



# The prognostic and predictive value of the 8th American Joint Committee on Cancer (AJCC) staging system among early breast cancer patients aged <50 years

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**Background:** This study respectively analyzed the prognostic value and the role in treatment decision-making [breast-conserving surgery (BCS) + radiotherapy (RT) or mastectomy (MAST)] of the 8th American Joint Committee on Cancer (AJCC) pathological prognostic staging system compared with the 7th AJCC anatomical staging system among early breast cancer patients aged <50 years.

**Methods:** Patients with T1-2N0M0 breast cancer aged <50 years were extracted from the Surveillance, Epidemiology, and End Results database between 2010 and 2014. Breast cancer-specific survival (BCSS) was used as the primary endpoint. Chi-squared test, receiver operating characteristics analysis, Kaplan-Meier method, and multivariate Cox proportional models were used to conduct statistical analysis.

**Results:** A total of 22,640 female patients were identified, and 24.4% of them reallocated to new stage groups from the 7th to the 8th AJCC staging. Among them, 46.2% (n=10,450) and 53.8% (n=12,190) of patients received BCS + RT and MAST, respectively. The 8th AJCC staging system was an independent prognostic factor for BCSS. Patients treated with BCS + RT had better BCSS compared to those treated with MAST (P<0.001). According to the 8th AJCC staging, BCS + RT could improve 5-year BCSS compared with MAST in patients with stage IA (P=0.006) and stage IB (P=0.001) diseases, while comparable BCSS was found between the two treatment arms in patients' stage IIA disease (P=0.366). Multivariate analyses replicated similar findings after stratification by the 8th AJCC stages.

**Conclusions:** In patients with T1-2N0 breast cancer and aged <50 years, the 8th AJCC pathological staging system provides accurate prognostic information than the 7th anatomical staging. BCS + RT is the optimal local management for stage IA and IB diseases, while it is the optional management in stage IIA disease according to the 8th AJCC staging.

**Keywords:** Breast cancer; breast-conserving surgery (BCS); mastectomy (MAST); radiotherapy (RT); American Joint Committee on Cancer staging system (AJCC staging system)

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## Introduction

Breast cancer is a malignant disease with the highest prevalence and the leading cause of cancer death in women. Approximately 2 million women were newly diagnosed with breast cancer, and 630,000 died from breast cancer in 2018 worldwide (1). Patients with early breast cancer, especially T1–2 (tumor size  $\leq 5$  cm) and negative axillary lymph nodes (N0), were increasingly diagnosed due to the early detection by mammographic screening (2). In the current clinical practice, breast-conserving surgery (BCS) + adjuvant radiotherapy (RT) or mastectomy (MAST) was the optional locoregional management for patients with early breast cancer (3).

The traditional American Joint Committee on Cancer (AJCC) staging system has been widely used for prognosis predicting and treatment decision-making in breast cancer, which was based on anatomic information including tumor size, lymph node status, and distant metastasis (4). Considering the remarkable progress and importance of biologic markers such as histological grade, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 (HER2) in breast cancer, the 8th AJCC staging system incorporated indicators mentioned above to better distinguish the prognosis of breast cancer patients (5,6). However, the effect of the 8th AJCC staging system on surgical decision-making remains unclear in breast cancer. Previous trials have demonstrated BCS + RT achieved at least equivalent survival compared with MAST in patients with T1–2N0 breast cancer based on the 7th AJCC staging criterion (7–14). However, whether the results were still applicable based on the new staging system was not well elaborated.

Several studies have shown a higher local recurrence rate and inferior overall survival in patients aged  $<50$  years compared to those aged  $\geq 50$  years (15,16). In the current clinical practice, approximately 50–63% of the patients aged  $<50$  years opted for the MAST procedure (17,18). However, the impact of surgical approaches on the survival of breast cancer patients with a younger age has yielded conflicting results (19,20). The study from Laurberg *et al.* showed that younger patients with BCS + RT had higher local recurrence risk and mortality than those with MAST (19), while comparable survival was found between BCS + RT and MAST in a systematic meta-analysis (20). Therefore, our study aimed to evaluate the prognostic value and the role in treatment decision-making (BCS + RT or MAST) of the 8th AJCC staging system compared with the 7th AJCC

staging system among patients with early breast cancer aged  $<50$  years.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/gs-20-587>).

