The prognostic role of surgery and a nomogram to predict the survival of stage IV breast cancer patients

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Background: Since numerous retrospective studies and prospective trials have shown divergent results, whether the surgical excision of the primary tumor results in survival benefits for *de novo* stage IV breast cancer patients is inconclusive. Consequently, we need a prediction model of prognosis, judge the efficiency of breast surgery, and identify the advanced breast cancer patients who would benefit from surgery.

Methods: We analyzed the data of 2,747 metastatic breast cancer patients (the surgery group) and 4,508 patients (the non-surgery group) from the Surveillance, Epidemiology, and End Results (SEER) database during 2010–2015. Propensity score matching (PSM) was used to attain a balance between the covariates of both groups. We then assessed the potential risk factors for the breast cancer-specific survival (BCSS) of patients in the non-surgery group by Cox regression and constructed a nomogram to predict BCSS. All the patients were classified into different risk groups based on the median risk score obtained from the nomogram. The hazard ratios of BCSS and overall survival (OS) of patients in the two groups were calculated.

Results: After PSM, 2,288 patients severally in the two groups (the surgery group and the non-surgery group) were enrolled in the study. A nomogram incorporating 13 potential risk factors (i.e., age, race, cohabitation status, income, tumor grade, histotype, tumor size, lymph node status, molecular subtype, metastasis to brain, liver, lung, and chemotherapy) was constructed using the data of patients in the non-surgery group. The C statistics for the internal (patients in the non-surgery group) and external (patients in the surgery group) validation of the nomogram were 0.70 [95% confidence interval (CI), 0.69–0.71] and 0.73 (95% CI, 0.72–0.74), respectively. In the low-risk group, patients in the surgery group had lower risks of breast cancer-specific mortality (BCSM) (hazard ratio =0.53; 95% CI, 0.47–0.59; P for interaction =0.014) and overall mortality (OM) (hazard ratio =0.52; 95% CI, 0.46–0.58; P for interaction =0.002) than those in the non-surgery group.

Conclusions: Breast surgery might improve the survival of metastatic breast cancer patients in the low-risk group. The established nomogram could provide a reference for clinicians in enabling personalized treatment among advanced breast cancer patients.

Keywords: Metastasis; breast cancer; surgery; nomogram

Introduction

The incidence of newly diagnosed primary metastatic breast cancer (pMBC) is between 3% and 25% (1,2). The 5- and 10-year overall survival (OS) rates for women with metastatic breast cancer are only approximately 28% and 13%, respectively (3). The treatment for breast cancer is comprehensive (4). Systemic therapy is the cornerstone of treatment (5); however, controversy remains as to whether the surgical excision of the primary tumor in pMBC patients produces survival benefits (6). Previous evidence indicates that the growth of metastatic lesions (7) might be accelerated by the surgical excision and result in diminished therapeutic effects. Conversely, a number of retrospective (8) studies have suggested that surgical resection is correlated with a survival benefit in pMBC patients (9,10). However, selection bias (11) and other potential confounding factors (12) may have affected these results.

Several prospective trials have shown divergent results (13). For example, the Tata trial and TBCRC 013 (14) found no evidence of a boost in survival benefit due to surgical excision after induction treatment in primary stage IV breast cancer patients (7). Similarly, the ABCSG-28 POSYTIVE trial also found no survival benefit among pMBC patients who underwent surgical excision of the primary tumor followed by systemic therapy (4). Conversely, the MF07-01 trial found a survival benefit among pMBC patients who underwent excision of the primary tumor followed by systemic therapy at a median follow-up period of 40 months (15).

The 5th European School of Oncology-European Society for Medical Oncology international consensus guidelines (16) for breast cancer (version 4.2021), which featured updates to the National Comprehensive Cancer Network guidelines (17), do not provide definite views on surgical therapy for *de novo* metastatic breast cancer patients. Similarly, at the 17th St. Gallen International Breast Cancer Conference (18), it was noted that due to the many controversies related to the surgical resection of metastatic breast cancer, more randomized data and further research efforts are needed.

Since there is no conclusive conclusion on the efficiency of breast surgery on pMBC patients, we need a prediction model of prognosis, judge the impact of resection of the primary tumor, and identify the metastatic breast cancer patients who would benefit from it. We analyzed data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database, performed 1:1 matched propensity score matching (PSM), constructed a nomogram, performed mutual validation, and divided the stage IV breast cancer patients into a low-risk group and a high-risk group. We present the following article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-330/rc).

Methods

Study population

We analyzed data of pMBC patients from the National Cancer Institute's SEER Program database between January 1, 2010, and December 31, 2015. Updated annually, SEER currently collects and publishes cancer incidence, and survival data from population-based cancer registries, which routinely collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, the first course of treatment, and follow-up for vital status. The population data used by SEER in calculating cancer rates are obtained periodically from the Census Bureau, and the mortality data reported are provided by the National Center for Health Statistics. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

