MIBC, the principles of both systemic and non-surgical local treatment are the same as those for unifocal breast cancer. One study concluded that there was no significant difference in the local recurrence rate and overall survival (OS) of MIBC patients undergoing breast-conserving surgery (BCS) and radiotherapy versus those undergoing mastectomy (8). In the 2017 edition of St. Gallen, stemming from a meta-analysis (9), most experts also endorse performing BCS in patients with MIBC, but stress the need to ensure negative margins, recommend radiotherapy, and the preservation of a satisfactory appearance (10). However, MIBC patients in this meta-analysis were not the main study population, nor performing subgroup analysis (9). Another meta-analysis had apparently similar rates of locoregional recurrence (LRR) for BCS compared with mastectomy, it supported the feasibility of BCS in this group of patients, especially in low-risk patients, but the studies included in the analysis were moderate quality, older trials with incomplete follow-up data and selection bias, with a limited level of clinical evidence (11). Therefore, only patients with MIBC were included in this study, and a large number of patients in the Surveillance, Epidemiology, and End Results (SEER) database were retrospectively analyzed to compare the impact of 2 surgical approaches (BCS and mastectomy) on the survival of patients with MIBC, with the aim of exploring better treatment options and providing a better basis for clinical decision making of MIBC patients. We present the following article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-682/rc).

Highlight box

Key findings

- In early, good prognosis, treatment-sensitive patients with multifocal multicenter breast cancer, there is no survival advantage for BCS and more BCSS and OS benefit for mastectomy patients.

What is known and what is new?

- In the 2017 edition of St. Gallen, stemming from a meta-analysis, most experts endorse performing BCS in patients with MIBC. Another meta-analysis supported the feasibility of BCS in this group of patients, especially in low-risk patients.
- In this study, the impact of 2 surgical approaches (BCS and mastectomy alone) on the survival of patients with MIBC was compared using a retrospective data analysis method to explore better treatment options and providing a better basis for clinical decision making in MIBC patients.

What is the implication, and what should change now?

- We should choose a surgical treatment carefully for patients with multifocal multicenter breast cancer. Mastectomy is a better choice in early, good prognosis, treatment-sensitive patients.

Methods

Screening database and inclusion population

The study aimed to use the SEER database to evaluate the effects of BCS and mastectomy on the survival of multifocal

multicenter breast cancer female patients. We conducted a retrospective analysis of the data in the SEER database of female patients with pathologically confirmed multifocal multicentric invasive breast cancer from 2000 to 2018 by using the SEER database 8.3.9 software to extract, excluding those with distant metastases, patients with <3 months of follow-up, and those with incomplete data included in the analysis. The SEER database is free to use, and a Data-Use Agreement for the SEER 1973–2018 Research Data File was completed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Relevant data extracted included the following: age, race, marital status, history of benign tumor, surgical modality, histological grade, hormone receptor/human epidermal growth factor receptor 2 (HR/HER2) status, staging, whether chemotherapy was administered, and whether radiotherapy was administered.

According to Surgery Codes Breast C500-C509 in the SEER Program Coding and Staging Manual 2021 (12), BCS is defined as surgery to remove the primary tumor of the breast and a portion of the breast tissue, where residual cancer can be present. Mastectomy is defined as a procedure that removes at least all breast tissue and may also include simple subcutaneous excision with preservation of the nipple-areola complex and reconstruction, simple mastectomy with removal of the nipple-areola complex and a portion of the skin or modified radical surgery with axillary lymph node dissection, radical surgery with excision including the pectoralis minor muscle or with addition of the pectoralis major muscle, and extended radical surgery with excision including lymph nodes in the internal breast area.

According to the Breast Equivalent Terms and Definitions in the SEER Program Coding and Staging Manual 2021 (12), there is no clear quadrant in the SEER database for multicentric and MFBCs. For multiple lesions, the last digit code is registered as "9", which is denoted as NOS (C509), therefore, this study did not differentiate between multicenter and multifocal. Patients were divided into a breast-conserving group and a mastectomy group according to the surgical approaches. The age at diagnosis was divided into ≤39, 40–59, 60–69, and ≥70 years. Race was divided into white, black, and other, and marital status was divided into married, divorced and separated, single, and widowed. Lateral was divided into left and right. Tumor histology was classified as prognostic malignancy, invasive carcinoma, septic carcinoma, nonspecific carcinoma, and other. Grading included I, II, III, and undifferentiated groups. The staging of patients included in the registry included patients according to the 6th, 7th, and 8th editions of the American Joint Committee on Cancer (AJCC), respectively. We compared the staging differences between the 3 editions and unified the data from the three editions of staging. According to the data provided in the database, staging included HR+/HER2–, HR+/HER2+, HR–/HER2+, and HR–/HER2–. The number of lesions and whether the patient underwent chemotherapy and radiotherapy were also included.

As HER2 expression in breast cancer patients started to be recorded in the SEER database from 2010, it will affect the accuracy in stratification to a certain extent.

Observation indicators

Our observational analysis metrics were breast cancer-specific survival (BCSS) and OS. BCSS is the time from diagnosis to death from breast cancer, and OS is the time from diagnosis to death from any cause.

Statistical analysis

Figure 1 shows the number and percentage of clinical, pathological, and treatment indicators for the 2 included populations. In total, 38,164 patients were included in this study, of which 14,533 (38.08%) patients were in the BCS group and 23,631 (61.92%) patients were in the mastectomy group. We determined the risk factors associated with OS and BCSS in the overall population by hazard ratio (HR) results of 95% confidence interval (CI) for univariate and multifactorial analyses, and performed multifactorial Cox proportional model analysis of prognostic risk and survival analysis for both surgical approaches. Since the number of patients with 4–6 lesions was 1,724 (4.52%), they were combined into 1 group for analysis. The Kaplan-Meier (KM) curve and log-rank test were used to compare BCSS and OS for different numbers of lesions, whether to apply chemotherapy or not, whether to apply radiotherapy or not, and different status of HR/HER2, and all outcome indicators were set with $P<0.05$ indicating statistically significant differences. In addition, some indicators had large missing values; instead of deleting the missing values, data analysis was conducted directly on the data containing null values.

All statistical analyses and survival curves were performed using R software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria, http://www.Rproject.org/).

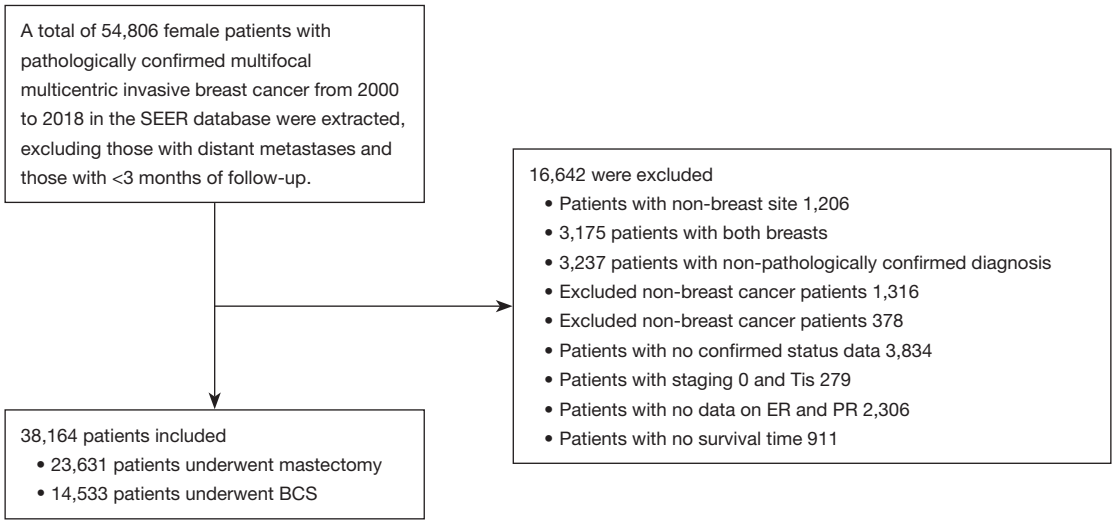

Figure 1 Flow scheme of the study. SEER, Surveillance, Epidemiology, and End Results; BCS, breast-conserving surgery; ER, estrogen receptor; PR, progesterone receptor.