## Methods

### *Surveillance, Epidemiology, and End Results (SEER) database and patients*

The SEER database was utilized to extract the patient listing between 2010 and 2014. The SEER database collects data from 18 national cancer registries and captures 30% of the population in the United States, which consists of detailed information about demographics, tumor characteristics, intervention, and survival status in cancer patients (21).

Eligible patients were defined using the following criteria: (I) women with a definite pathological diagnosis of primary non-metastatic breast cancer and aged less than 50 years; (II) patients with stage T1–2N0M0 cancers; (III) knowing the status of ER, PR, HER2, and tumor grade; (IV) receiving BCS followed by postoperative RT or MAST alone. Criteria for study exclusions were as follows: (I) without a definite pathological diagnosis; (II) not receiving surgery procedures, receiving BCS without following RT, or receiving MAST followed by RT. The AJCC staging systems were based on the 7th edition of the AJCC anatomical staging and the 8th edition of the AJCC pathological prognostic staging. This study was exempted from the approval of the Institutional Review Board of the First Affiliated Hospital of Xiamen University due to the anonymous information in the SEER database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

We collected the information of the following variables: age, race/ethnicity, tumor size, histological grade, hormone receptor status, HER2 status, surgery procedures, and RT administration. Breast cancer-specific survival (BCSS) was used as the primary endpoint in this study, which was measured from the date of diagnosis to the date of death from breast cancer.

### *Statistical analysis*

All of the statistical analyses were conducted using the IBM SPSS Statistics (Version 22.0; IBM Corp., New

**Table 1** Demographics and clinical characteristics of the patients with T1-2N0 breast cancer aged <50 years (n=22,640)

Variables	BCS + RT (%)	MAST (%)	P
Age (years)			<0.001
<40	1,320 (12.6)	2,803 (23.0)	
≥40	9,130 (87.4)	9,387 (77.0)	
Race/ethnicity			<0.001
Non-Hispanic White	6,436 (61.6)	7,622 (62.5)	
Non-Hispanic Black	1,231 (11.8)	1,200 (9.8)	
Hispanic	1,384 (13.2)	1,772 (14.5)	
Other	1,399 (13.4)	1,596 (13.1)	
Grade			<0.001
Well differentiated	2,783 (26.6)	2,428 (19.9)	
Moderately differentiated	4,230 (40.5)	4,960 (40.7)	
Poorly differentiated/ undifferentiated	3,437 (32.9)	4,802 (39.4)	
T stage			<0.001
T1	7,852 (75.1)	8,242 (67.6)	
T2	2,598 (24.9)	3,948 (32.4)	
The 7th AJCC staging			<0.001
IA	7,852 (75.1)	8,242 (67.6)	
IIA	2,598 (24.9)	3,948 (32.4)	
The 8th AJCC staging			<0.001
IA	8,321 (79.6)	9,113 (74.8)	
IB	1,102 (10.5)	1,518 (12.5)	
IIA	1,027 (9.8)	1,559 (12.8)	
ER status			<0.001
Negative	1,743 (16.7)	2,619 (21.5)	
Positive	8,707 (83.3)	9,571 (78.5)	
PR status			<0.001
Negative	2,281 (21.8)	3,448 (28.3)	
Positive	8,169 (78.2)	8,742 (71.7)	
HER2 status			<0.001
Negative	9,104 (87.1)	9,995 (82)	
Positive	1,346 (12.9)	2,195 (18)	

BCS, breast-conserving surgery; RT, radiotherapy; MAST, mastectomy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; AJCC, American Joint Committee on Cancer.