We included 278,163 patients with primary invasive breast cancer confirmed by pathological diagnosis and excluded 255,094 patients with non-metastatic breast cancer. Patients who were male (n=155), who were younger than 18 years at diagnosis (n=11), and who did not have accurate follow-up dates (n=8,313) were excluded from the study. In addition, patients with unknown information on their cohabitation status (n=875), race (n=43), status of estrogen receptor (ER; n=1,363), status of progestogen receptor (PR; n=150), status of human epidermal growth factor receptor-2 (HER2; n=750), tumor grade (n=2,110), surgery (n=65), bone metastasis (n=146), brain metastasis
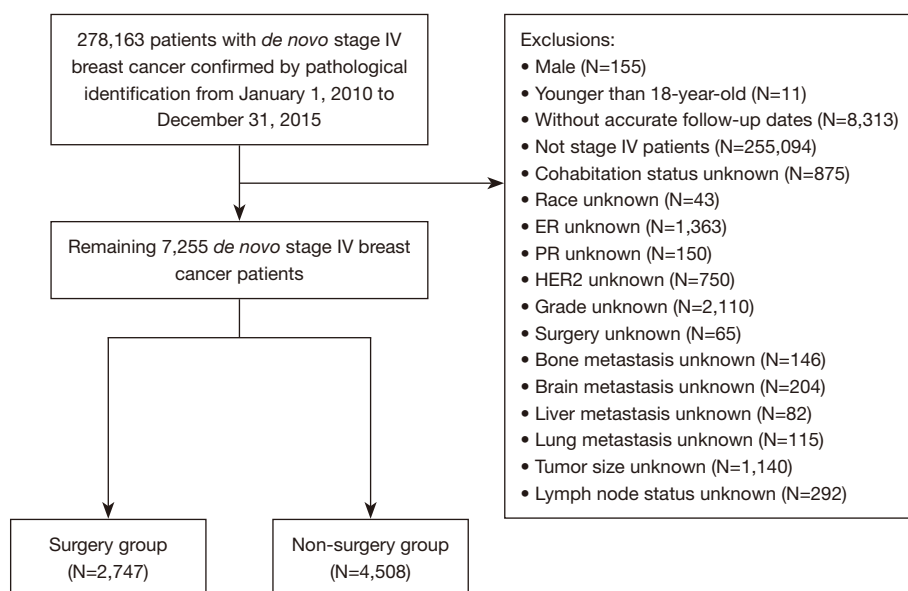
Figure 1 Study flow chart. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2.

(n=204), liver metastasis (n=82), lung metastasis (n=115), tumor size (n=1,140), and lymph node status (n=292) were also excluded from the study. The follow-up period ran from the date of breast cancer diagnosis to death or December 31, 2015. The inclusion process is illustrated in *Figure 1*. Ultimately, 4,508 and 2,747 metastatic breast cancer patients were included in the non-surgery and surgery groups, respectively. Patients in the non-surgery group were assigned to the training set, and those in the surgery group were assigned to the validation set.

Demographic, clinicopathological and treatment characteristics

We extracted information on demographic (age at diagnosis, year of diagnosis, race, cohabitation status, education, and income), tumor (stage, size, lymph node status, histotype, grade, ER, PR, and HER2 statuses, and metastasis to the bone, liver, lung, and brain) and treatment (surgery, radiotherapy, and chemotherapy) characteristics and categorized patients into different risk groups based on the median of risk score.

The primary and secondary outcomes were breast cancer-specific survival (BCSS) and OS, respectively. Breast cancer-specific mortality (BCSM; code: 26000) was clarified by the Cause of Death Recode.

Statistical analysis

The characteristics of patients in the surgery group and the non-surgery group were compared by the Student's *t*-test or the chi-square test. PSM was applied to establish a 1:1 matched sample comprising pairs of subjects in the surgery group and non-surgery group by the optimal matching algorithm with the "nearest" method and a caliper value of 0.02. A survival analysis was conducted to determine the BCSS and OS of patients in the surgery group and non-surgery group using Kaplan-Meier curves and the log-rank test. Cumulative mortality rates were plotted by considering the competing risks. The mortality rates and hazard ratios of OS and BSCM were calculated to compare patients in the surgery group and non-surgery group.

The potential risk factors that influenced BCSS among patients in the non-surgery group were identified by univariate and multivariate Cox regression models. Covariates with a P value <0.1 in the univariate Cox model were taken into consideration, and those with a P value <0.05 were identified as candidate risk factors in the multivariate model. Based on the scores of the candidate risk factors, a nomogram was constructed to predict BCSS among patients in the non-surgery group at 3 and 5 years after cancer diagnosis. Patients in the non-surgery group were assigned to the training set, and those in the surgery group were assigned to the validation set. Internal validation

in the training set and external validation in the validation set were performed to assess the precision of the nomogram using a bootstrap validation method with 1,000 resamples. The concordance index and calibration curves were applied to measure the discrimination of the model. All the patients were further classified into two low- and high-risk groups based on the median of the total score derived from the candidate risk factors in the nomogram. Stratified analyses and tested potential interactions between the risk score groups and surgery were performed using the Wald test.

All the statistical analyses were completed with STATA version 14.1 and various packages (e.g., matchit, tableone, and survival) in R software (version 3.6.1). A P value <0.05 was considered statistically significant.

Results

Patient characteristics

Compared to patients with pMBC in the non-surgery group, those in the surgery group were more likely to be diagnosed in earlier years [2010–2012], be younger at the time of diagnosis, cohabit, and have achieved higher levels of education, but have lower income levels. Additionally, patients in the surgery group had larger tumor sizes, more positive lymph nodes, and better tumor grades, and were more likely to have triple-negative breast cancer (TNBC) but less likely to have metastatic sites in the lung, brain, liver or bone than patients in the non-surgery group. Additionally, patients in the surgery group underwent more radiotherapy and chemotherapy than their counterparts in the non-surgery group (see Table 1).

Survival and cumulative mortality rates after PSM

After PSM, the total number of patients in both groups (surgery and non-surgery) was 2,288. The covariates between the two groups were comparable (see Table 2). The median follow-up time of patients in the surgery and non-surgery groups was both 23 months. There are 1,023 breast cancer-specific deaths in the surgery group and 1,313 deaths in the non-surgery group. The cumulative rate of BCSM in the non-surgery group (see Figure 2A) was higher than that in the surgery group (72.10% vs. 54.10%, respectively) (see Figure 2B). Additionally, during the 5-year follow-up period after cancer diagnosis, both the OS (see Figure 2C) and BCSS (see Figure 2D) of the patients in the surgery group were significantly improved compared to those in the non-surgery group.

