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Original article

Locoregional surgical treatment improves the prognosis in primary metastatic breast cancer patients with a single distant metastasis except for brain metastasis

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ABSTRACT

Background: We aimed to validate the clinical significance of locoregional surgery in improving the prognosis of primary metastatic breast cancer (pMBC).
Methods: We conducted a population-based retrospective study by analyzing clinical data obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. Stratification analysis was employed to assess the effect of breast surgery on breast cancer-specific survival and overall survival. Then propensity score matching and COX regression models were employed to evaluate the survival advantages of breast surgery, if any in patients with pMBC.
Results: The median BCSS and OS in the surgery group were almost twice of that in the group without surgery. Breast surgery provided a survival advantage for patients with a single metastasis in the bone, liver or lung, but not in the brain. We found that axillary lymph node dissection performed in combination with specific breast surgical procedures did not result in a significant improvement in survival. Additionally, when combined with radiotherapy and/or chemotherapy, surgery significantly improved the survival and was not influenced by the molecular subtype and tumor size. Finally, using COX regression models before and after propensity score matching, breast surgery was found to reduce the risk of mortality in patients with MBC by more than 40%.
Conclusions: The effect of locoregional surgery has been underestimated in pMBC patients. Surgical procedures should be seriously considered when planning combination treatments for pMBC patients with a single metastasis except for brain metastasis.

Introduction

Breast cancer is the most common malignancy all over the world and remains the leading cause of cancer-related deaths in women. Among patients with breast cancer, approximately 6% have stage IV disease with distant metastasis at their first diagnosis [1]. The most frequently involved distant organs are the bones, liver, lung, and brain.

For stage IV breast cancer, systemic therapies consisting of chemo, hormonal, targeted, and immune therapies are recommended. Nevertheless, whether to perform a local surgery for primary metastatic breast cancer (pMBC) remains debatable. Traditionally, surgical treatment for patients with distant metastasis is not recommended since stage IV breast cancer is considered incurable. Patients with MBC usually undergo local surgery as a palliative treatment to relieve symptoms such as pain, bleeding, and infection. In addition, it is reported that resection of the primary tumor may promote distant metastases [2], though this hypothesis has not been backed by clinical evidence. Several recent studies have demonstrated improved prognosis of metastatic diseases following aggressive local surgeries [3,4], which has prompted researchers to investigate the efficacy of breast surgery in improving the overall survival (OS) in pMBC patients.

Over the past two decades, multiple retrospective studies have demonstrated a longer survival in patients who underwent breast surgery compared to those who did not [5–18]. On the other hand, although several studies have also reported that breast surgery does not improve the prognosis of pMBC patients, these studies have not been conclusive due to their small sample sizes [19–21].

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Several prospective clinical trials were conducted to provide more credible evidence for the benefits of locoregional treatment in pMBC patients. Only two of these randomized controlled trials (RCTs) are completed with full-text available. Soran et al. pointed out that locoregional treatment in *de novo* MBC is not always recommended and should only serve as an optional therapy for these patients [22]. However, another RCT conducted by the Tata Memorial Centre in India, concluded that breast surgery does not increase the OS in pMBC patients [23]. A recent systemic review by the Cochrane Breast Cancer Group, which included these two completed RCTs, reported that it is not possible to make definitive conclusions on the benefits and risks of breast surgery along with systemic treatment in women diagnosed with pMBC [24]. They also indicated that the decision to perform the surgery should be individualized and made after evaluating the potential risks, benefits, and costs in each case.

To further investigate the benefits of primary tumor removal, we sought to explore the data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program database to conduct this population-based epidemiologic study. Sites of metastasis, specific surgical procedures, chemotherapy, radiotherapy, molecular subtypes, and tumor sizes were used as stratification factors to analyze the OS and breast cancer-specific survival (BCSS). Based on the results of the univariate and multivariate analysis, we concluded that locoregional treatment of primary breast tumors could provide a survival advantage for pMBC patients.

Methods

Data acquisition and processing

Data for this population-based retrospective study was downloaded from the SEER database using the official software SEERStat on May 23, 2018. Complete demographic information on 1,342,410 women with breast cancer was obtained. After screening the data based on the 7th AJCC staging system, patients staged M1 with at least one distant metastasis involving the bone, liver, lung, or brain were included in this study. Our final cohort included 20,870 pMBC patients diagnosed from 2010 to 2015.

Patients were stratified based on whether they underwent locoregional surgery to resect the primary breast tumor after the initial diagnosis. Age at diagnosis was categorized into three groups, younger than 50, 50 to 69, and 70 years and older. Based on race, patients were categorized as White, Black, Asian or Pacific Islander and American Indian/Alaska Native. Based on the 7th AJCC staging system, patients with N0 were assigned as lymph node negative while the others were all lymph node-positive. Molecular subtypes included HR+/HER2-, HR+/HER2+, HR-/HER2+, and triple negative breast cancer (TNBC). Patients who underwent lumpectomy, subcutaneous mastectomy, or total mastectomy were assigned to the “lumpectomy or mastectomy” group, while those who received a radical mastectomy, modified radical mastectomy, or extended radical mastectomy were assigned to the “radical mastectomy” group. Data on chemotherapy was obtained, but the exact chemotherapy regimens were not in the SEER database. Patients received radiation therapy as part of the first course of treatment (regardless of the sequence of radiation and surgery).