York, USA). Chi-square test was performed to analyze the clinicopathological characteristics, including age, race/ethnicity, tumor size, histological grade, hormone receptor status, and HER2 status between BCS + RT and MAST groups. The receiver operating characteristics (ROC) curve was used to assess the discriminatory ability between the 7th and the 8th AJCC staging system in predicting survival outcome. Kaplan-Meier method was applied to draw survival curves to estimate the crude trend of BCSS. Multivariate Cox proportional hazards models were used to determine the potential confounding predictors for BCSS. A P value <0.05 (two-tail) was considered statistically significant.

## Results

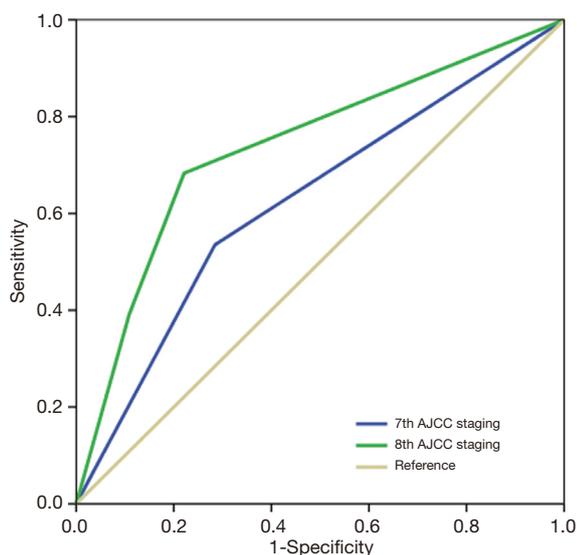
### *Clinicopathological characteristics*

A total of 22,640 female patients were identified. *Table 1* depicted the detailed information on patient demographics and tumor characteristics in this study. The mean age of diagnosis was 45 years (range, 18–49 years). Of the patients, 62.1%, 10.7%, 13.9%, and 13.2% of them were non-Hispanic White, non-Hispanic Black, Hispanic, and other race/ethnicity, respectively. With regard to tumor characteristics, the majority of them were stage T1 disease (71.1%), ER-positive (80.7%), PR-positive (74.7%), and HER2 negative (84.4%).

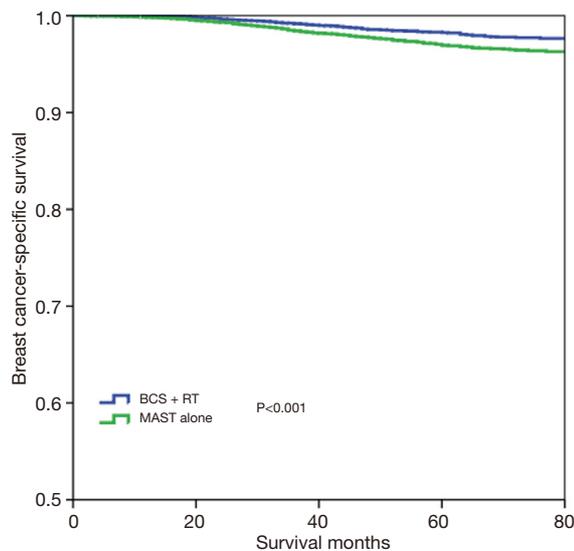
In the entire cohort, 46.2% (n=10,450) and 53.8% (n=12,190) of them were treated with BCS + RT and MAST, respectively. Patient treated with BCS + RT were more likely to be lower tumor grade (P<0.001), smaller tumor size (P<0.001), early-stage (P<0.001), ER-positive (P<0.001), PR-positive (P<0.001), and HER2 negative (P<0.001) compared to those treated with MAST (*Table 1*).