Results

Characteristics of included cases

A total of 38,164 patients were included in this study, of which 14,533 (38.08%) patients were in the BCS group and 23,631 (61.92%) patients were in the mastectomy group. By the number of lesions, 29,502 patients (77.3%) had 2 lesions, 6,938 patients (18.18%) had 3 lesions, and 1,724 patients (4.52%) had 4 or more lesions. Relevant data extracted from both the BCS and mastectomy groups, respectively, included age, race, marital status, laterality of tumor occurrence, histology, grading, staging, HR/HER2 status, ER status, PR status, HER2 status, HR status, number of tumors, and whether they received chemotherapy and radiotherapy, and only the laterality of tumor occurrence (P=0.437) and number of tumors (P=0.263) were not statistically different, whereas all others were statistically significantly different (P<0.001) (*Table 1*). The median follow-up time was 108 months [interquartile range (IQR): 64–162 months].

Prognostic analysis of MIBC patients

For univariate analysis of all included multifocal multicenter patients, age, grading, staging, HR/HER2 status, number of lesions, chemotherapy, and radiotherapy were independent factors affecting BCSS, whereas age, grading, staging, HR/HER2 status, chemotherapy, radiotherapy, and BCS were independent factors affecting OS (*Table 2*). We deleted the missing data and made a sensitivity analysis, it showed that radiotherapy did not affect BCSS (Table S1).

Based on the univariate analysis results, further multivariate analysis was performed, and the results showed that age, grading, staging, PR status, number of lesions, radiotherapy, and BCS were independent factors affecting BCSS, whereas age, grading, staging, estrogen receptor (ER) status, progesterone receptor (PR) status, number of lesions, chemotherapy, radiotherapy, and BCS were independent factors affecting OS (*Table 3*). In the sensitivity analysis, chemotherapy was a dependent factor for OS (Table S2).

After survival analysis, there was no statistically significant difference in BCSS for different number of lesions (P=0.71) and a statistically significant difference in OS (P<0.0001) (*Figure 2*). In patients without chemotherapy, there was a statistically significant difference in BCSS (P=0.00011) and OS (P<0.0001) in the mastectomy group. Among patients treated with chemotherapy, there was a statistically significant difference in BCSS in the breast-conserving group (P=0.00019), but there was no statistically significant difference in OS (P=0.066). Among patients without radiotherapy, there was a statistically significant difference in BCSS (P<0.0001) and OS (P<0.0001) in the mastectomy group. Among patients treated with radiotherapy, there was a statistically significant difference in BCSS (P<0.0001) and OS (P<0.0001) in the breast-conserving group (*Figure 3*). We also analyzed patients with different HR/HER2 status, and there was no statistically significant difference in BCSS between the 2 surgical approaches for patients in both the

Table 1 Characteristics of including patients

Characteristics	All N (%)	Mastectomy N (%)	BCS N (%)	P value
Age (years)				<0.001
≤39	1,193 (3.13)	826 (3.5)	367 (2.5)	
40–59	13,108 (34.35)	8,807 (37.3)	4,301 (29.6)	
60–69	9,711 (25.45)	6,040 (25.6)	3,671 (25.3)	
≥70	14,152 (37.08)	7,958 (33.7)	6,194 (42.6)	
Race				<0.001
Black	4,047 (10.60)	2,408 (10.2)	1,639 (11.3)	
White	31,856 (83.47)	19,679 (83.3)	12,177 (83.8)	
Others	2,261 (5.92)	1,544 (6.5)	717 (4.9)	
Marital status				<0.001
Married	19,279 (50.52)	12,428 (52.6)	6,851 (47.1)	
Separated	4,199 (11.00)	2,675 (11.3)	1,524 (10.5)	
Single	4,892 (12.82)	3,078 (13.0)	1,814 (12.5)	
Widowed	7,122 (18.66)	4,186 (17.7)	2,936 (20.2)	
Missing/unknown	2,672 (7.00)	1,264 (5.3)	1,408 (9.7)	
Laterality				0.437
Left	19,515 (51.13)	12,121 (51.3)	7,394 (50.9)	
Right	18,649 (48.87)	11,510 (48.7)	7,139 (49.1)	
Histology				<0.001
Favorable	1,467 (3.84)	728 (3.1)	739 (5.1)	
ILC	5,011 (13.13)	3,583 (15.2)	1,428 (9.8)	
Metaplastic	143 (0.37)	89 (0.4)	54 (0.4)	
NST	30,644 (80.30)	18,724 (79.2)	11,920 (82.0)	
Others	899 (2.36)	507 (2.1)	392 (2.7)	
Grade				<0.001
I	7,556 (19.80)	4,342 (18.4)	3,214 (22.1)	
II	15,201 (39.83)	9,796 (41.5)	5,405 (37.2)	
III	9,855 (25.82)	6,467 (27.4)	3,388 (23.3)	
Undifferentiated	410 (1.07)	275 (1.2)	135 (0.9)	
Missing/unknown	5,142 (13.47)	2,751 (11.6)	2,391 (16.5)	
Stage				<0.001
I	18,015 (47.20)	10,160 (43.0)	7,855 (54.0)	
IIA	8,066 (21.14)	5,337 (22.6)	2,729 (18.8)	
IIB	3,571 (9.36)	2,735 (11.6)	836 (5.8)	
IIIA	2,585 (6.77)	2,155 (9.1)	430 (3.0)	
IIIB	1,133 (2.97)	749 (3.2)	384 (2.6)	
IIIC	1,125 (2.95)	973 (4.1)	152 (1.0)	
Missing/unknown	3,669 (9.61)	1,522 (6.4)	2,147 (14.8)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	All N (%)	Mastectomy N (%)	BCS N (%)	P value
Subtype				<0.001
HR−/HER2+	507 (1.33)	337 (1.4)	170 (1.2)	
HR+/HER2−	9,550 (25.02)	6,138 (26.0)	3,412 (23.5)	
HR+/HER2+	1,181 (3.09)	827 (3.5)	354 (2.4)	
HR−/HER2−	1,051 (2.75)	707 (3)	344 (2.4)	
Missing/unknown	25,875 (67.80)	15,622 (66.1)	10,253 (70.5)	
ER status				<0.001
Negative	5,478 (14.35)	3,506 (14.8)	1,972 (13.6)	
Positive	27,354 (71.67)	17,118 (72.4)	10,236 (70.4)	
Missing/unknown	5,332 (13.97)	3,007 (12.7)	2,325 (16.0)	
PR status				<0.001
Negative	9,517 (24.94)	6,032 (25.5)	3,485 (24.0)	
Positive	22,862 (59.90)	14,325 (60.6)	8,537 (58.7)	
Missing/unknown	5,785 (15.16)	3,274 (13.9)	2,511 (17.3)	
HER2 status				<0.001
Negative	10,657 (27.92)	6,878 (29.1)	3,779 (26.0)	
Positive	1,700 (4.45)	1,172 (5.0)	528 (3.6)	
Missing/unknown	25,807 (67.62)	15,581 (65.9)	10,226 (70.4)	
HR status				<0.001
Negative	5,076 (13.30)	3,250 (13.8)	1,826 (12.6)	
Positive	27,243 (71.38)	17,068 (72.2)	10,175 (70.0)	
Missing/unknown	5,845 (15.32)	3,313 (14.0)	2,532 (17.4)	
Multicentral				0.263
2	29,502 (77.30)	18,303 (77.5)	11,199 (77.1)	
3	6,938 (18.18)	4,270 (18.1)	2,668 (18.4)	
4	1,365 (3.58)	841 (3.6)	524 (3.6)	
5	270 (0.71)	155 (0.7)	115 (0.8)	
≥6	89 (0.23)	62 (0.3)	27 (0.2)	
Chemotherapy				<0.001
No	25,798 (67.60)	14,785 (62.6)	11,013 (75.8)	
Yes	12,366 (32.40)	8,846 (37.4)	3,520 (24.2)	
Radiation				<0.0001
No	26,402 (69.18)	18,944 (80.2)	7,458 (51.3)	
Yes	11,107 (29.10)	4,314 (18.3)	6,793 (46.7)	
Missing/unknown	655 (1.72)	373 (1.6)	282 (1.9)	

BCS, breast conserving surgery; ILC, invasive lobar carcinoma; NST, no special type; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor.