Potential risk factors and prognostic nomogram for BCSS in patients in the non-surgery group after PSM

Of the initial 17 variables that were identified to predict the BCSS of patients in the non-surgery group in the univariable Cox regression, 4 variables (i.e., education, year of diagnosis, bone metastasis, and radiotherapy) were excluded. In the multivariable Cox model, we ultimately identified 13 variables (i.e., age, race, cohabitation status, income, tumor grade, histotype, tumor size, lymph node status, molecular subtype, brain metastasis, liver metastasis, lung metastasis, and chemotherapy) as independent predictors of BCSS (see Table 3) and incorporated them into the nomogram (see Figure 3). The scores of the included variables in the nomogram are shown in Table S1. The C statistics for the internal (patients in the non-surgery group) and external (patients in the surgery group) validation of the nomogram were 0.70 [95% confidence interval (CI), 0.69–0.71] and 0.73 (95% CI, 0.72–0.74), respectively. The calibration curves for the nomogram in the training set and validation set also showed high uniformity between the observed outcomes and the nomogram-predicted survival probabilities (see Figure S1).

BCSS and OS of patients in the surgery and non-surgery groups by risk stratification

The risk score derived from patients in the non-surgery group was applied to those in the surgery group. Based on the median risk score, all of the patients were categorized into the following two groups: (I) the low-risk group (a score ≤158, n=3484, 48.0%); and (II) the high-risk group (a score >158, n=3771, 52.0%). As Figure 4 shows, in the low- and high-risk groups, both BCSS and OS were improved among patients in the surgery group. In the low-risk group, patients in the surgery group had lower risks of BCSM (hazard ratio =0.53; 95% CI, 0.47–0.59; P for interaction =0.014) and overall mortality (OM) (hazard ratio =0.52; 95% CI, 0.46–0.58; P for interaction =0.002) than those in the non-surgery group (see Table 4).

Discussion

As stage IV breast cancer is generally uncurable (7), the main goals of de novo metastatic breast cancer treatment are the prolongation of survival, the palliation of symptoms, and the provision of supportive care (19). Controversy remains as to whether the surgical excision of the primary tumor improves the survival of pMBC patients (20).

Table 1 Baseline characteristics of the study population before PSM

Variables	All patients		Non-surgery group		Surgery group		P value
	N=7,255	%	N=4,508	%	N=2,747	%	
Age (years), mean ± SD	59.5±14.2		60.5±14.1		57.9±14.2		<0.001
Age (years)							<0.001
18–39	626	8.6	330	7.3	296	10.8	
40–59	3,053	42.1	1,829	40.6	1,224	44.6	
≥60	3,576	49.3	2,349	52.1	1,227	44.7	
Race							0.64
White	5,423	74.7	3,360	74.5	2,063	75.1	
Black	1,252	17.3	792	17.6	460	16.7	
Other	580	8.0	356	7.9	224	8.2	
Cohabitation status							<0.001
Non-cohabitation	3,824	52.7	2,503	55.5	1,321	48.1	
Cohabitation	3,431	47.3	2,005	44.5	1,426	51.9	
Education							<0.001
Low	3,385	46.7	2,186	48.5	1,199	43.6	
High	3,870	53.3	2,322	51.5	1,548	56.4	
Income							<0.001
Low	3,943	54.3	2,380	52.8	1,563	56.9	
High	3,312	45.7	2,128	47.2	1,184	43.1	
Year of diagnosis							<0.001
2010–2012	3,361	46.3	1,878	41.7	1,483	54.0	
2013–2015	3,894	53.7	2,630	58.3	1,264	46.0	
Tumor grade							<0.001
Well/moderately differentiated	2,424	53.8	1,128	41.1	2,424	53.8	
Poorly/un-differentiated	2,084	46.2	1,619	58.9	2,084	46.2	
Histotype							0.24
IDC	5,731	79.0	3,572	79.2	2,159	78.6	
ILC	626	8.6	399	8.9	227	8.3	
Others	898	12.4	537	11.9	361	13.1	
Tumor size (cm)							0.023
(0–2]	1,073	14.8	707	15.7	366	13.3	
(2–5]	3,438	47.4	2,110	46.8	1,328	48.3	
>5	2,744	37.8	1,691	37.5	1,053	38.3	
Lymph node status							<0.001
Negative	1,477	20.4	1,042	23.1	435	15.8	
Positive	5,778	79.6	3,466	76.9	2,312	84.2	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	All patients		Non-surgery group		Surgery group		P value
	N=7,255	%	N=4,508	%	N=2,747	%	
ER status							<0.001
Positive	5,382	74.2	3,428	76.0	1,954	71.1	
Negative	1873	25.8	1,080	24.0	793	28.9	
PR status							<0.001
Positive	4,365	60.2	2,791	61.9	1,574	57.3	
Negative	2,890	39.8	1,717	38.1	1,173	42.7	
HER2 status							0.79
Positive	1,968	27.1	1,218	27.0	750	27.3	
Negative	5,287	72.9	3,290	73.0	1,997	72.7	
Molecular subtype							<0.001
$HR^+/HER2^+$	1,294	17.8	810	18.0	484	17.6	
$HR^-/HER2^+$	674	9.3	408	9.1	266	9.7	
$HR^+/HER2^-$	4,210	58.0	2,695	59.8	1,515	55.2	
TN	1,077	14.8	595	13.2	482	17.5	
Bone metastasis							<0.001
Yes	4,977	68.6	3,242	71.9	1,735	63.2	
No	2,278	31.4	1,266	28.1	1,012	36.8	
Brain metastasis							<0.001
Yes	503	6.9	389	8.6	114	4.1	
No	6,752	93.1	4,119	91.4	2,633	95.9	
Liver metastasis							<0.001
Yes	2,007	27.7	1,386	30.7	621	22.6	
No	5,248	72.3	3,122	69.3	2,126	77.4	
Lung metastasis							<0.001
Yes	2,380	32.8	1,634	36.2	746	27.2	
No	4,875	67.2	2,874	63.8	2,001	72.8	
Chemotherapy							<0.001
No/unknown	2,874	39.6	2,034	45.1	840	30.6	
Yes	4,381	60.4	2,474	54.9	1,907	69.4	
Radiotherapy							<0.001
No/unknown	4,679	64.5	3,189	70.7	1,490	54.2	
Yes	2,576	35.5	1,319	29.3	1,257	45.8	

PSM, propensity score matching; SD, standard deviation; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; TN, triple-negative (HR^-HER2^-).