### *Restaging and ROC analysis*

Of the patients in this study, 71.1% (n=16,094) and 28.9% (n=6,546) had traditional anatomical staging of IA and IIA, while 77.0% (n=17,434), 11.6% (n=2,620), and 11.4% (n=2,586) of the patients were stage IA, IB, and IIA in the 8th staging, respectively. A total of 24.4% (n=5,517) of the patients reallocated to new stage groups. Among them, 6.9% (n=1,557) upstaged from stage IA in the 7th to stage IB in the 8th AJCC staging, 12.8% (n=2,897) downstaged from IIA to IA, and 4.7% (n=1,063) migrated from stage



**Figure 1** Receiver operating characteristics curve for predicting the breast cancer-specific survival between the 7th and the 8th American Joint Committee on Cancer staging system.



**Figure 2** Survival curves between breast-conserving surgery (BCS) + radiotherapy (RT) and mastectomy (MAST) groups for the whole group.

IIA to stage IB. The ROC analysis demonstrated that the 8th AJCC staging [the area under the curve (AUC) 0.737, 95% confidence interval (CI): 0.711–0.763] had the better discriminative ability to predict BCSS rate compared with the 7th staging (AUC 0.625, 95% CI: 0.593–0.653)

( $P < 0.001$ ) (Figure 1).

### Survival analysis

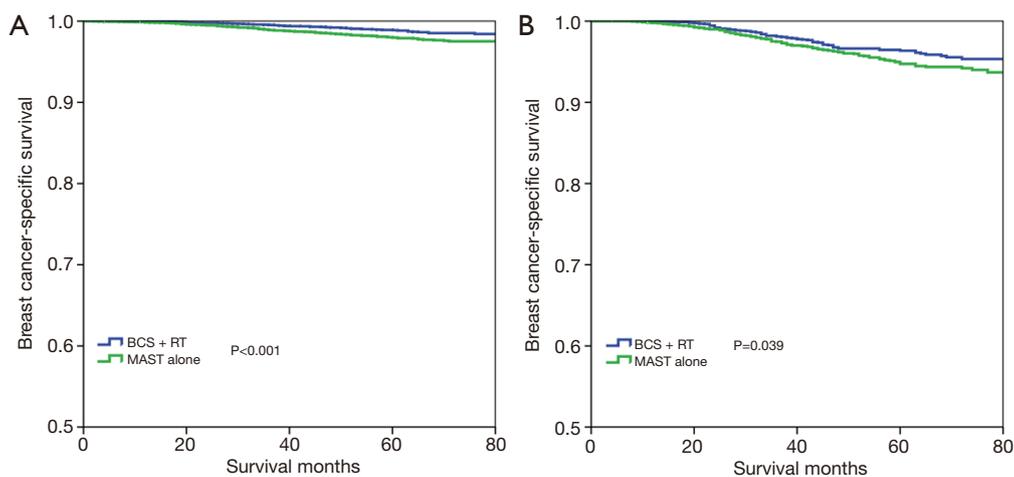
With a median follow-up time of 49 months (range, 0–83 months), the 5-year BCSS was 97.6%. Patients who received BCS + RT had better 5-year BCSS compared to those treated with MAST in the entire group (98.3% vs. 96.9%,  $P < 0.001$ ) (Figure 2). When stratifying according to the stage, in the 7th AJCC system, BCS + RT had better 5-year BCSS than MAST in stage IA (98.9% vs. 98.0%,  $P < 0.001$ ) (Figure 3A) and stage IIA (96.4% vs. 94.7%,  $P = 0.039$ ) diseases (Figure 3B). In the 8th AJCC staging criterion, BCS + RT could improve 5-year BCSS compared with MAST in patients with stage IA (99.3% vs. 98.7%,  $P = 0.006$ ) (Figure 4A) and stage IB (96.2% vs. 92.4%,  $P = 0.001$ ) (Figure 4B) diseases, while comparable BCSS was found between BCS + RT and MAST in patients with stage IIA disease (92.5% vs. 91.3%,  $P = 0.366$ ) (Figure 4C).