Table 2 Univariate analysis of BCSS and OS

Characteristics	BCSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
≤39	1 (ref.)		1 (ref.)	
40–59	0.66 (0.58–0.74)	<0.001	0.87 (0.78–0.97)	0.0138
60–69	0.62 (0.55–0.71)	<0.001	1.33 (1.19–1.48)	<0.001
≥70	0.95 (0.84–1.07)	0.37	3.21 (2.89–3.58)	<0.001
Race				
Black	1 (ref.)		1 (ref.)	
White	0.62 (0.58–0.67)	<0.001	0.8 (0.76–0.84)	<0.001
Others	0.63 (0.56–0.71)	<0.001	0.61 (0.56–0.67)	<0.001
Marital status				
Married	1 (ref.)		1 (ref.)	
Separated	1.2 (1.1–1.3)	<0.001	1.26 (1.2–1.33)	<0.001
Single	1.43 (1.32–1.54)	<0.001	1.34 (1.27–1.4)	<0.001
Widowed	1.55 (1.45–1.66)	<0.001	2.54 (2.45–2.64)	<0.001
Laterality				
Left	1 (ref.)		1 (ref.)	
Right	0.99 (0.95–1.05)	0.832	1 (0.97–1.03)	0.924
Histology				
Favorable	1 (ref.)		1 (ref.)	
ILC	2.53 (2.09–3.05)	<0.001	1.08 (0.99–1.18)	0.081
Metaplastic	5.83 (4.13–8.24)	<0.001	2.26 (1.8–2.84)	<0.001
NST	2.08 (1.73–2.49)	<0.001	1.01 (0.94–1.09)	0.77
Others	1.96 (1.54–2.5)	<0.001	1.07 (0.95–1.21)	0.28
Grade				
I	1 (ref.)		1 (ref.)	
II	1.62 (1.48–1.76)	<0.001	1.12 (1.07–1.17)	<0.001
III	2.85 (2.61–3.11)	<0.001	1.37 (1.31–1.43)	<0.001
Undifferentiated	2.58 (2.1–3.18)	<0.001	1.12 (0.97–1.3)	0.108
Stage				
I	1 (ref.)		1 (ref.)	
IIA	1.74 (1.61–1.87)	<0.001	1.23 (1.18–1.28)	<0.001
IIB	2.43 (2.22–2.65)	<0.001	1.4 (1.32–1.48)	<0.001
IIIA	3.93 (3.61–4.28)	<0.001	1.77 (1.67–1.87)	<0.001
IIIB	6.47 (5.81–7.21)	<0.001	2.89 (2.67–3.13)	<0.001
IIIC	6.59 (5.96–7.29)	<0.001	2.48 (2.29–2.68)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	BCSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Subtype				
HR–/HER2+	1 (ref.)		1 (ref.)	
HR+/HER2–	0.48 (0.39–0.6)	<0.001	0.69 (0.58–0.81)	<0.001
HR+/HER2+	0.55 (0.42–0.72)	<0.001	0.7 (0.57–0.86)	<0.001
HR–/HER2–	1.22 (0.96–1.56)	0.103	1.21 (1–1.46)	0.049
ER status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.55 (0.52–0.59)	<0.001	0.81 (0.78–0.85)	<0.001
PR status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.53 (0.5–0.56)	<0.001	0.76 (0.74–0.79)	<0.001
HER2 status				
Negative	1 (ref.)		1 (ref.)	
Positive	1.24 (1.07–1.43)	0.004	1.08 (0.97–1.2)	0.157
HR status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.54 (0.51–0.58)	<0.001	0.81 (0.78–0.85)	<0.001
Multicentral				
2	1 (ref.)		1 (ref.)	
3	1.02 (0.95–1.09)	0.589	1.19 (1.15–1.24)	<0.001
≥4	1.04 (0.92–1.18)	0.493	1.34 (1.25–1.44)	<0.001
Chemotherapy				
No	1 (ref.)		1 (ref.)	
Yes	1.44 (1.37–1.52)	<0.001	0.76 (0.73–0.78)	<0.001
Radiation				
No	1 (ref.)		1 (ref.)	
Yes	0.93 (0.88–0.98)	0.009	0.8 (0.77–0.83)	<0.001
Breast conserving				
No	1 (ref.)		1 (ref.)	
Yes	0.98 (0.93–1.03)	0.352	1.14 (1.1–1.17)	<0.001

BCSS, breast cancer-specific survival; OS, overall survival; ILC, invasive lobar carcinoma; NST, no special type; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; HR, hazard ratio; CI, confidence interval.

Table 3 Multivariate of BCSS or OS

Characteristics	BCSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
≤39	1 (ref.)		1 (ref.)	
40–59	0.77 (0.66–0.9)	<0.001	0.97 (0.84–1.12)	0.678
60–69	0.78 (0.66–0.92)	0.003	1.47 (1.28–1.7)	<0.001
≥70	1.29 (1.09–1.52)	0.003	3.32 (2.88–3.82)	<0.001
Race				
Black	1 (ref.)		1 (ref.)	
White	0.78 (0.71–0.86)	<0.001	0.82 (0.77–0.87)	<0.001
Others	0.76 (0.64–0.89)	<0.001	0.71 (0.63–0.79)	<0.001
Marital status				
Married	1 (ref.)		1 (ref.)	
Separated	1.28 (1.16–1.41)	0.06	1.21 (1.13–1.29)	<0.001
Single	1.28 (1.17–1.41)	<0.001	1.32 (1.24–1.41)	<0.001
Widowed	1.38 (1.07–1.78)	<0.001	1.5 (1.43–1.58)	<0.001
Histology				
Favorable	1 (ref.)		1 (ref.)	
ILC	1.38 (1.07–1.78)	0.013	0.96 (0.85–1.09)	0.53
Metaplastic	1.52 (0.92–2.52)	0.102	1.28 (0.92–1.78)	0.139
NST	1.13 (0.89–1.44)	0.317	0.96 (0.86–1.08)	0.512
Others	1.06 (0.76–1.49)	0.724	0.98 (0.82–1.17)	0.826
Grade				
I	1 (ref.)		1 (ref.)	
II	1.31 (1.18–1.46)	<0.001	1.07 (1.01–1.13)	0.018
III	1.76 (1.57–1.98)	<0.001	1.24 (1.16–1.32)	<0.001
Undifferentiated	1.63 (1.24–2.16)	<0.001	1.06 (0.88–1.28)	0.543
Stage				
I	1 (ref.)		1 (ref.)	
IIA	1.64 (1.5–1.8)	<0.001	1.35 (1.29–1.42)	<0.001
IIB	2.35 (2.11–2.62)	<0.001	1.69 (1.57–1.81)	<0.001
IIIA	4.17 (3.73–4.66)	<0.001	2.51 (2.33–2.71)	<0.001
IIIB	5.82 (5.08–6.68)	<0.001	3.06 (2.77–3.38)	<0.001
IIIC	7 (6.14–7.98)	<0.001	3.74 (3.39–4.12)	<0.001
ER status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.91 (0.82–1)	0.062	0.88 (0.82–0.94)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	BCSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
PR status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.66 (0.61–0.72)	<0.001	0.83 (0.78–0.87)	<0.001
Multicentral				
2	1 (ref.)		1 (ref.)	
3	1.04 (0.95–1.13)	0.390	1.12 (1.07–1.18)	<0.001
≥4	1.23 (1.06–1.43)	0.007	1.22 (1.12–1.33)	<0.001
Chemotherapy				
No	1 (ref.)		1 (ref.)	
Yes	1.02 (0.94–1.1)	0.673	0.86 (0.82–0.91)	<0.001
Radiation				
No	1 (ref.)		1 (ref.)	
Yes	0.73 (0.68–0.79)	<0.001	0.76 (0.72–0.8)	<0.001
Breast conserving				
No	1 (ref.)		1 (ref.)	
Yes	1.2 (1.11–1.3)	<0.001	1.24 (1.19–1.3)	<0.001

BCSS, breast cancer-specific survival; OS, overall survival; ILC, invasive lobar carcinoma; NST, no special type; ER, estrogen receptor; PR, progesterone receptor; HR, hazard ratio; CI, confidence interval.

