Impact of surgical treatment on survival for patients with stage IV breast cancer: a population-based propensity score matching analysis (#41899)

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Impact of surgical treatment on survival for patients with stage IV breast cancer: a population-based propensity score matching analysis

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Background: Surgical treatment for stage IV breast cancer remains controversial. The aim of this study was to investigate the impact of surgical treatment on survival of stage IV breast cancer patients based on the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015.

Methods: In total, 13,034 patients were selected and divided into surgery and non-surgery groups. Propensity score matching method was utilized to achieve balance covariates across different groups. One-to-one (1:1) PSM was conducted to construct a matched sample consisting of pairs of surgery and non-surgery subjects by optimal matching algorithm. Breast cancer-specific survival (BCSS) and overall survival (OS) of the two groups were assessed by Kaplan-Meier plots and Cox proportional hazard regression models. Stratified analysis according to different variables were also performed.

Results: After propensity score matching, the surgery and non-surgery group consisted of 2,269 patients respectively. The median survival time was 43 months for the surgery group and 27 months for the non-surgery group. Kaplan-Meier curves indicated that surgical treatments could clearly improved both the BCSS and OS for patients with stage IV breast cancer. On multivariate analysis, surgery group was associated with a better survival compared with the non-surgery group (BCSS: HR=0.542, 95% CI=0.499-0.589, p<0.001; OS: HR=0.555, 95% CI=0.512-0.601, p<0.001). Furthermore, this survival advantage persisted in all subgroups irrespective of age, race, tumor size, nodal status, histology grade, molecular subtype, chemotherapy status or status of distant metastasis.

Conclusion: Our study provided additional evidence that patients with stage IV breast cancer could benefit from surgical treatment and it might play a more important role in multiplicity therapy.

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Abstract

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Methods: In total, 13,034 patients were selected and divided into surgery and non-surgery groups. Propensity score matching method was utilized to achieve balance covariates across different groups. One-to-one (1:1) PSM was conducted to construct a matched sample consisting of pairs of surgery and non-surgery subjects by optimal matching algorithm. Breast cancer-specific survival (BCSS) and overall survival (OS) of the two groups were assessed by Kaplan-Meier plots and Cox proportional hazard regression models. Stratified analysis according to different variables were also performed.

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Conclusion: Our study provided additional evidence that patients with stage IV breast cancer could benefit from surgical treatment and it might play a more important role in multiplicity therapy.

Keywords: Stage IV breast cancer; Prognosis; Surgical treatment; Stratified analysis

Introduction

Stage IV breast cancer (BC) refers to the tumor which has been transferred to the site away from the breast. It is estimated that 5-10% of female breast cancer patients might have metastatic disease at presentation [1-3]. The main purpose of treatment for de novo stage IV breast cancer is to alleviate symptoms, improve the quality of life and prolong survival [4]. Therefore, systemic treatment have played a crucial role in stage IV breast cancer, with which surgical treatment has been considered as an auxiliary means of systemic therapy and was generally not the first choice by clinicians.

However, with the advances in systemic treatment have greatly improved the control of metastases disease and prolonged survival, the utility of surgical treatment has therefore become a question worth discussing. Several retrospective studies have demonstrated that local surgery was associated with a better survival in women with metastatic breast cancer. [5-10]. While three prospective randomized trials have revealed discordant results with conflicting data [11-13]. In addition, it is noted that the act of surgery might accelerate metastatic growth and have an adverse effect on survival [14-16]. Therefore, most guidelines still recommend surgical intervention in palliative situations or selected patients after response to initial systemic therapy.

To date, the role of surgery for de novo stage IV breast cancer patients is still ambiguous and no consensus exist. Accordingly, we conducted this propensity score matching analysis to investigate the impact of surgical treatment on survival of stage IV breast cancer patients with data from a large population-based database (the Surveillance, Epidemiology, and End Results, SEER) collected from 2010 to 2015.