### Prognostic factors

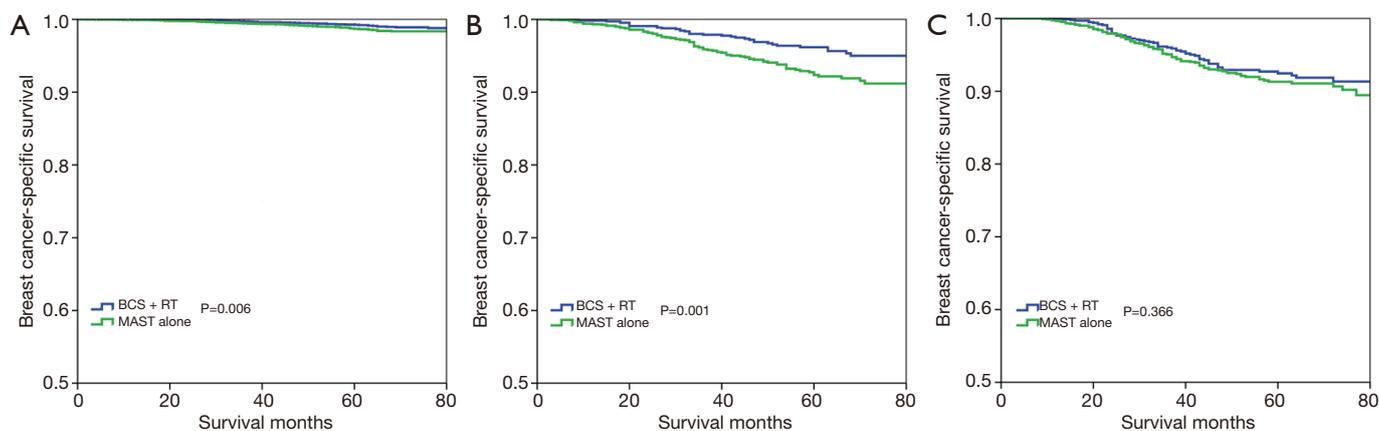
Cox proportional hazards models were conducted to analyze the independent prognostic factors associated with BCSS. The result showed that T stage ( $P < 0.001$ ), race/ethnicity ( $< 0.001$ ), tumor grade ( $P < 0.001$ ), ER status ( $P = 0.002$ ), PR status ( $P < 0.001$ ), HER2 status ( $P < 0.001$ ), and surgical approach ( $P < 0.001$ ) were the independent prognostic factors for BCSS (Table 2). The 8th AJCC staging system was also an independent prognostic factor for BCSS (Table 3). After adjusting tumor grade, ER status, PR status, and HER2 status in the 7th AJCC staging system, patients who received MAST had inferior BCSS compared to those treated with BCS + RT in stage IA [hazard ratio (HR) 1.741, 95% CI: 1.297–2.338,  $P < 0.001$ ] and stage IIA (HR 1.342, 95% CI: 1.017–1.769,  $P = 0.037$ ) diseases (Table 4). In the 8th AJCC staging, patients who received MAST was also had inferior BCSS than those treated with BCS + RT in stage IA (HR 1.601, 95% CI: 1.125–2.278,  $P = 0.009$ ) and stage IB (HR 1.827, 95% CI: 1.234–2.704,  $P = 0.003$ ) disease, while similar BCSS was found between BCS + RT and MAST groups in stage IIA (HR 1.265, 95% CI: 0.919–1.741,  $P = 0.149$ ) disease (Table 4).

### Discussion

In this study, we aimed to assess the prognostic and predictive value of the 8th AJCC staging system in patients



**Figure 3** Survival curves between breast-conserving surgery (BCS) + radiotherapy (RT) and mastectomy (MAST) groups in stage IA (A) and IIA (B) in the 7th American Joint Committee on Cancer staging system.