Table 2 Baseline characteristics after PSM

Variables	Non-surgery group		Surgery group		P value
	N=2,288	%	N=2,288	%	
Age (years), mean ± SD	59.1±13.7		58.8±14.3		0.48
Age (years)					0.139
18–39	191	8.3	226	9.9	
40–59	1,015	44.4	971	42.4	
≥60	1,082	47.3	1,091	47.7	
Race					0.534
White	1,727	75.5	1,721	75.2	
Black	395	17.3	382	16.7	
Other	166	7.3	185	8.1	
Cohabitation status					0.679
Non-cohabitation	1,140	49.8	1,155	50.5	
Cohabitation	1,148	50.2	1,133	49.5	
Education					0.812
Low	1,004	43.9	1,013	44.3	
High	1,284	56.1	1,275	55.7	
Income					0.613
Low	1,294	56.6	1,276	55.8	
High	994	43.4	1,012	44.2	
Year of diagnosis					0.375
2010–2012	1,167	51.0	1,136	49.7	
2013–2015	1,121	49.0	1,152	50.3	
Tumor grade					0.721
Well/moderately differentiated	1,026	44.8	1,013	44.3	
Poorly/un-differentiated	1,262	55.2	1,275	55.7	
Histotype					0.659
IDC	1,814	79.3	1,789	78.2	
ILC	187	8.2	199	8.7	
Others	287	12.5	300	13.1	
Tumor size (cm)					0.846
(0–2]	329	14.4	329	14.4	
(2–5]	1,077	47.1	1,095	47.9	
>5	882	38.5	864	37.8	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Non-surgery group		Surgery group		P value
	N=2,288	%	N=2,288	%	
Lymph node status					0.36
Negative	434	19.0	409	17.9	
Positive	1,854	81.0	1,879	82.1	
Molecular subtype					0.85
HR$^+$/HER2$^+$	391	17.1	408	17.8	
HR$^-$/HER2$^+$	227	9.9	216	9.4	
HR$^+$/HER2$^-$	1,307	57.1	1,293	56.5	
TN	363	15.9	371	16.2	
Bone metastasis					1
Yes	1,512	66.1	1,511	66.0	
No	776	33.9	777	34.0	
Brain metastasis					0.674
Yes	103	4.5	110	4.8	
No	2,185	95.5	2,178	95.2	
Liver metastasis					0.676
Yes	531	23.2	544	23.8	
No	1,757	76.8	1,744	76.2	
Lung metastasis					0.625
Yes	653	28.5	669	29.2	
No	1,635	71.5	1,619	70.8	
Chemotherapy					0.459
No/unknown	828	36.2	803	35.1	
Yes	1,460	63.8	1,485	64.9	
Radiotherapy					0.359
No/unknown	1,454	63.5	1,423	62.2	
Yes	834	36.5	865	37.8	

PSM, propensity score matching; SD, standard deviation; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, human epidermal growth factor receptor-2; TN, triple-negative (HR$^-$HER2$^-$).

Traditionally, locoregional surgery for patients with distant metastasis is not recommended (21) and has only been used for the control of pain, ulceration, bleeding (22), infection, and fungation.

It is contradictory in terms of the micro mechanism regarding whether locoregional surgery improves the survival of pMBC patients. An analysis of animal models in various cancer experiments indicated that the surgical excision of the primary tumor could accelerate metastatic growth (23,24) by increasing tumor growth factors, fresh surgical dissemination, surgery-induced immunosuppression, and the inflammatory cascade. However, such surgical excision has been shown to lessen the overall tumor burden (25), eliminate the major source
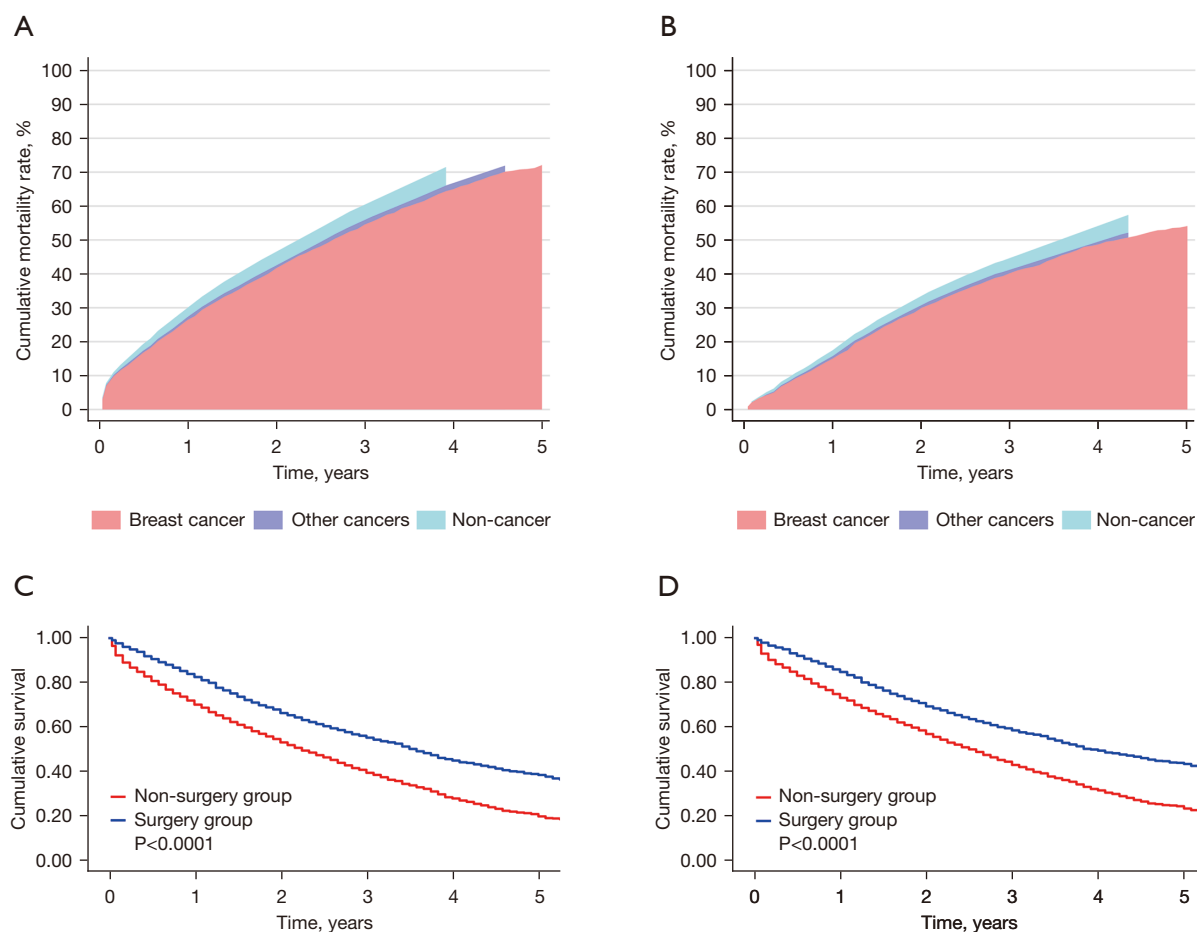
Figure 2 Cumulative mortality rates of the non-surgery (A) and surgery groups (B). PSM Kaplan-Meier survival analysis showing significant differences in OS (C) and BCSS (D). PSM, propensity score matching; OS, overall survival; BCSS, breast cancer-specific survival.