Statistical analysis

The distribution differences between locoregional surgery and demographic information were analyzed using the chi-square test or Wilcoxon signed-ranks test. While for BCSS, only death due to breast cancer was considered as an event occurrence, for OS, it was death due to any cause. In the univariate analysis, the effects of demographic factors on OS and BCSS were determined using the log-rank test and hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated. Variables that emerged as statistically significant in the univariate analysis were then enrolled in building a COX regression model using a stepwise conditional method. To further adjust for potential baseline confounders, 1:1 propensity score matching (PSM) was performed by logistic regression using the software SPSS 22.0. After PSM, no significant difference remained in the baseline characteristics of the matched patients between two groups. Data analysis was performed using the software SAS 8.02, and a *P* value of less than 0.05 was considered to be statistically significant.

Results

Demographic characteristics of the patients

Of the 20,870 patients who were diagnosed with pMBC between 2010 and 2015, 5779 (27.7%) of them underwent breast surgery, while 15,091 (72.3%) did not. Table 1 summarizes the clinical information for these patients. The median age for the surgery group was 59 years, while it was 63 years for the non-surgery group, indicating that younger patients were more likely to choose aggressive breast surgery. Race did not appear to influence the decision to remove the primary breast tumor. Based on the AJCC staging records, locoregional surgery was preferentially performed in patients with T1, T2 and T3 breast tumors compared with those having local advanced breast tumors ($P < 0.0001$). Compared to the non-surgery group, the surgery group had fewer patients who were lymph node negative (31.5% vs. 20.8%, $P < 0.0001$). The tumors resected from patients who had breast surgery were more likely to be Grade III, and less likely to be hormone receptor positive compared to tumors in patients who did not undergo surgery ($P < 0.0001$). While over half of the patients in the surgery group received systemic chemotherapy, less than half of them received it in the non-surgery group. Most patients did not receive radiotherapy if they did not undergo breast surgery. Among patients with only one distant organ involved in their first diagnosis of MBC, the number of women who did and did not opt for surgery was comparable. However, much fewer women with pMBC opted for primary breast surgery when multiple distant organs were affected. Finally, there was no difference in the distribution of removing distant metastases between the surgery and non-surgery groups.

Analysis of BCSS and OS

BCSS and OS were assessed to analyze the effects of local breast surgery in patients with pMBC. As shown in Fig. 1, locoregional surgery provided a prominent survival advantage. The median BCSS was 61 months for the surgery group, which was almost twice as long as that for the non-surgery group (Fig. 1A). Similar trends were seen in the OS as well (Fig. 1B).

Data were stratified based on the distant organs involved (bone, liver, lung, and brain) in order to eliminate the bias of site-specific metastasis on survival analysis. The distribution of pMBC patients with distant metastases is shown in Supplementary Table S1 and S2. Local breast surgery was found to significantly improve the BCSS and OS in patients with metastasis to just one distant site including the bone, liver, and lung (Fig. 1C–E and Supplementary Fig. S1A-C). Nevertheless, the survival of patients with brain metastases could not be prolonged via locoregional treatment (Fig. 1F and Supplementary Fig. S1D).

The combined effects of local and distant organ surgeries on survival were also evaluated. Though patients who underwent

Table 1
Characteristics of women diagnosed with primary metastatic breast cancer included in SEER database.