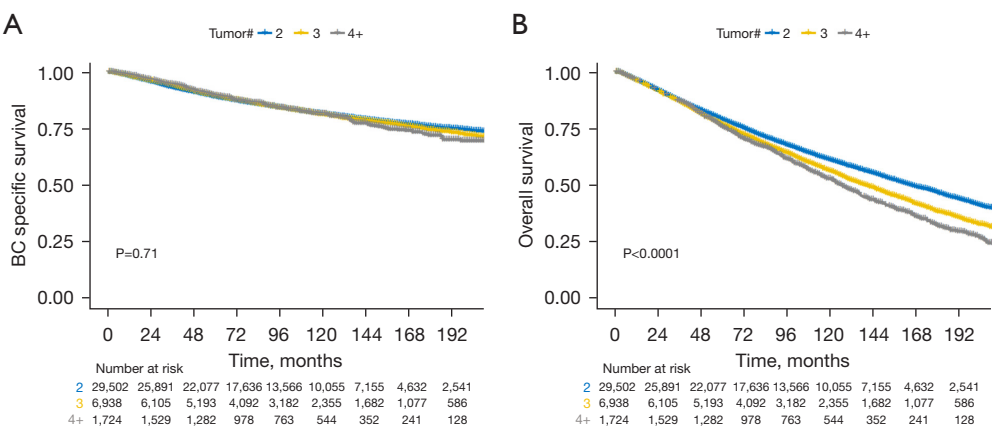

Figure 2 BCSS (A) and OS (B) of including patients with different foci. BCSS, breast cancer-specific survival; OS, overall survival.

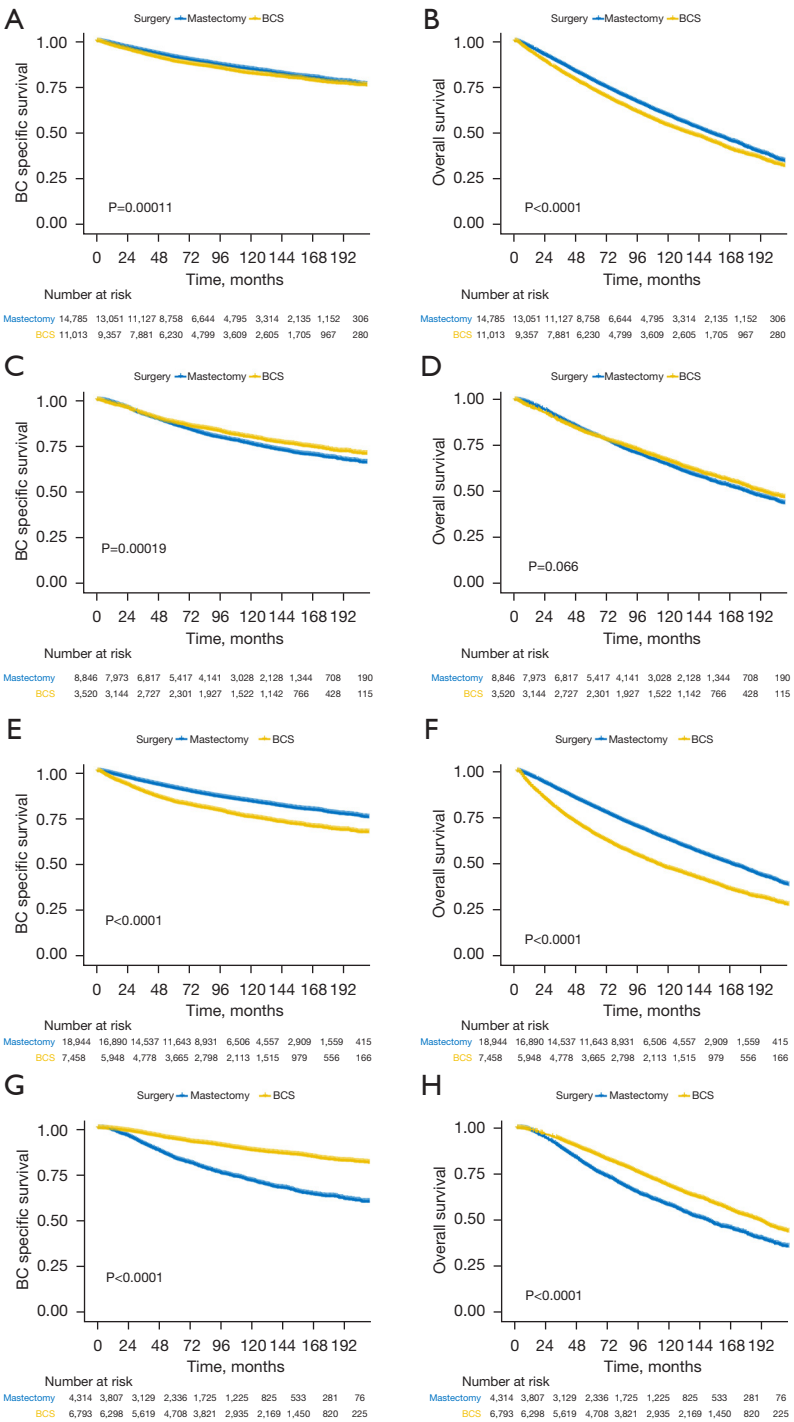

Figure 3 BCSS (A,C,E,G) and OS (B,D,F,H) of including patients with or without chemotherapy or radiotherapy. (A) Comparison of BCSS in patients without chemotherapy after two surgical approaches. (B) Comparison of OS in patients without chemotherapy after two surgical approaches. (C) Comparison of BCSS in patients with chemotherapy after two surgical approaches. (D) Comparison of OS in patients with chemotherapy after two surgical approaches. (E) Comparison of BCSS in patients without radiotherapy after two surgical approaches. (F) Comparison of OS in patients without radiotherapy after two surgical approaches. (G) Comparison of BCSS in patients with radiotherapy after two surgical approaches. (H) Comparison of OS in patients with radiotherapy after two surgical approaches. BCS, breast-conserving surgery; BCSS, breast cancer-specific survival; OS, overall survival.

HR+/HER2+ status group (P=0.32) and the HR–/HER2– status group (P=0.12), but for patients in the HR+/HER2– status group (P<0.0001) and the HR–/HER2+ status group (P=0.032), there was a statistically significant difference in BCSS. There was a statistically significant difference in OS for all patients with different HR/HER2 status (*Figure 4*).

Value of breast conservation in different subgroups of patients

The cases were divided into different subgroups according to the clinicopathological characteristics of the patients, and the effect of BCS on BCSS and OS in different subgroups was evaluated using a multifactorial Cox proportional risk model. The analysis showed that BCSS and OS in the BCS group were related to age, grade, stage, number of lesions, HR status, and whether chemotherapy and radiotherapy were administered. In the BCS group, there were statistically significant differences in BCSS among patients over 70 years of age, stage I and II, HR-positivity, 2–3 lesions, no radiotherapy, radiotherapy and no chemotherapy, and no statistically significant differences among patients with different grading and HR/HER2 status; in the BCS group, there were statistically significant differences in OS for patients over 40 years of age, stage I, II, IIIC, 2–3 lesions, no radiotherapy, radiotherapy and no chemotherapy, and no statistically significant differences for patients with breast cancer of different grades, HR/HER2 status, and HR status. Multivariate Cox regression showed that BCS is an adverse factor for BCSS [adjusted HR 1.2 (1.11–1.3), P<0.001] and OS [adjusted HR 1.24 (1.19–1.3), P<0.001] (*Table 4*). The multifactorial Cox regression analyses to identify factors associated with survival in MIBC patients with BCS and mastectomy being one potential prognostic factor, and adjustment analyses was to ascertain the independent prognostic role of BCS and mastectomy. In the sensitivity analysis, there were also statistically significant differences in BCSS among patients under 59 years, different numbers of lesions and whether to chemotherapy, while there were also statistically significant differences in OS among patients with different age, number of lesions and whether to chemotherapy (Table S3).

Discussion

In this study, we retrospectively analyzed the survival impact of BCS and mastectomy on MIBC patients using clinical data from a large sample in the SEER database. We analyzed 38,164 multicenter multifocal female breast cancer patients and showed a greater benefit of mastectomy on BCSS and OS.