of cancer stem cells and tissues that are not sensitive to chemotherapy, and restore immunocompetence (26,27).

Numerous observational studies have shown that locoregional treatment has a favorable effect among women with pMBC (28-30), especially those with limited disease burdens. The reported rate of mortality reduction due to the primary resection ranges from 18–37% (31). However, others have contended that this correlation may be the result of significant biases, and matched analyses have found no survival benefit associated with surgical excision (32). Possible biases include the following: (I) the participants in the studies who agree to the excision of the primary tumor are stage IV breast cancer patients who are healthier and have less underlying disease; (II) the surgery tends to be performed in patients with a lower metastatic disease burden and not in patients with poor projected survival; and (III) the metastatic breast cancer patients who undergo

locoregional surgery are more likely to receive more aggressive multimodal therapy.

Some randomized controlled trials, including the Tata trial, TBCRC 013 trial, and ABCSG-28 trial, failed to demonstrate a survival benefit from the resection of the primary tumor in *de novo* stage IV breast cancer patients, but also found that it causes no survival damage. The Tata trial has been criticized for including patients with considerably advanced disease (74% of the patients had >3 metastatic sites), adopting insufficient systemic therapy strategies, and using outdated treatment sequences. The TBCRC 013 trial was criticized as the follow-up period was not long enough, and the sample size was relatively small, while the ABCSG-28 trial was criticized for failing to obtain negative surgical margins in 20% of patients in the surgery arm, having a small sample size due to poor recruitment, and failing to measure BCSS. In the MF07-01 trial, a statistically

Table 3 Univariate and multivariate Cox regression model analysis of the prognosis factors of BCSS among patients in the non-surgery group after PSM

Variables	Univariable		Multivariable	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (years)		<0.001		<0.001
18–39	1 (Reference)		1 (Reference)	
40–59	1.45 (1.15–1.83)	0.002	1.43 (1.13–1.82)	0.003
≥60	1.82 (1.45–2.29)	0.000	1.78 (1.40–2.27)	0.000
Race		<0.001		0.007
White	1 (Reference)		1 (Reference)	
Black	1.44 (1.26–1.65)	0.000	1.25 (1.08–1.44)	0.002
Other	0.93 (0.75–1.16)	0.510	0.96 (0.77–1.19)	0.686
Cohabitation status		0.000		0.014
Non-cohabitation	1 (Reference)		1 (Reference)	
Cohabitation	0.80 (0.72–0.89)		0.87 (0.78–0.97)	
Education		0.091		0.188
Low	1 (Reference)		1 (Reference)	
High	1.10 (0.99–1.23)		0.92 (0.81–1.04)	
Income		0.000		0.000
Low	1 (Reference)		1 (Reference)	
High	0.76 (0.68–0.85)		0.77 (0.68–0.88)	
Year of diagnosis		0.086		0.464
2010–2012	1 (Reference)		1 (Reference)	
2013–2015	0.90 (0.80–1.01)		0.96 (0.85–1.08)	
Tumor grade		<0.001		<0.001
Well/moderately differentiated	1 (Reference)		1 (Reference)	
Poorly/un-differentiated	1.70 (1.52–1.90)		1.46 (1.29–1.66)	
Histotype		0.041		0.014
IDC	1 (Reference)			
ILC	0.96 (0.79–1.18)	0.717	1.26 (1.02–1.56)	0.029
Others	1.22 (1.04–1.43)	0.013	1.20 (1.02–1.41)	0.027
Tumor size (cm)		<0.001		0.008
(0–2]	1 (Reference)		1 (Reference)	
(2–5]	1.01 (0.85–1.19)	0.915	1.07 (0.90–1.26)	0.462
>5	1.33 (1.13–1.58)	0.001	1.25 (1.05–1.49)	0.011