	Before PSM				After PSM			
	All	No Surgery	Surgery	P value	All	No Surgery (921; 50%)	Surgery (921; 50%)	P value
Age	20870	63 (54–74)	59 (50–69)	<0.0001		61 (53–72)	62 (53–71)	**0.9168**
Race				0.3465				**0.5861**
White	15733	11391 (75.8)	4342 (75.3)		1515	760 (82.5)	755 (82.0)	
Black	3501	2537 (16.9)	964 (16.7)		243	122 (13.3)	121 (13.1)	
Asian or Pacific Islander	1421	999 (6.7)	422 (7.3)		79	38 (4.1)	41 (4.5)	
American Indian/Alaska Native	133	93 (0.6)	40 (0.7)		5	1 (0.1)	4 (0.4)	
AJCC T stage				<0.0001				**0.0500**
0	483	475 (4.1)	8 (0.1)		3	3 (0.3)	0 (0)	
1	2407	1600 (13.8)	807 (14.5)		240	132 (14.3)	108 (11.7)	
2	5425	3389 (29.1)	2036 (36.5)		710	349 (37.9)	361 (39.2)	
3	2855	1810 (15.6)	1045 (18.7)		288	128 (13.9)	160 (17.4)	
4	6043	4364 (37.5)	1679 (30.1)		601	309 (33.6)	292 (31.7)	
Axillary lymph node				<0.0001				**0.2706**
Negative	5183	4021 (31.5)	1162 (20.8)		373	196 (21.3)	177 (19.2)	
Positive	13149	8736 (68.5)	4413 (79.2)		1469	725 (78.7)	744 (80.8)	
Grade				<0.0001				**0.6731**
I	1310	940 (9.4)	370 (6.9)		143	65 (7.1)	78 (8.5)	
II	6440	4517 (15.2)	1923 (36.0)		853	435 (47.2)	418 (45.4)	
III	7468	4460 (44.6)	3008 (56.2)		840	418 (45.4)	422 (45.8)	
IV	131	83 (0.8)	48 (0.9)		6	3 (0.3)	3 (0.3)	
Molecular subtype				<0.0001				**0.7427**
HR + /HER2-	10660	7656 (63.5)	3004 (55.9)		1309	644 (69.9)	665 (72.2)	
HR + /HER2 +	2809	1898 (15.7)	911 (17.0)		222	114 (12.4)	108 (11.7)	
HR-/HER2 +	1531	999 (8.3)	532 (9.9)		100	53 (5.8)	47 (5.1)	
TNBC	2432	1506 (12.5)	926 (17.2)		211	110 (11.9)	101 (11.0)	
Chemotherapy				<0.0001				**0.6412**
No	10379	8440 (55.9)	1939 (33.6)		912	451 (49)	461 (50.1)	
Yes	10491	6651 (44.1)	3840 (66.4)		930	470 (51)	460 (50)	
Radiation				<0.0001				**0.9292**
No	17660	17276 (94.6)	3384 (58.6)		1705	852 (92.5)	853 (92.6)	
Yes	3210	815 (5.4)	2395 (41.4)		137	69 (7.5)	68 (7.4)	
Distant metastasis				<0.0001				**0.5294**
multiple sites	6482	5454 (40.5)	1028 (22.7)		600	313 (34)	287 (31.2)	
bone only	7312	5608 (41.6)	2244 (49.5)		1000	493 (53.5)	507 (55.1)	
liver only	1356	857 (6.4)	499 (11.0)		99	43 (4.7)	56 (6.1)	
lung only	2043	1355 (10.1)	688 (15.2)		136	68 (7.4)	68 (7.4)	
brain only	278	206 (1.5)	72 (1.6)		7	4 (0.4)	3 (0.3)	
Distant surgery				0.6281				**0.2176**
No	19886	14377 (95.6)	5509 (95.4)		1818	912 (99.0)	906 (98.4)	
Yes	925	662 (4.4)	263 (4.6)		24	9 (1.0)	15 (1.6)	

Data are n (%) or median (IQR). *Data are not available in SEER database.

resection for distant metastasis had better survival rates compared to those who did not, the survival was significantly better when the primary breast tumor was resected (Fig. 2A and Supplementary Fig. S2A).

To analyze the effects of specific surgical procedures on BCSS and OS, local surgeries were categorized into the "Lumpectomy or Mastectomy" group (without axillary lymph node dissection) and "Radical mastectomy" group (with axillary lymph node dissection). Axillary lymph node dissection did not significantly affect the survival of patients with metastasis to a single site (bone, liver, or lung) as can be seen by the small differences observed in the survival curves (Fig. 2B–E and Supplementary Fig. S2B-E). Likewise, in cases with brain metastases, axillary lymph node dissection did not provide any additional survival advantage to the patients (Fig. 2F and Supplementary Fig. S2F), which was similar to the findings described earlier with locoregional surgeries alone.

We next analyzed the effects of chemotherapy and/or radiotherapy together with local surgery on survival in patients with pMBC (Fig. 3). Although locoregional treatments combined with chemotherapy or radiotherapy provided better OS compared with breast surgery alone, this advantage diminished for BCSS. However, while prognosis was poor for patients who underwent only chemotherapy or only radiotherapy, it was poorer for those who did not undergo any of the treatments.

Data stratified on the basis of molecular subtypes, and tumor size showed that they did not influence the survival advantage provided by locoregional surgery (Fig. 4 and Supplementary Fig. S3).

Univariate and multivariate analysis

To avoid potential confounding and selection bias, a 1:1 PSM procedure was performed, and 1842 patients were enrolled into the propensity model with 921 patients in each group. And the distribution of all the clinicopathological characteristics showed no significant difference (Table 1). We then performed univariate and multivariate analyses to evaluate the effects of the baseline factors on OS and BCSS (Table 2 and Supplementary Table 3).

As illustrated in Table 2 and Supplementary Table 3, the risk of pMBC-related death increased with age. Similarly, black women were at a higher risk of cancer-related mortality compared to their white counterparts. Tumors with higher AJCC T stage and grade had a poor prognosis. Compared to the HR+/HER2-subtype, patients with HR+/HER2+ tumors were at a lower risk of mortality, while the TNBC patients were at a higher risk. After PSM, only TNBC subtype showed a higher mortality risk. Chemotherapy, as a systemic treatment, provides better survival for pMBC patients, while chemotherapy did not show any significance in BCSS after