The findings of previous studies have varied widely. A systematic review published in 2018 (11) analyzed 6 studies conducted from 1988 to 2015 comparing MIBC patients undergoing BCS and mastectomy with a median follow-up of 59.5 months, with 694 patients undergoing BCS and 1,627 patients undergoing mastectomy. The results suggest that for low-risk patients, BCS has a lower risk of local recurrence, but there is no significant difference in disease-free survival (DFS) and OS between BCS and mastectomy. A retrospective analysis was published in 2012 (13) comparing the risk of local recurrence between breast-conserving treatment (BCT; BCS and radiotherapy) and mastectomy with a median follow-up of 7.9 years. A total of 887 of the stratified patients underwent mastectomy and 300 patients underwent BCT, of whom treated multi-centered/multifocal (MC/MF) patients were aged 50–69 years, did not have extensive ductal carcinoma in situ (DCIS), and had small tumors (T1a-b). The results showed a difference in the 10-year local recurrence rate, which was 4.6% for BCT and 5.8% for the mastectomy group. However, there was no significant difference in OS and DFS between the 2 groups. A study published in 2009 (14) retrospectively analyzed 478 patients with MIBC, of whom 147 underwent BCS and 331 underwent mastectomy. The median follow-up was 59.33 months in the BCS group and 64.98 months in the mastectomy group. The 5-year OS was 93.38% in the BCS group and 94.53% in the mastectomy group. The 5-year DFS was 89.08% for the BCS group and 91.88% for the mastectomy group, with no statistical difference. A study published in 2014 (15) suggested that BCS was superior to mastectomy. The study retrospectively analyzed 222 patients with MIBC, among which 119 patients underwent BCS and 103 patients underwent mastectomy, with a median follow-up of 55 months. There was no difference in LRR between the 2 groups, but OS was 92% for patients in the BCS group and 72% for patients in the mastectomy group. A study published in 2015 (6) retrospectively analyzed 1,158 patients with stage I–III breast cancer, of whom 191 patients had MIBC, with 115 patients undergoing mastectomy and 76 patients receiving BCS. BCSS was better in patients with BCS than in patients with mastectomy, but there was no difference in the incidence of local and distant metastases.

Previous prognostic studies in MIBC patients (6,11,13-15) have compared survival or risk of local recurrence in subgroup analyses, but our study included only MIBC

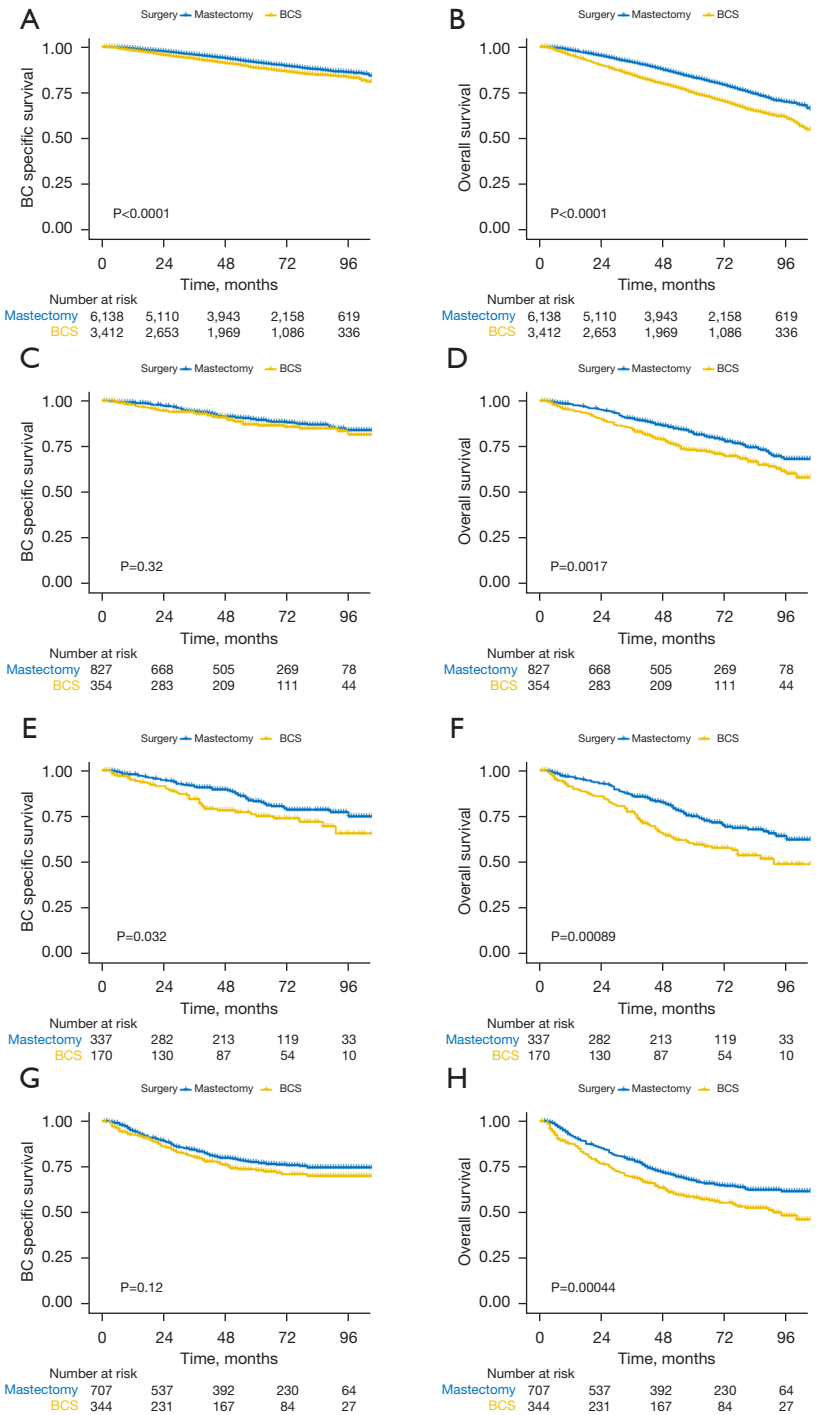

Figure 4 BCSS (A,C,E,G) and OS (B,D,F,H) of including patients with different HR/HER2 status. (A) Comparison of BCSS in patients of HR+/HER2− after two surgical approaches. (B) Comparison of OS in patients of HR+/HER2− after two surgical approaches. (C) Comparison of BCSS in patients of HR+/HER2+ after two surgical approaches. (D). Comparison of OS in patients of HR+/HER2+ after two surgical approaches. (E) Comparison of BCSS in patients of HR−/HER2+ after two surgical approaches. (F) Comparison of OS in patients of HR−/HER2+ after two surgical approaches. (G) Comparison of BCSS in patients of HR−/HER2− after two surgical approaches. (H) Comparison of OS in patients of HR−/HER2− after two surgical approaches. BCS, breast-conserving surgery; BCSS, breast cancer-specific survival; OS, overall survival; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

Table 4 Multivariate Cox regression analysis the influence of BCS on survival in different subgroups