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Univariable		Multivariable	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Lymph node status		0.004		0.040
Negative	1 (Reference)		1 (Reference)	
Positive	1.23 (1.07–1.42)		1.17 (1.01–1.36)	
Molecular subtype		<0.001		<0.001
$HR^+/HER2^+$	1 (Reference)		1 (Reference)	
$HR^-/HER2^+$	1.28 (1.01–1.63)	0.039	1.22 (0.96–1.55)	0.111
$HR^+/HER2^-$	1.28 (1.09–1.51)	0.003	1.31 (1.09–1.56)	0.004
TN	3.71 (3.07–4.49)	0.000	3.34 (2.75–4.07)	0.000
Bone metastasis		<0.001		0.143
Yes	1 (Reference)		1 (Reference)	
No	1.25 (1.12–1.40)		0.91 (0.80–1.03)	
Brain metastasis		<0.001		<0.001
Yes	1 (Reference)		1 (Reference)	
No	0.36 (0.29–0.45)		0.41 (0.32–0.52)	
Liver metastasis		<0.001		<0.001
Yes	1 (Reference)		1 (Reference)	
No	0.75 (0.66–0.85)		0.62 (0.54–0.71)	
Lung metastasis		<0.001		<0.001
Yes	1 (Reference)		1 (Reference)	
No	0.70 (0.63–0.79)		0.79 (0.69–0.89)	
Chemotherapy		0.003		<0.001
No/unknown	1 (Reference)		1 (Reference)	
Yes	0.82 (0.74–0.92)		0.66 (0.58–0.76)	
Radiotherapy		0.047		0.110
No/unknown	1 (Reference)		1 (Reference)	
Yes	1.12 (1.00–1.25)		1.11 (0.98–1.25)	

BCSS, breast cancer-specific survival; PSM, propensity score matching; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, human epidermal growth factor receptor-2; TN, triple-negative (HR^-HER2^-); CI, confidence interval.

significant improvement in survival was observed (median follow-up =40 months) following upfront surgery for stage IV breast cancer patients. However, the patients in the surgery group tended to be younger than 55 years, have ER-positive and HER2-negative tumors, and 47% of the subjects in the Turkish trial had bone-only disease. Thus, these patients may have had early-stage disease rather than

advanced disease. The MF07-01 and Tata trials also have a lack of blind method and missing data. Further, they did not measure BCSS or the surgical margins, which led to weak stratification analyses and indeterminate results. Thus, the trials were underpowered and firm conclusions cannot be drawn. In such circumstances, the SEER database is suitable for the study of metastatic breast cancer for its large sample
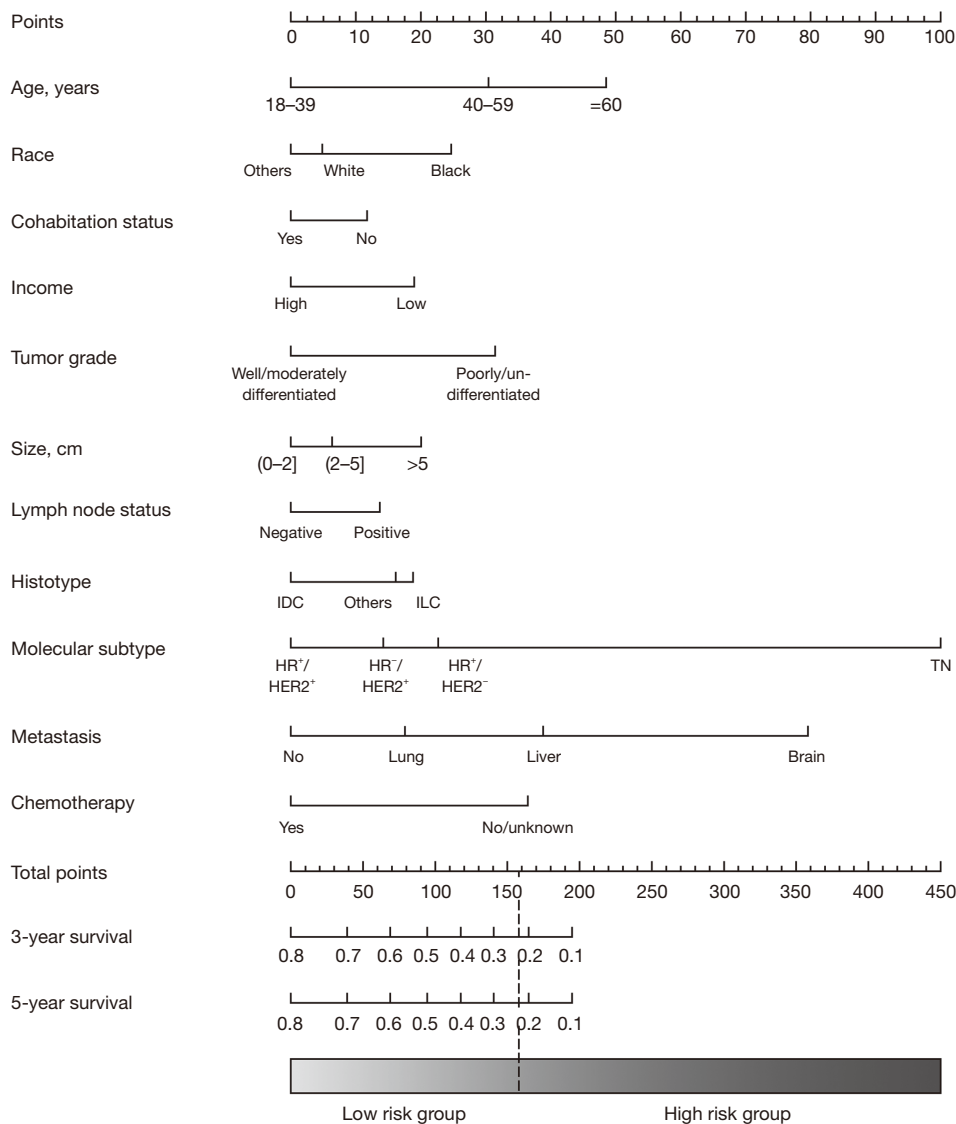
Figure 3 Nomogram for predicting 3- and 5-year BCSS among patients in the non-surgery group after PSM. IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, human epidermal growth factor receptor-2; TN, triple-negative (HR⁻HER2⁻); BCSS, breast cancer-specific survival; PSM, propensity score matching.

size and relatively long follow-up time.