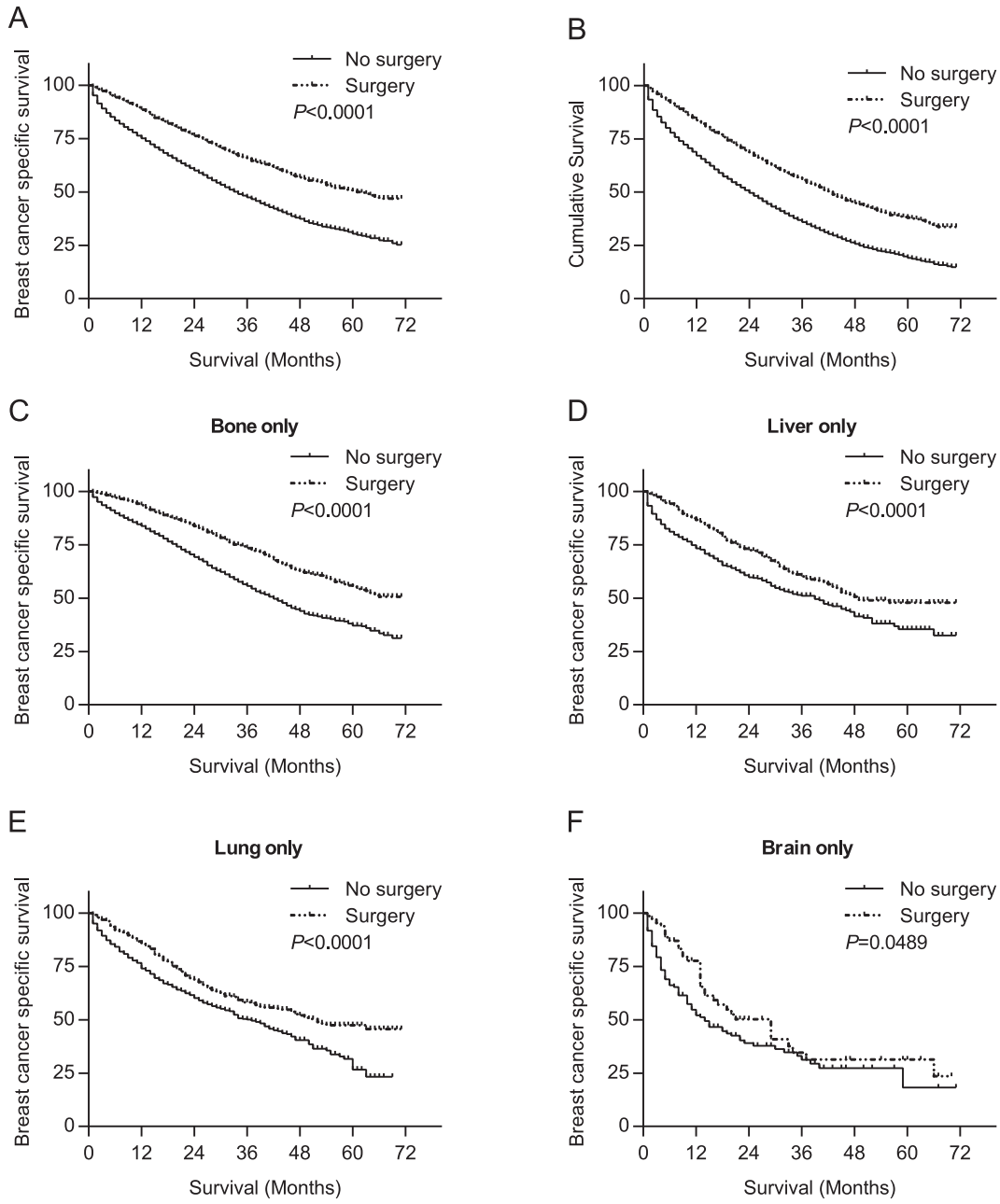

Fig. 1. Survival of pMBC patients. Survival curves showing BCSS (A) and OS (B) in the surgery and no-surgery groups. C-F, BCSS curves classified by distant involved organs.

matching. However, local radiotherapy does not improve the BCSS before and after matching, although it prolonged the OS in these patients before PSM (OS: HR 0.84, 95% CI 0.77–0.90). In the unmatched dataset, women with metastasis to only the bone or lung had better OS and BCSS compared to those with multiple distant organ involvements, while women with metastasis to only the bone had better survival in the matched dataset. However, when the brain was affected, survival was worse than in cases with metastases to multiple organs. Resection of distant metastases provided a better BCSS only before matching (BCSS: HR 0.81, 95% CI 0.69–0.95), while it did not improve the OS.

Local breast surgery, therefore, significantly improved the survival of patients, reducing the MBC-associated mortality rate by about 50%. After PSM, breast surgery was also found to reduce the risk of mortality in patients with MBC by almost 40%. Our findings demonstrate that regional treatment of primary tumors is an independent prognosis factor and is of vital significance in prolonging the survival of pMBC patients.