Subgroups	All N (%)	BCSS		OS	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (years)					
≤39	1,193 (3.13)	1.29 (0.9–1.86)	0.163	1.18 (0.84–1.64)	0.338
40–59	13,108 (34.35)	1.07 (0.94–1.22)	0.316	1.15 (1.04–1.27)	0.008
60–69	9,711 (25.45)	1.17 (0.99–1.39)	0.063	1.18 (1.07–1.32)	0.002
≥70	14,152 (37.08)	1.35 (1.2–1.53)	<0.001	1.31 (1.23–1.39)	<0.001
Race					
Black	4,047 (10.6)	1.18 (0.98–1.43)	0.084	1.1 (0.96–1.25)	0.173
White	31,856 (83.47)	1.24 (1.13–1.35)	<0.001	1.27 (1.21–1.34)	<0.001
Others	2,261 (5.92)	0.86 (0.6–1.25)	0.433	1.13 (0.89–1.44)	0.317
Marital status					
Unknown	2,672 [7]	1.41 (1.05–1.88)	0.023	1.31 (1.09–1.58)	0.004
Married	19,279 (50.52)	1.18 (1.06–1.32)	0.003	1.23 (1.15–1.33)	<0.001
Separated	4,199 [11]	1.26 (1.02–1.56)	0.0322	1.16 (1.01–1.33)	0.032
Single	4,892 (12.82)	1.09 (0.9–1.32)	0.385	1.12 (0.99–1.28)	0.080
Widowed	7,122 (18.66)	1.31 (1.12–1.52)	<0.001	1.34 (1.23–1.45)	<0.001
Laterality					
Left	19,515 (51.13)	1.17 (1.05–1.3)	0.004	1.22 (1.14–1.3)	<0.001
Right	18,649 (48.87)	1.23 (1.1–1.37)	<0.001	1.27 (1.19–1.36)	<0.001
Histology					
Favorable	1,467 (3.84)	1.29 (0.76–2.21)	0.344	1.42 (1.11–1.81)	0.005
ILC	5,011 (13.13)	1.42 (1.11–1.81)	0.006	1.41 (1.21–1.65)	<0.001
Metaplastic	143 (0.37)	1.49 (0.29–7.58)	0.629	1.18 (0.46–3.06)	0.732
NST	30,644 (80.3)	1.21 (1.11–1.31)	<0.001	1.24 (1.18–1.3)	<0.001
Others	899 (2.36)	0.63 (0.35–1.15)	0.137	0.94 (0.67–1.33)	0.733
Grade					
I	7,556 (19.8)	1.38 (1.1–1.72)	0.005	1.48 (1.33–1.64)	<0.001
II	15,201 (39.83)	1.23 (1.09–1.39)	<0.001	1.28 (1.2–1.37)	<0.001
III	9,855 (25.82)	1.19 (1.06–1.33)	0.002	1.1 (1.02–1.2)	0.014
Undifferentiated	410 (1.07)	0.98 (0.5–1.91)	0.942	1.38 (0.87–2.2)	0.173
N/A	5,142 (13.47)	1.33 (1.08–1.64)	0.007	1.23 (1.07–1.4)	0.003
Stage					
I	18,015 (47.2)	1.54 (1.33–1.78)	<0.001	1.46 (1.35–1.56)	<0.001
IIA	8,066 (21.14)	1.19 (1.02–1.39)	0.027	1.2 (1.09–1.32)	<0.001
IIB	3,571 (9.36)	1.34 (1.09–1.64)	0.005	1.16 (1.01–1.34)	0.041
IIIA	2,585 (6.77)	0.86 (0.68–1.08)	0.19	0.9 (0.75–1.07)	0.241
IIIB	1,133 (2.97)	1.12 (0.85–1.47)	0.428	1.14 (0.92–1.41)	0.223
IIIC	1,125 (2.95)	0.68 (0.46–0.99)	0.043	0.65 (0.47–0.89)	0.007
N/A	3,669 (9.61)	1.94 (1.52–2.47)	<0.001	1.73 (1.47–2.05)	<0.001

Table 4 (*continued*)

Table 4 (*continued*)

Subgroups	All N (%)	BCSS		OS	
		HR (95% CI)	P value	HR (95% CI)	P value
Subtype					
HR–/HER2+	507 (1.33)	1.94 (1.1–3.43)	0.022	2.16 (1.39–3.36)	0.001
HR+/HER2-	9,550 (25.02)	1.55 (1.3–1.86)	<0.001	1.52 (1.35–1.7)	<0.001
HR+/HER2+	1,181 (3.09)	1.43 (0.89–2.29)	0.136	1.61 (1.16–2.23)	0.004
HR–/HER2–	1,051 (2.75)	1.45 (0.99–2.11)	0.054	1.71 (1.28–2.28)	<0.001
N/A	25,875 (67.80)	1.11 (1.01–1.21)	0.023	1.17 (1.11–1.23)	<0.001
ER status					
Negative	5,478 (14.35)	1.1 (0.95–1.28)	0.192	1.1 (0.95–1.28)	0.192
Positive	27,354 (71.67)	1.27 (1.16–1.39)	<0.001	1.27 (1.16–1.39)	<0.001
N/A	5,332 (13.97)	4.17E+09 (0–Inf)	1	5,135.3 (5.71–4.62E+06)	0.014
PR status					
Negative	9,517 (24.94)	1.16 (1.03–1.3)	0.011	1.21 (1.12–1.31)	<0.001
Positive	22,862 (59.90)	1.25 (1.13–1.39)	<0.001	1.26 (1.19–1.34)	<0.001
N/A	5,785 (15.16)	0.83 (0.48–1.41)	0.482	1.38 (0.96–2)	0.084
HER2 status					
Negative	10,657 (27.92)	1.53 (1.3–1.8)	<0.001	1.55 (1.39–1.72)	<0.001
Positive	1,700 (4.45)	1.55 (1.09–2.22)	0.015	1.69 (1.31–2.19)	<0.001
N/A	25,807 (67.62)	1.11 (1.01–1.21)	0.023	1.17 (1.11–1.23)	<0.001
HR status					
Negative	5,076 (13.30)	1.1 (0.94–1.28)	0.226	1.13 (1.02–1.26)	0.023
Positive	27,243 (71.38)	1.26 (1.16–1.38)	<0.001	1.28 (1.21–1.34)	<0.001
N/A	5,845 (15.32)	1.08 (0.9–1.31)	0.404	1.22 (1.09–1.35)	<0.001
Multicentral					
2	29,502 (77.30)	1.18 (1.08–1.29)	<0.001	1.26 (1.2–1.33)	<0.001
3	6,938 (18.18)	1.28 (1.07–1.54)	0.007	1.21 (1.09–1.34)	<0.001
≥4	1,724 (4.52)	1.24 (0.86–1.78)	0.252	1.21 (0.99–1.49)	0.068
Chemotherapy					
No	25,798 (67.60)	1.42 (1.28–1.57)	<0.001	1.36 (1.29–1.44)	<0.001
Yes	12,366 (32.40)	0.99 (0.87–1.11)	0.810	1.04 (0.95–1.14)	0.351
Radiation					
No	26,402 (69.18)	1.46 (1.33–1.6)	<0.001	1.38 (1.31–1.46)	<0.001
Yes	11,107 (29.10)	0.72 (0.62–0.84)	<0.001	0.86 (0.78–0.95)	0.002
N/A	655 (1.72)	1.08 (0.6–1.96)	0.791	1.22 (0.83–1.79)	0.316
Surgery alone					
No	17,993 (47.15)	0.85 (0.77–0.94)	0.001	1 (0.94–1.07)	0.911
Yes	19,854 (52.02)	1.56 (1.4–1.74)	<0.001	1.42 (1.34–1.51)	<0.001
N/A	317 (0.83)	1.04 (0.34–3.23)	0.942	1.28 (0.71–2.29)	0.415

BCS, breast-conserving surgery; BCSS, breast cancer-specific survival; OS, overall survival; ILC, invasive lobar carcinoma; NST, no special type; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; HR, hazard ratio; CI, confidence interval; N/A, not applicable.

patients and went further with a stratified analysis. Prognostic analysis suggests that BCS reduces BCSS in patients older than 70 years, staged I and II, HR positive, 2–3 lesions, no radiotherapy, and no chemotherapy, and also reduces OS in patients older than 40 years, staged I, II, and IIIC, 2–3 lesions, no radiotherapy, and no chemotherapy. Our results suggest that for early, prognostic, treatment-sensitive patients, BCS has no survival advantage, and mastectomy has more BCSS and OS benefit. Sensitivity analysis also confirmed our results. Excluding some patients who cannot tolerate or refuse chemotherapy, we will only select a subset of early-stage patients to be exempted from chemotherapy in clinical practice, again suggesting that the benefit of mastectomy is more significant for early-stage patients. In addition, when choosing between BCS or mastectomy, the staging of breast-conserving patients is relatively early, with 43% of stage I patients having mastectomy and 54% of patients having BCS (*Table 1*). Based on the staging percentage of this study and the actual clinical situation, we believe that patients who underwent radiotherapy after mastectomy must have had relatively later staging and worse prognosis, so the superior BCSS and OS of breast-conserving plus radiotherapy patients than the mastectomy group does not exclude that there are certain factors to be attributed to its own earlier staging.

A study published in 2010 (16) reported an increased risk of lymph node involvement when the maximum tumor diameter in MIBC was similar to that of single-foci breast cancer, which may suggest that MIBC is a more aggressive type. Our study did not compare patients with multifocal lesions and single lesions, but both univariate and multivariate analyses suggested that multifocal multicentricity was associated with prognosis, and in the univariate analysis, the more lesions there were, the more pronounced was the tendency for prognosis to be affected. In the results of the multivariate analysis, BCSS was better for 2 and 3 lesions than for 4 as well as for upper lesions, and OS was better for 2 lesions than for 3 and 4 and more, again suggesting that MIBC itself is a prognostic correlate of breast cancer.