By analyzing the data from the National Cancer Institute's SEER Program database, conducting PSM, identifying the potential risk factors that influence the BCSS of patients in the non-surgery group, constructing a nomogram, and conducting mutual validation, we categorized all patients into two groups (low- and high-risk). Compared to patients with metastatic breast cancer in the high-risk group, those in the low-risk group were more likely to be younger at the time of diagnosis,

cohabit, have a higher income level, better tumor grades, a histological classification of invasive ductal carcinoma (IDC), smaller tumor sizes, and undergo treatment with more chemotherapy. Conversely, patients in the high-risk group were more likely to be black, have more positive lymph nodes, have TNBC, and have metastatic sites in the brain, liver, and lung.

We found that the excision of the primary tumor distinctly improved the survival of *de novo* metastatic breast cancer patients in the low-risk group, reducing the OM and
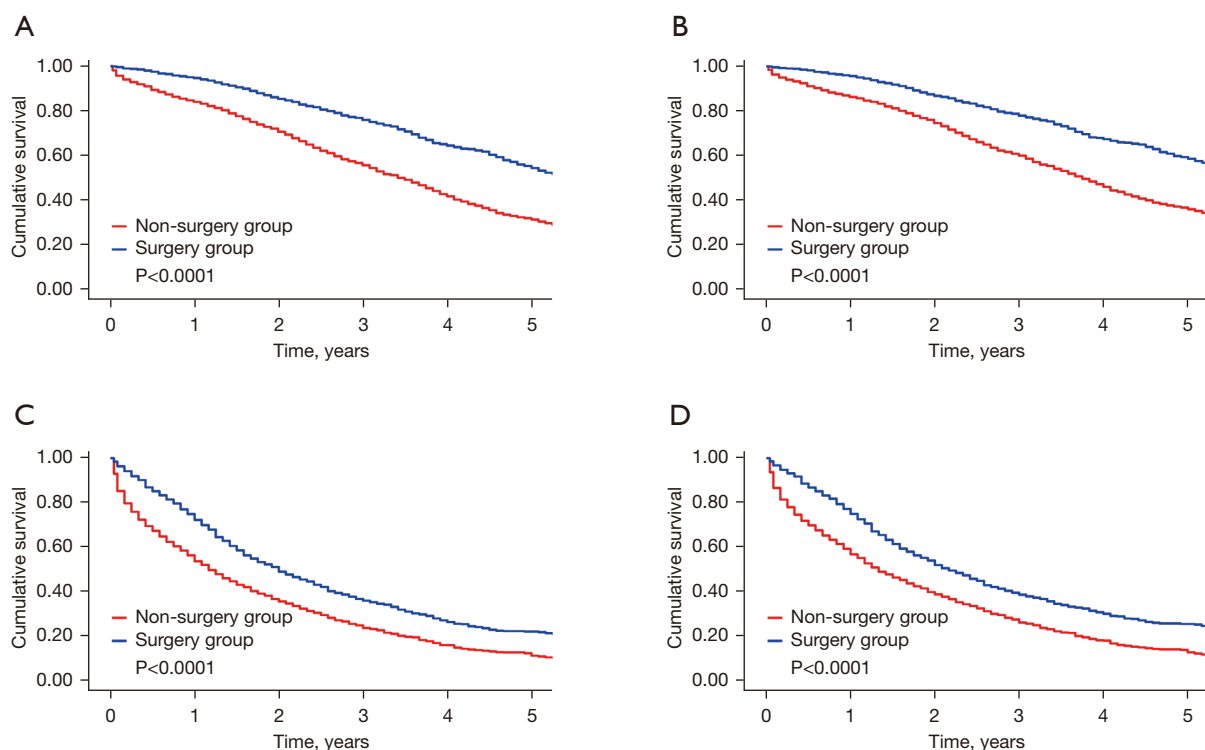
Figure 4 Kaplan-Meier survival analysis showing the survival benefit of locoregional surgery in the risk stratification groups. (A) OS in the low-risk group; (B) BCSS in the low-risk group; (C) OS in the high-risk group; (D) BCSS in the high-risk group. OS, overall survival; BCSS, breast cancer-specific survival.

Table 4 Univariable hazard ratios of OM and BCSM among patients in the non-surgery group, stratified by risk group, compared to patients in the surgery group

Mortality	Non-surgery group		Surgery group		Hazard ratio (95% CI)	P value
	N	MR	N	MR		
OM						0.002
Low-risk group	975	20.3	474	10.5	0.52 (0.46–0.58)	
High-risk group	1,840	53.1	917	33.1	0.63 (0.59–0.69)	
BCSM						0.014
Low-risk group	845	17.6	420	9.3	0.53 (0.47–0.59)	
High-risk group	1,661	47.9	822	29.6	0.63 (0.58–0.68)	

Risk category defined as low risk (a score ≤158) or high risk (a score >158). OM, overall mortality; BCSM, breast cancer-specific mortality; N, number of deaths; MR, mortality rate per 100 person-years; CI, confidence interval.

BCSM by up to 48% and 47%, respectively. The low-risk group were more likely to obtain benefits from locoregional surgery than the high-risk group (P for interaction of BCSM: 0.014; P for interaction of OM: 0.002). Due to the intrinsic retrospective quality of this study, no decisive conclusion can be drawn at present; however, we found a survival difference between the two groups. Combined with the outcome that the locoregional excision of the primary tumor did not harm the survival outcomes of the pMBC patients, as indicated in some large-scale randomized

clinical trials and retrospective studies, we can deduce that the resection of the primary lesion is very likely to be beneficial for patients who meet the characteristics of the low-risk group; however, it is not yet clear whether the locoregional surgery is beneficial for patients who meet the characteristics of the high-risk group. Future multicenter, large-scale prospective studies with long-term follow-up need to be conducted.