Discussion

Basically, the outcomes of treatments for stage IV breast cancer including pMBC depend on the patient's response to systemic therapy. Surgical treatments for primary breast tumors can have positive outcomes only in women who respond well to systemic treatment. In this study, however, we focused on the role of locoregional management in promoting the survival of patients with pMBC. In recent years, multiple retrospective studies have highlighted the effects of surgical procedures on improving survival in patients with pMBC. A retrospective study by Khan et al. with a

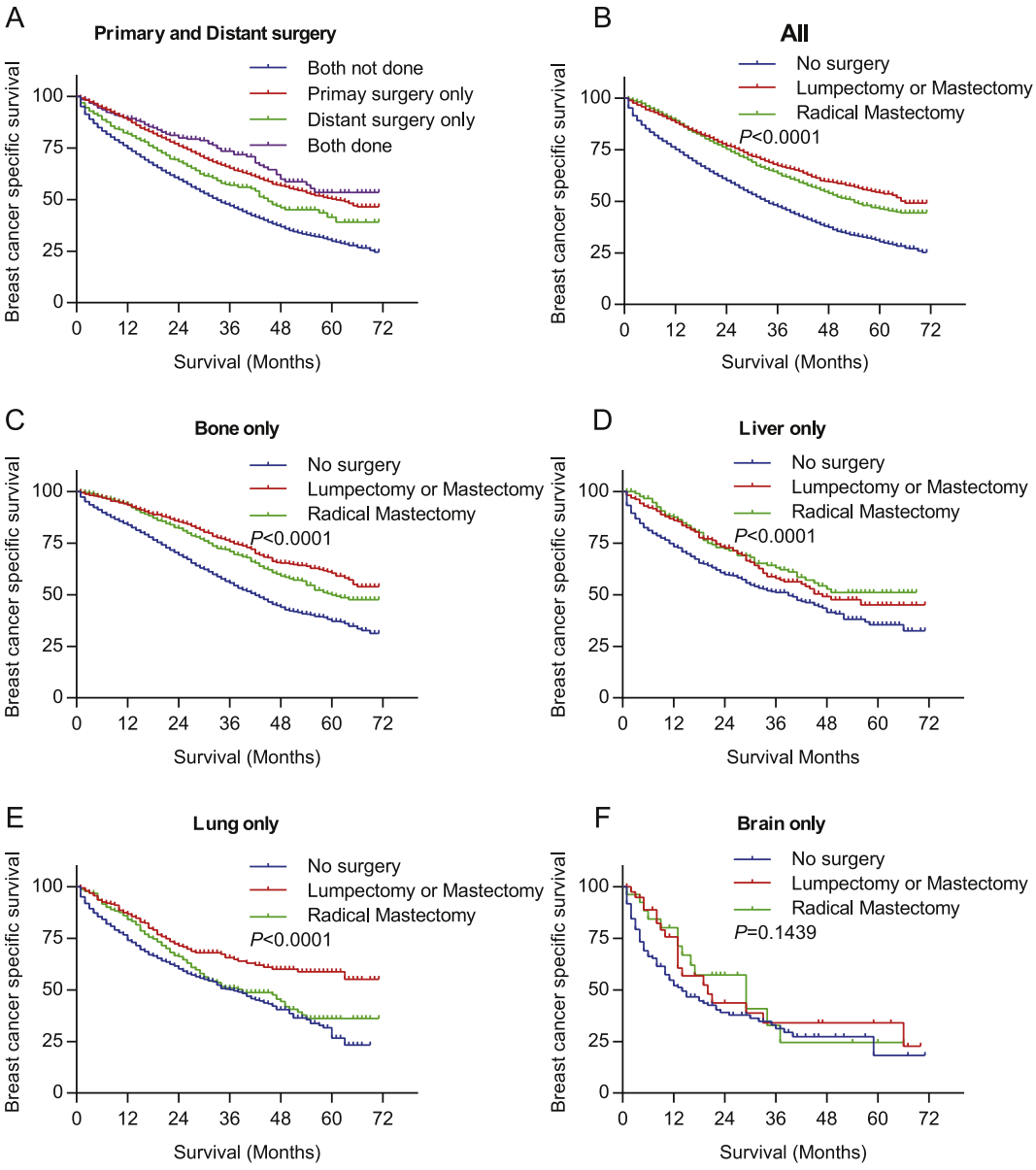

Fig. 2. BCSS curves with different surgical procedures. A, BCSS of pMBC females combined with breast surgery and removal of distant metastasis. B, BCSS of females with at least one distant organ infringed. C-F, Survival of patients with no breast surgery and patients who underwent lumpectomy or mastectomy, or radical mastectomy.

large sample size of 16,023 patients, indicates that the 3-year survival in the partial mastectomy (27.7%) and the total or modified radical mastectomy (31.8%) groups were significantly longer than that in the non-surgery group (17.3%; ref. 15). A clear surgical margin was further stressed as an independent prognostic variate, with a hazard ratio of 0.61 (95% CI 0.58–0.65; ref. 15). Another study by Rapiti et al. revealed that patients who underwent complete excision of the primary tumor with negative surgical margins had a 40% reduced mortality risk compared to those who did not have breast surgery [11]. This effect was particularly significant in women with only bone metastasis (HR 0.2, 95% CI 0.1–0.4; ref. 11). Among the published retrospective studies, about 33%–61% of patients underwent breast lesion excision [25], and the pooled hazard ratio for the overall mortality was 0.65 (95% CI 0.59–0.72; ref. 26).