Some studies (16-21) have found that the prognosis of MIBC was related to age, tumor size, invasive lobular carcinoma, higher nuclear grade, lymphovascular infiltration, ER positivity, and lymph node metastasis, whereas our study, after multivariate analysis, also showed that the prognosis of MIBC was related to age, grade and stage, HR status, and number of lesions, and in addition, the clinical interventions of chemotherapy, radiotherapy, and surgical approaches also affect the prognosis. Therefore, the prognosis of MIBC patients should be evaluated by a comprehensive assessment of clinical and pathological features to avoid underestimating the risk of tumor recurrence, and the choice of treatment should also be evaluated comprehensively to provide patients with better treatment options.

MIBC is divided into MFBC and MCBC, and several methods are commonly used clinically to distinguish between MFBC and MCBC: one is the quadrant method (10), another method is judged by the distance between lesions (11), and there is also the "sick lobe hypothesis" (sick lobe) based on anatomical features (22). It has also been suggested that the distinction between MFBC and MCBC should be based on molecular subtypes and gene expression as a basis for classification to determine whether they are homologous (23). In contrast, the SEER database does not clearly differentiate between multicentric breast cancer and MFBC, and multiple lesions are registered in only one quadrant, so further differentiation and study of multicentric and multifocal could not be performed in this study. There was no significant difference in the proportion of molecular subtype distribution in MIBC compared to single focal breast cancer (24). A study showed that the proportion of distribution of different molecular subtypes in breast cancer was 68.7% in luminal subtype, 14% in HER2-positive subtype, and 10.3% in triple negative subtype (25). In contrast, in our study, after excluding patients with missing or unclear values, 87.3% of patients were luminal subtype, 4.13% were HER2-positive subtype, and 8.54% were triple-negative subtype. This is mainly because the SEER database started to record HER2 expression in breast cancer patients from 2010, with a short follow-up period, and the proportion of patients with missing values or unclear was too large, so there was some inaccuracy in stratification.

This study used the SEER database, which includes a large sample size of patients and objective results. However, it was a retrospective analysis with selection bias. Our results suggest that there is no survival advantage of BCS for early, prognostic, treatment-sensitive patients, and more BCSS and OS benefit for mastectomy patients. Although the data in this study are more adequate, it is still a retrospective analysis, and we need to conduct more prospective, high-quality trials and studies to further improve the diagnosis and treatment of patients with multifocal multicenter breast cancer.

Conclusions

By retrospective analysis of survival rates for BCS and mastectomy in patients with multifocal, multicenter breast cancer, we conclude that there is no survival advantage for BCS and a greater survival advantage for mastectomy in patients with early stage, good prognosis and treatment-sensitive.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-682/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-682/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Univariate sensitive analysis of BCSS and OS

Characteristics	BCSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
≤39	1 (ref.)		1 (ref.)	
40–59	0.63 (0.44–0.89)	0.01	0.74 (0.54–1.02)	0.067
60–69	0.51 (0.36–0.74)	<0.001	0.94 (0.68–1.29)	0.699
≥70	0.92 (0.65–1.30)	0.621	2.25 (1.65–3.08)	<0.001
Race				
Black	1 (ref.)		1 (ref.)	
White	0.68 (0.56–0.81)	<0.001	0.75 (0.66–0.85)	<0.001
Others	0.67 (0.50–0.91)	0.01	0.58 (0.46–0.72)	<0.001
Marital status				
Married	1 (ref.)		1 (ref.)	
Separated	1.16 (0.94–1.42)	0.164	1.4 (1.22–1.61)	<0.001
Single	1.39 (1.16–1.66)	<0.001	1.5 (1.32–1.7)	<0.001
Widowed	1.64 (1.39–1.93)	<0.001	2.68 (2.42–2.97)	<0.001
Laterality				
Left	1 (ref.)		1 (ref.)	
Right	1.22 (1.07–1.38)	0.003	1.02 (0.94–1.11)	0.661
Histology				
Favorable	1 (ref.)		1 (ref.)	
ILC	1.64 (0.99–2.70)	0.054	0.82 (0.63–1.06)	0.133
Metaplastic	6.57 (2.93–14.75)	<0.001	2.51 (1.39–4.55)	0.002
NST	1.48 (0.91–2.39)	0.11	0.82 (0.65–1.05)	0.119
Others	1.23 (0.55–2.77)	0.61	1.04 (0.68–1.6)	0.855
Grade				
I	1 (ref.)		1 (ref.)	
II	1.61 (1.31–1.99)	<0.001	1.18 (1.05–1.33)	0.005
III	3.67 (2.99–4.49)	<0.001	1.79 (1.59–2.02)	<0.001
Undifferentiated	1.61 (0.40–6.52)	0.504	1.15 (0.48–2.78)	0.753
Stage				
I	1 (ref.)		1 (ref.)	
IIA	1.77 (1.48–2.13)	<0.001	1.44 (1.29–1.6)	<0.001
IIB	2.49 (2.03–3.06)	<0.001	1.47 (1.28–1.69)	<0.001
IIIA	4.24 (3.47–5.19)	<0.001	2.19 (1.9–2.53)	<0.001
IIIB	7.45 (5.85–9.50)	<0.001	3.64 (3.03–4.38)	<0.001
IIIC	6.89 (5.41–8.78)	<0.001	3.12 (2.58–3.77)	<0.001
Subtype				
HR–/HER2+	1 (ref.)		1 (ref.)	
HR+/HER2–	0.45 (0.35–0.58)	<0.001	0.69 (0.57–0.84)	<0.001
HR+/HER2+	0.56 (0.41–0.76)	<0.001	0.74 (0.58–0.93)	0.015
HR–/HER2–	1.21 (0.91–1.61)	0.181	1.27 (1.02–1.59)	0.035
ER status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.40 (0.34–0.46)	<0.001	0.58 (0.52–0.65)	<0.001
PR status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.42 (0.37–0.48)	<0.001	0.63 (0.57–0.69)	<0.001
HER2status				
Negative	1 (ref.)		1 (ref.)	
Positive	1.33 (1.13–1.58)	<0.001	1.09 (0.97–1.24)	0.148
HR status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.40 (0.35–0.47)	<0.001	0.59 (0.53–0.66)	<0.001
Multicentral				
2	1 (ref.)		1 (ref.)	
3	1.13 (0.96–1.33)	0.149	1.42 (1.28–1.57)	<0.001
≥4	1.38 (1.04–1.83)	0.025	1.50 (1.24–1.81)	<0.001
Chemotherapy				
No	1 (ref.)		1 (ref.)	
Yes	1.63 (1.43–1.85)	<0.001	0.89 (0.81–0.97)	0.01
Radiation				
No	1 (ref.)		1 (ref.)	
Yes	0.96 (0.84–1.10)	0.59	0.83 (0.75–0.91)	<0.001
Breast Conserving				
No	1 (ref.)		1 (ref.)	
Yes	1.07 (0.93–1.22)	0.363	1.33 (1.22–1.45)	<0.001

BCSS, breast cancer-specific survival; ILC, invasive lobar carcinoma; NST, no special type; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; OS, overall survival; HR, hazard ratio; CI, confidence interval.