**Figure 4** Survival curves between breast-conserving surgery (BCS) + radiotherapy (RT) and mastectomy (MAST) groups in stage IA (A), IB (B), and IIA (C) in the 8th American Joint Committee on Cancer staging system.

with T1-2N0 breast cancer aged <math>< 50</math> years, and our findings demonstrated that the new pathological prognostic staging system had a better staging system compared to the conventional anatomic system. In addition, BCS + RT achieved better 5-year BCSS than MAST in stage IA and stage IB diseases, while comparable BCSS found between the two treatment arms in stage IIA disease. Our study was the first to assess the effect of surgical approach selection using the 8th pathological staging criterion in young breast cancer with T1-2N0 disease.

The further understanding of biomarkers of breast cancer is closely relationship to treatment decision-making (22-24). The 8th edition of the AJCC pathological staging system,

which incorporated anatomical information, pathological finding, and biological markers (ER, PR, and HER2 status), was initially established using the information of 305,519 patients from the National Cancer Database in 2018 (25). Several studies have validated the superior prognostic accuracy of the 8th AJCC pathological staging compared to the 7th anatomical staging (6,26,27). However, limited studies focused on the effect of the 8th AJCC manual in patients with stage T1-2N0 disease. In this study with a large sample size ( $n=22,640$ ), approximately 25% of the patients upstaged or downstaged from the 7th AJCC staging to the 8th AJCC staging, and the 8th AJCC staging system performed well discriminatory ability in concordance with

**Table 2** Multivariate analysis of prognostic factors for breast cancer-specific survival in the entire group

Variables	HR	95% CI	P
Age (years)			
<40	1.000		
≥40	0.978	0.785–1.219	0.844
Race/ethnicity			
Non-Hispanic White	1.000		
Non-Hispanic Black	1.520	1.199–1.927	<0.001
Hispanic	0.782	0.578–1.058	0.111
Other	0.575	0.389–0.851	0.006
Grade			
Well differentiated	1.000		
Moderately differentiated	4.027	2.084–7.779	<0.001
Poorly differentiated/ undifferentiated	9.949	5.167–19.154	<0.001
T stage			
T1	1.000		
T2	1.584	1.300–1.929	<0.001
ER status			
Negative	1.000		
Positive	0.629	0.471–0.841	0.002
PR status			
Negative	1.000		
Positive	0.574	0.422–0.781	<0.001
HER2 status			
Negative	1.000		
Positive	0.566	0.425–0.755	<0.001
Surgical approach			
BCS + RT	1.000		
MAST alone	1.470	1.200–1.801	<0.001

HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BCS, breast-conserving surgery; RT, radiotherapy; MAST, mastectomy.

the stage. Therefore, the new AJCC staging criterion could better guide the individualized management and prognosis evaluation in T1-2N0 patients.

The decision of surgical procedure in patients with

**Table 3** Multivariate analysis of prognostic factors for breast cancer-specific survival in the whole group

Variables	HR	95% CI	P
Age (years)			
<40	1.000		
≥40	0.928	0.745–1.157	0.506
Race/ethnicity			
Non-Hispanic White	1.000		
Non-Hispanic Black	1.637	1.291–2.076	<0.001
Hispanic	0.787	0.582–1.065	0.121
Other	0.567	0.384–0.839	0.005
T stage			
T1	1.000		
T2	0.778	0.578–1.046	0.097
The 8th AJCC staging			
IA	1.000		
IB	5.989	4.649–7.716	<0.001
IIA	9.589	6.787–13.546	<0.001
Surgical approach			
BCS + RT	1.000		
MAST alone	1.527	1.247–1.870	<0.001

HR, hazard ratio; CI, confidence interval; BCS, breast-conserving surgery; RT, radiotherapy; MAST, mastectomy; AJCC, American Joint Committee on Cancer.