In this study, based on the SEER database, we found that excision of the primary breast tumor significantly improved the survival in patients with pMBC, reducing the risk of mortality by about 40%–50%. Consistent with previous findings [5–18], we found that the younger patients and patients with smaller tumors were more likely to have better survival after excision of the primary tumor. Moreover, the stratified analysis demonstrated that breast surgery resulted in better survival in pMBC patients with metastasis to just one distant organ such as the bone, liver, and lung, but not the brain. In line with previous studies [9,10,15], women with metastases to multiple distant organs had worse survival compared with those having one metastatic lesion. Considering surgical margin status as a hierarchical factor, comparable survival was seen in patients who underwent partial mastectomy, and total mastectomy or modified radical mastectomy [14,15]. Our findings were in line with these previous results. In patients with metastasis to one distant organ (except brain), there were no prominent survival differences between women who had lumpectomy or mastectomy and those who had a radical mastectomy. Axillary lymph node dissection, therefore appeared not to affect patient survival,

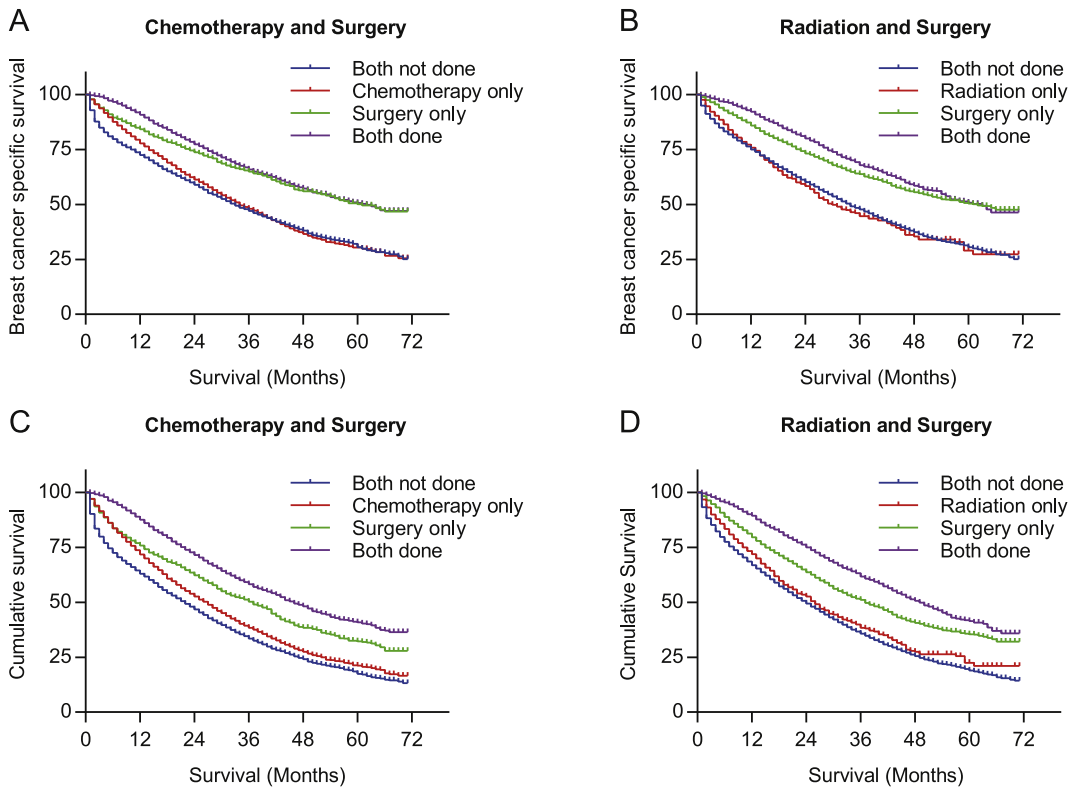

Fig. 3. Survival of pMBC with chemotherapy or radiotherapy.

suggesting that hematogenous metastasis is probably the major pathway for distant organ metastasis while the lymphatic pathway is relatively less important. Multiple studies have emphasized the importance of a negative surgical margin for better survival [7,10,15,18]. Unfortunately, we could not obtain data on surgical margin status from the SEER database.

Therefore, pMBC patients would benefit from primary breast tumor excision if they were younger, had a small primary tumor, a solo distant metastasis, and/or a negative surgical margin. Several reasons might help explain why breast surgery would contribute to improving the prognosis in pMBC. First, surgical removal of the primary tumor reduces the tumor burden thereby, preventing rapid tumor growth and distant metastasis [16]. Second, immunocompetence is restored due to a quantitative decrease in the production of immunosuppressive cytokines after primary tumor excision [27]. Third, breast surgery resects the necrotic centric areas which are inaccessible to drugs, thereby increasing the efficacy of adjuvant treatment and decreasing or limiting the occurrence of chemoresistant cells [28,29]. However, it has been reported that the surgical wound could result in a surge of growth factors, which would be unfavorable for the control of breast cancer [30]. Additionally, the primary tumor excision could result in a decrease in angiostatin levels, which in turn could lead to a burst of angiogenesis in distant dormant micrometastases [2,30]. On the other hand, abundant blood vessels make distant metastases more sensitive to chemotherapeutic drugs. Consequently, we preferentially hold the opinion that locoregional surgery to remove primary breast tumor with a clear surgical margin in combination with systemic treatment significantly improves the therapeutic efficacy by lowering the tumor burden, especially in women with single distant metastasis. Some of these patients might even undergo resection of the metastatic lesion to obtain a better survival. Although we had hoped to include the data on surgical margin and quality of life (QOL) to make this study more comprehensive, the data were not available in the database.