Our study had the following limitations: (I) data on patients' health status, comorbidities, and complications were not collected; (II) detailed information on chemotherapy, radiotherapy, and other systemic treatment strategies was not available in the SEER database, which may be crucial to prognosis; (III) information on the metastasis sites except for bone, lung, liver, and brain, and the number and size of metastases was not available in the SEER database; (IV) information on the timing of surgery of the intact primary tumor, the surgical margin, and patients' quality of life was not available in the SEER database; (V) the nomograms established in this study have not yet been verified in real-world patients; and (VI) the C statistics for the internal and external validation of the nomogram were 0.70 and 0.73, respectively. Despite the C-index not belonging to high accuracy, the study remains a valuable reference in predicting the survival of stage IV breast cancer patients for its large population.

In conclusion, this study indicated that the surgical removal of the primary tumor might improve the survival of *de novo* metastatic breast cancer patients in the low-risk group. The established nomogram could provide a reference for clinicians in enabling personalized treatment among advanced breast cancer patients.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-330/rc

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

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Table S1 Point assignments for each variable in the nomogram

Factors	Score
Age (years)	
18–39	0
40–59	30
≥60	49
Race	
White	5
Black	25
Others	0
Cohabitation status	
Non-cohabitation	12
Cohabitation	0
Income	
Low	19
High	0
Tumor size (cm)	
(0–2]	0
(2–5]	6
>5	20
Lymph node status	
No	0
Yes	14
Tumor grade	
Well/moderately differentiated	0
Poorly/un-differentiated	31
Histotype	
IDC	0
ILC	19
Others	16
Molecular subtype	
$HR^+/HER2^+$	0
$HR^-/HER2^+$	14
$HR^+/HER2^-$	23
TN	100

Table S1 (continued)

Table S1 (continued)

Factors	Score
Brain metastasis	
Yes	80
No	0
Liver metastasis	
Yes	39
No	0
Lung metastasis	
Yes	18
No	0
Chemotherapy	
No/unknown	36
Yes	0

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, human epidermal growth factor receptor-2; TN, triple-negative (HR^-HER2^-).
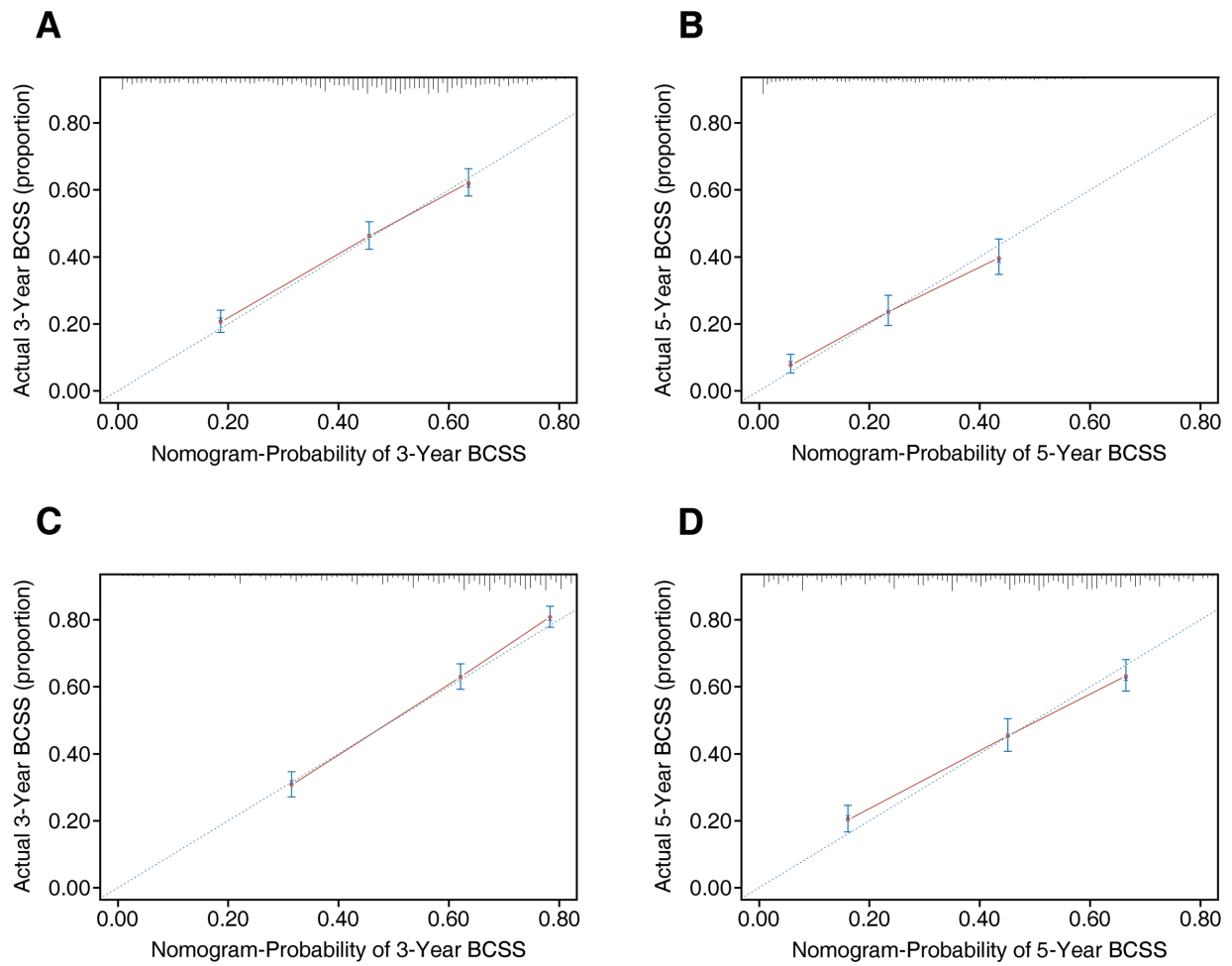
Figure S1 Calibration curves for the 3- and 5-year BCSS of the non-surgery group. (A) Internal validation for the 3-year BCSS of the non-surgery group. (B) Internal validation for the 5-year BCSS of the non-surgery group. (C) External validation for the 3-year BCSS of the non-surgery group. (D) External validation for the 5-year BCSS of the non-surgery group. BCSS, breast cancer-specific survival.