T1-2N0 breast cancer has been well elaborated in the 7th AJCC staging system, and BCS + RT had at least comparable survival compared to MAST in patients with early breast cancer (8,10,11,13,14). However, the surgical selection building upon the 8th AJCC manual was unclear. Almost all patients who established the 8th AJCC manual received systemic therapy. Thus, the effect of locoregional treatment should be validated before it was applied to clinical practice. In our study, BCS + RT achieved a better BCSS rate than MAST in T1-2N0 patients aged <50 years using traditional anatomical staging. When using the 8th pathological staging, BCS + RT had better BCSS compared with MAST in stage IA and IB diseases, while comparable survival was found in stage IIA diseases between the two treatment arms. Therefore, patients with stage IIA disease should be individually managed when applying an updated staging system. For pregnancy-associated breast cancer,

**Table 4** Sensitivity analysis of the effect of surgical approach on prognosis after stratification by the 7th and the 8th AJCC staging

Variables	HR	95% CI	P
The 7th AJCC staging			
Stage IA			
BCS + RT	1.000		
MAST alone	1.741	1.297–2.338	<0.001
Stage IIA			
BCS + RT	1.000		
MAST alone	1.342	1.017–1.769	0.037
The 8th AJCC staging			
Stage IA			
BCS + RT	1.000		
MAST alone	1.601	1.125–2.278	0.009
Stage IB			
BCS + RT	1.000		
MAST alone	1.827	1.234–2.704	0.003
Stage IIA			
BCS + RT	1.000		
MAST alone	1.265	0.919–1.741	0.149

HR, hazard ratio; CI, confidence interval; BCS, breast-conserving surgery; RT, radiotherapy; MAST, mastectomy; AJCC, American Joint Committee on Cancer.

claustrophobia patients, patients refusing breast radiation or unable to tolerate RT, and institutions without RT equipment, MAST could be an optional choice for patients with stage IIA disease (28).

Among the patients in this study, 46.2% of them received the BCS + RT procedure, which was significantly lower than previous studies in patients of all ages (56.3–57.3%) (29,30). We demonstrated that patients with adverse prognostic factors such as large tumor size, ER/PR negative, and HER2 positive, were associated with increased rates of MAST, and the result was similar to prior studies (29,30). Although the receipt of BCS had an upward trend over time (29), the possibility of the receipt of BCS was still lower than MAST. Several studies have suggested that patients undergoing BCS have more advantages than patients undergoing MAST, including faster recovery (31), better compliance for postoperative medical surveillance and follow-up by surgeon teams (32), better sexual well-

being and life satisfaction (33,34). Therefore, according to our findings, BCS + RT was the optimal local treatment for breast cancer patients at a young age.

Several potential limitations should be acknowledged in this study. Firstly, the data in our study was extracted from the SEER database, and selection biases in the retrospective study were inevitable. Secondly, the SEER database lacks sufficient details about systemic therapy (chemotherapy protocol, endocrine therapy, and anti-HER2 targeted therapies), radiation therapy (RT technique, RT dose, and target volume). In addition, the patterns of locoregional recurrence and distant metastasis were also not recorded in the SEER database. Finally, the follow-up period might be relatively short in this study due to the better survival in patients with T1-2N0 breast cancer. The primary strength of our study was that we detailedly verify the effect of BCS + RT and MAST with a large sample size of 22,640 patients in early breast cancer based on the 8th AJCC staging system.

## Conclusions

In conclusion, our study demonstrated that the 8th AJCC pathological staging system had better prognostic accuracy than the 7th anatomical staging. In addition, in terms of surgical decision-making, BCS + RT was still the standard treatment for stage IA and IB, while it was optional management in stage IIA in patients with T1-2N0 breast cancer aged <50 years in the basis of the 8th AJCC staging.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/gs-20-587>

*Conflicts of Interest:* All authors have completed the ICMJE

uniform disclosure form (available at <http://dx.doi.org/10.21037/gs-20-587>). 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 approval process of Institutional Review Board was waived because of the de-identified information of the patients included in the SEER. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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