The diversity of breast cancer metastases makes MBC a rather complex disease. Studies with large sample size and comprehensive stratifications are needed to investigate the effect of a certain factor on MBC survival, taking the homogeneity and comparability into consideration as carefully as possible. Consequently, an RCT with a small sample size may not be capable of such an analysis and could be less convictive than retrospective studies with large sample sizes. Up to now, while there are several on-going RCTs, only two of them involving 624 women are available with complete results. However, the findings of these studies are debatable. One of them was a study from the Tata Memorial Centre, India, which included 350 MBC patients [23]. About 74% of the patients had more than three metastatic sites, while less than 10% of the patients received systemic treatment which was effective in the improvement of OS. In the other Turkish study, only 274 patients were recruited [22]. Women in the surgery group tended to be younger than 55 years, ER-positive and HER2-negative, and with only metastasis to the bone. Both studies lacked blinding and missing data were not available. They also had small sample sizes, and surgical margins and QOL were not considered, which made the results inconclusive due to weak stratification analysis. Moreover, BCSS was not measured in both studies. Another recently published study in Austria drew the conclusion that surgical resection of the primary tumor did not have an OS benefit in *de novo* stage IV breast cancer [31]. Although surgical margin and QOL were included in this study, the sample size was small due to the poor recruitment and BCSS was not measured.

As analyzed above, the effect of locoregional surgery has been underestimated in pMBC patients. Most studies have confirmed that breast surgery performed in the right patients significantly improves the prognosis. Inspiring result was obtained from the

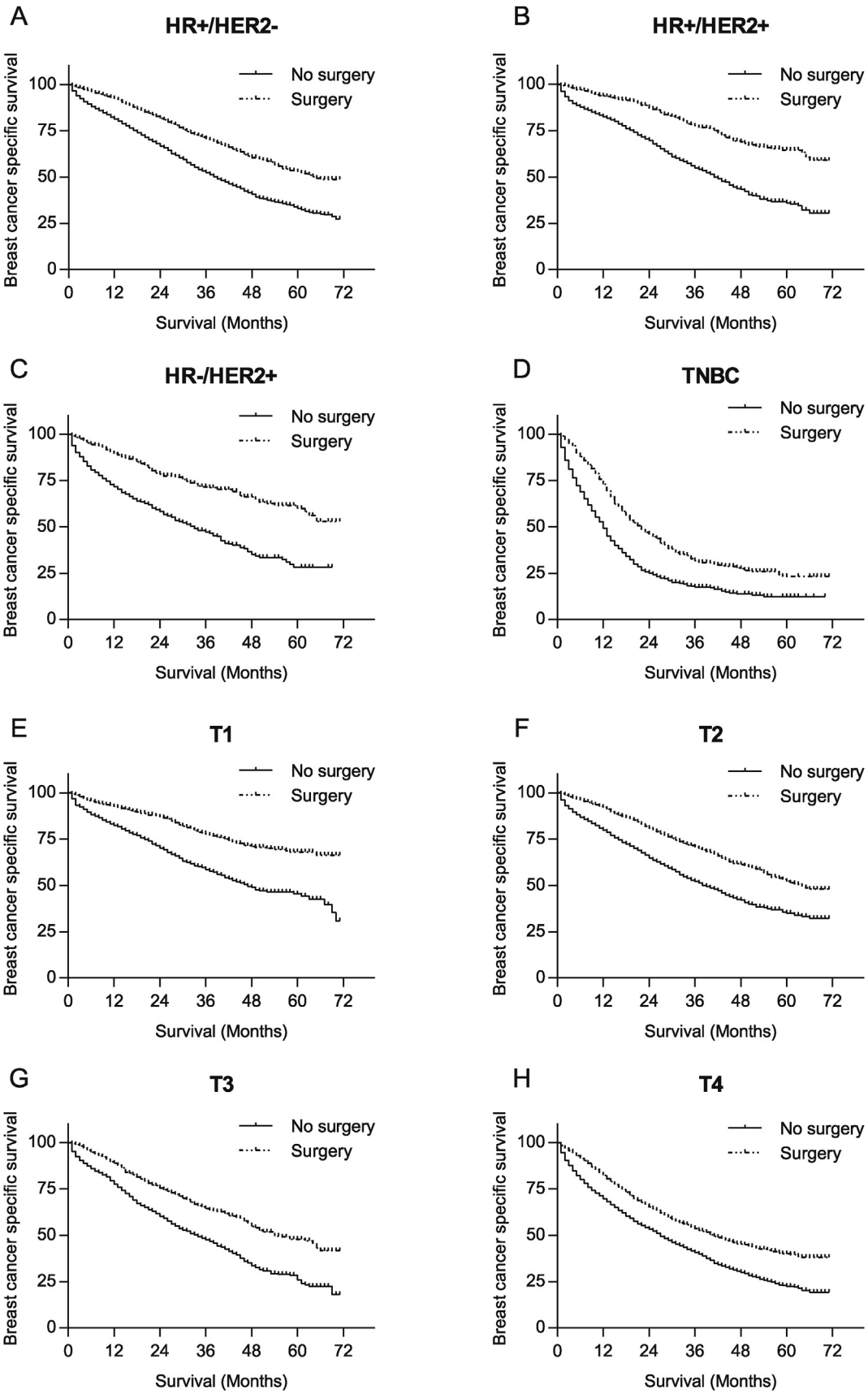

Fig. 4. BCSS curves stratified by molecular type and T stage.