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Table S2 Multivariate sensitive analysis of BCSS and OS

Characteristics	BCSS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
≤39	1 (ref.)		1 (ref.)	
40–59	0.79 (0.55–1.14)	0.208	0.86 (0.62–1.19)	0.359
60~69	0.67 (0.46–0.97)	0.036	1.05 (0.76–1.45)	0.762
≥70	1.17 (0.81–1.69)	0.413	2.16 (1.56–2.98)	<0.001
Race				
Black	1 (ref.)		1 (ref.)	
White	0.81 (0.67–0.98)	0.032	0.82 (0.72–0.94)	0.003
Others	0.76 (0.56–1.03)	0.078	0.70 (0.56–0.87)	0.001
Marital status				
Married	1 (ref.)		1 (ref.)	
Separated	1.10 (0.90–1.36)	0.35	1.29 (1.12–1.48)	<0.001
Single	1.23 (1.02–1.48)	0.027	1.44 (1.27–1.64)	<0.001
Widowed	1.24 (1.04–1.49)	0.018	1.63 (1.46–1.82)	<0.001
Histology				
Favorable	1 (ref.)		1 (ref.)	
ILC	1.24 (0.74–2.06)	0.412	0.80 (0.61–1.05)	0.109
Metaplastic	1.82 (0.80–4.16)	0.157	1.10 (0.60–2.02)	0.756
NST	0.93 (0.57–1.52)	0.778	0.76 (0.60–0.98)	0.033
Others	0.64 (0.28–1.44)	0.28	0.81 (0.52–1.25)	0.338
Grade				
I	1 (ref.)		1 (ref.)	
II	1.29 (1.04–1.60)	0.019	1.07 (0.95–1.21)	0.277
III	2.14 (1.71–2.69)	<0.001	1.40 (1.22–1.61)	<0.001
Undifferentiated	0.77 (0.19–3.14)	0.711	0.80 (0.33–1.96)	0.631
Stage				
I	1 (ref.)		1 (ref.)	
IIA	1.59 (1.32–1.92)	<0.001	1.44 (1.29–1.62)	<0.001
IIB	2.39 (1.93–2.96)	<0.001	1.72 (1.49–1.99)	<0.001
IIIA	4.73 (3.8–5.89)	<0.001	3.01 (2.57–3.51)	<0.001
IIIB	6.15 (4.78–7.91)	<0.001	3.43 (2.84–4.15)	<0.001
IIIC	8.18 (6.29–10.64)	<0.001	4.70 (3.83–5.76)	<0.001
ER status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.78 (0.63–0.95)	0.016	0.75 (0.64–0.87)	<0.001
PR status				
Negative	1 (ref.)		1 (ref.)	
Positive	0.58 (0.49–0.69)	<0.001	0.77 (0.68–0.87)	<0.001
Multicentral				
2	1 (ref.)		1 (ref.)	
3	1.15 (0.97–1.36)	0.104	1.28 (1.15–1.43)	<0.001
≥4	1.58 (1.19–2.10)	0.002	1.34 (1.11–1.62)	0.002
Chemotherapy				
No	1 (ref.)		1 (ref.)	
Yes	1.03 (0.88–1.20)	0.714	0.90 (0.80–1.00)	0.051
Radiation				
No	1 (ref.)		1 (ref.)	
Yes	0.64 (0.55–0.74)	<0.001	0.66 (0.60–0.74)	<0.001
Breast Conserving				
No	1 (ref.)		1 (ref.)	
Yes	1.55 (1.34–1.79)	<0.001	1.57 (1.43–1.73)	<0.001

BCSS, breast cancer-specific survival; ILC, invasive lobar carcinoma; NST, no special type; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; OS, overall survival; HR, hazard ratio; CI, confidence interval.

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Table S3 Multivariate Cox regression sensitive analysis the influence of BCS on survival in different subgroups

Subgroups	Patient No.	BCSS		OS	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (years)					
≤39	234	3.51 (1.27–9.69)	0.015	3.08 (1.24–7.67)	0.0156
40–59	3,120	1.74 (1.32–2.29)	<0.001	1.64 (1.30–2.06)	<0.001
60–69	2,704	1.32 (0.95–1.83)	0.093	1.38 (1.10–1.72)	0.0045
≥70	3,528	1.52 (1.23–1.88)	<0.001	1.58 (1.40–1.79)	<0.001
Race					
Black	970	1.93 (1.32–2.82)	<0.001	1.69 (1.30–2.20)	<0.001
White	7,924	1.55 (1.31–1.83)	<0.001	1.57 (1.41–1.75)	<0.001
Others	692	1.19 (0.60–2.37)	0.617	1.38 (0.87–2.19)	0.17
Marital status					
Married	5,254	1.47 (1.18–1.83)	<0.001	1.55 (1.33–1.81)	<0.001
Separated	1,208	1.54 (1.00–2.37)	0.052	1.67 (1.26–2.22)	<0.001
Single	1,456	1.62 (1.13–2.31)	0.00823	1.40 (1.09–1.80)	0.00845
Widowed	1,668	1.6 (1.19–2.15)	0.00177	1.70 (1.44–2.02)	<0.001
Laterality					
Left	4,957	1.66 (1.34–2.06)	<0.001	1.67 (1.46–1.92)	<0.001
Right	4,629	1.46 (1.19–1.78)	<0.001	1.48 (1.29–1.70)	<0.001
Histology					
Favorable	258	2.1 (0.59–7.45)	0.253	1.49 (0.84–2.62)	0.172
ILC	1,456	1.92 (1.27–2.90)	0.00189	1.93 (1.46–2.54)	<0.001
NST	7,726	1.50 (1.28–1.76)	<0.001	1.52 (1.37–1.70)	<0.001
Others	146	0.32 (0.06–1.63)	0.171	1.50 (0.49–4.53)	0.475
Grade					
I	2,308	1.67 (1.08–2.58)	0.0212	1.86 (1.49–2.33)	<0.001
II	4,659	1.59 (1.26–2.01)	<0.001	1.47 (1.27–1.70)	<0.001
III	2,598	1.48 (1.20–1.82)	<0.001	1.54 (1.31–1.81)	<0.001
Stage					
I	4,954	2.09 (1.55–2.81)	<0.001	2.00 (1.70–2.36)	<0.001
IIA	2,216	1.74 (1.28–2.38)	<0.001	1.64 (1.35–2.00)	<0.001
IIB	1,103	1.89 (1.30–2.76)	<0.001	1.58 (1.19–2.09)	0.00137
IIIA	713	0.85 (0.54–1.34)	0.489	0.85 (0.60–1.22)	0.378
IIIB	320	2.02 (1.26–3.26)	0.004	1.91 (1.30–2.81)	<0.001
IIIC	280	0.34 (0.12–0.96)	0.041	0.39 (0.17–0.90)	0.0282
Subtype					
HR–/HER2+	369	1.94 (1.10–3.43)	0.022	2.16 (1.39–3.36)	<0.001
HR+/HER2–	7,541	1.55 (1.30–1.86)	<0.001	1.52 (1.35–1.70)	<0.001
HR+/HER2+	895	1.43 (0.89–2.29)	0.136	1.61 (1.16–2.23)	0.004
HR–/HER2–	781	1.45 (0.99–2.11)	0.054	1.71 (1.28–2.28)	<0.001
ER status					
Negative	1,225	1.58 (1.18–2.13)	0.002	1.82 (1.45–2.27)	<0.001
Positive	8,361	1.55 (1.31–1.84)	<0.001	1.53 (1.37–1.71)	<0.001
PR status					
Negative	2,258	1.57 (1.25–1.97)	<0.001	1.67 (1.41–1.98)	<0.001
Positive	7,328	1.54 (1.27–1.86)	<0.001	1.52 (1.36–1.72)	<0.001
HER2status					
Negative	8,322	1.53 (1.30–1.80)	<0.001	1.55 (1.39–1.72)	<0.001
Positive	1,264	1.55 (1.09–2.22)	0.015	1.69 (1.31–2.19)	<0.001
HR status					
Negative	1,150	1.53 (1.13–2.09)	0.006	1.78 (1.40–2.25)	<0.001
Positive	8,436	1.57 (1.33–1.86)	<0.001	1.54 (1.38–1.71)	<0.001
Multicentral					
2	7,502	1.47 (1.24–1.74)	<0.001	1.53 (1.36–1.71)	<0.001
3	1,673	1.68 (1.20–2.36)	0.002	1.56 (1.26–1.92)	<0.001
≥4	411	4.07 (1.89–8.79)	<0.001	3.60 (2.24–5.79)	<0.001
Chemotherapy					
No	6,274	1.83 (1.50–2.24)	<0.001	1.76 (1.56–1.98)	<0.001
Yes	3,312	1.29 (1.03–1.63)	0.0284	1.38 (1.16–1.65)	<0.001
Radiation					
No	6,523	1.92 (1.62–2.28)	<0.001	1.86 (1.66–2.08)	<0.001
Yes	3,063	0.76 (0.55–1.04)	0.0813	0.88 (0.71–1.09)	0.228
Surgery alone					
No	4,832	1.01 (0.83–1.24)	0.924	1.16 (1.00–1.34)	0.0437
Yes	4,754	2.20 (1.77–2.73)	<0.001	1.96 (1.72–2.22)	<0.001

BCSS, breast cancer-specific survival; ILC, invasive lobar carcinoma; NST, no special type; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; OS, overall survival; HR, hazard ratio; CI, confidence interval.

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