Table 2
Univariate and multivariate analysis between clinicopathological characteristics and BCSS of breast cancer patients.

	Before PSM				After PSM			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age								
<50	reference	–	reference	–	reference	–	reference	–
50–69	1.30 (1.22–1.38)	<0.0001	1.17 (1.08–1.26)	<0.0001	0.97 (0.78–1.19)	0.7512	–	–
>70	1.85 (1.73–1.98)	<0.0001	1.51 (1.38–1.65)	<0.0001	1.35 (1.07–1.7)	0.0126	2.21 (1.91–2.56)	<0.0001
Race								
White	reference	–	reference	–	reference	–	reference	–
Black	1.28 (1.21–1.35)	<0.0001	1.26 (1.17–1.36)	<0.0001	1.91 (1.56–2.34)	<0.0001	1.41 (1.17–1.69)	0.0003
Asian or Pacific Islander	0.93 (0.85–1.02)	0.1077	–	–	1.1 (0.75–1.62)	0.6325	–	–
American Indian/Alaska Native	0.81 (0.60–1.09)	0.1547	–	–	0.94 (0.23–3.76)	0.9270	–	–
AJCC T stage (0/1/2/3/4)	1.25 (1.22–1.28)	<0.0001	1.20 (1.17–1.24)	<0.0001	1.38 (1.28–1.49)	<0.0001	1.13 (1.06–1.21)	0.0003
Axillary lymph node								
Negative	reference	–	reference	–	reference	–	reference	–
Positive	1.06 (1.01–1.12)	0.0276	–	–	1.55 (1.24–1.93)	0.0001	–	–
Grade (I/II/III/IV)	1.45 (1.39–1.51)	<0.0001	1.41 (1.34–1.48)	<0.0001	2.1 (1.83–2.41)	<0.0001	1.43 (1.26–1.62)	<0.0001
Molecular subtype								
HR+/HER2-	reference	–	reference	–	reference	–	reference	–
HR+/HER2+	0.74 (0.69–0.80)	<0.0001	0.85 (0.78–0.93)	0.0004	1.03 (0.79–1.34)	0.8293	–	–
HR-/HER2+	0.96 (0.88–1.05)	0.3291	–	–	1.41 (1.00–1.99)	0.0474	–	–
TNBC	2.00 (1.88–2.12)	<0.0001	2.53 (2.34–2.73)	<0.0001	4.15 (3.39–5.09)	<0.0001	2.46 (2.04–2.98)	<0.0001
Radiation-								
No	reference	–	reference	–	reference	–	reference	–
Yes	0.58 (0.55–0.62)	<0.0001	–	–	0.98 (0.73–1.31)	0.8969	–	–
Chemotherapy								
No	reference	–	reference	–	reference	–	reference	–
Yes	0.65 (0.62–0.68)	<0.0001	0.65 (1.61–0.69)	<0.0001	1.03 (0.88–1.21)	0.7071	–	–
Distant metastasis								
multiple sites	reference	–	reference	–	reference	–	reference	–
bone only	0.58 (0.55–0.61)	<0.0001	0.66 (0.61–0.70)	<0.0001	0.41 (0.35–0.49)	<0.0001	0.57 (0.49–0.66)	<0.0001
liver only	0.80 (0.73–0.88)	<0.0001	–	–	0.69 (0.48–0.99)	0.0411	–	–
lung only	0.80 (0.74–0.86)	<0.0001	0.72 (0.66–0.80)	<0.0001	0.91 (0.68–1.22)	0.5413	–	–
brain only	1.41 (1.20–1.67)	<0.0001	1.69 (1.35–2.11)	<0.0001	3.22 (1.43–7.23)	0.0048	2.48 (1.10–5.58)	0.0291
Distant Surgery								
No	reference	–	reference	–	reference	–	reference	–
Yes	0.73 (0.65–0.81)	<0.0001	0.81 (0.69–0.95)	0.0092	0.69 (0.31–1.54)	0.3650	–	–
Primary Surgery								
No	reference	-	reference	-	reference	-	reference	-
Yes	0.48 (0.45–0.50)	<0.0001	0.50 (0.47–0.54)	<0.0001	0.59 (0.50–0.69)	<0.0001	0.60 (0.52–0.68)	<0.0001

database analysis, although we can't draw a final conclusion at present for the retrospective nature of this study causing an inherent risk of selection and performance bias. We acquired the data with a huge sample size and all statistical analyses were in accordance with the original database without any unnecessary screening in case of additional bias caused by statistical approach. Based on our study, we concluded prudently that surgical procedures in combination with systemic treatment have some positive effects on younger patients with a small primary tumor and a single distant metastasis except for brain metastasis. At the same time, we believe that an RCT consisting of younger female pMBC patients with solo distant metastasis except for brain metastasis should be initialed to compare the difference between surgery and no surgery, also the surgical margin and QOL deserve more attention in future studies.

Conflicts of interest statement

No potential conflicts of interest were disclosed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.03.006.

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