Material and methods

Study Patients

We performed a retrospective study of women with an initial primary diagnosis of stage IV breast cancer who were recorded in the SEER*Stat version 8.3.4 database from 2010 to 2015 to ensure complete data and adequate follow-up duration. In our study, we analyzed age, race, histological grade, tumor size, nodal status, breast subtype, radiation status, chemotherapy status and status of distant metastasis. In order to assess the effect of status of distant metastasis on survival, we divided those patients into solitary bone metastasis group and non-solitary bone metastasis (visceral metastasis) groups, the non-solitary bone metastasis groups include patients with visceral only metastasis and both bone and visceral metastases. For stage T0 indicates that the tumor is not visible, and Tx or Nx indicate that the primary tumor cannot be determined by clinical examination, we excluded all women with T0, Tx, or Nx classifications. Patients with an unknown surgical history or only received biopsy and lacked of treatment information (ER, estogen receptor, PR, progesterone receptor, HER2, human epidermal growth factor receptor-2, chemotherapy or radiation status) were also excluded. Well, moderate and poorly differentiated tumor grades were identical to grade I, II and III, with undifferentiated and anaplastic tumor grades were identical to grade IV.

Statistical analysis

Among women diagnosed with stage IV disease, we sought to compare the overall survival (OS) and breast cancer specific survival (BCSS) between patients who did and did not receive surgical treatment for their primary tumor. The median survival time was also calculated. All subjects who received surgical treatment related to the primary tumor (masctomy or breast conserving surgery) were included in the surgery group. Patients who did not receive any formal resection of their primary tumor were categorized as not having surgery. *P*-values for comparisons of different variables were calculated by chi-squared ($\chi 2$) test. Propensity score matching (PSM) could help achieve balance covariates across different groups. One-to-one (1:1) PSM was conducted to construct a matched sample consisting of pairs of surgery and non-surgery subjects by optimal matching algorithm. Variables that were significantly different between the two groups were utilized to generate propensity scores. Kaplan-Meier survival curves were generated to compare differences in survival probabilities over time between the surgery and non-surgery groups. Cox regression models were used to describe the associations between surgery and survival risk. Specifically, we also conducted a stratified analysis with respect to BCSS and OS by age, race, tumor size, nodal status, grade, molecular subtype, chemotherapy status and solitary bone metastasis or not. Psmatch2 module were used to perform propensity score matching in Stata version 13.0 (SAS Institute Inc., Cary, NC, USA). Other statistical analyses were performed with Statistical Package for the Social Sciences (SPSS, version 24.0) for Windows (Chicago, USA), with a two-sided *P* value of less than 0.05 was considered statistically significant.

Results

Patient characteristics before and after propensity score matching

In total, 13,034 patients with a diagnosis of stage IV breast cancer between 2010-2015 who had complete information of surgical treatment were included in this study. As shown in Table 1, 9,151 (70.2%) patients did not receive surgery and 3,883 (29.8%) were treated with surgery. There were significant differences between these two groups. Patients treated with surgery were more likely to be younger, smaller tumor size, more advanced nodal status, worse histology grade and higher proportion of solitary bone metastasis. Furthermore, those who received chemotherapy and radiotherapy also tended to be treated with surgery.

Propensity score matching (optimal, 1:1) between the surgery and non-surgery groups was conducted by all variables (age, race, T and N categories, histology, grade, molecular subtype, chemotherapy or radiation status, solitary bone metastasis or not). After PSM, the surgery and non-surgery group consisted of 2,269 patients respectively. No statistical differences were observed between the two groups.

Comparison of survival between the surgery and non-surgery groups

Kaplan-Meier curves of the BCSS and OS in the surgery and non-surgery groups after PSM are presented in Figure 1. Surgical treatments clearly improved both the BCSS and OS for patients with de novo stage IV breast cancer. The median survival time was 43 months for the surgery group with 27 months for the non-surgery group. To further analyze the factors that affected the prognosis, a multivariate analysis using the Cox proportional hazards model was performed, with the relevant results are shown in Table 2. For both BCSS and OS, older age, more advanced T or N stage, higher histology grades, triple negative breast cancer, non-solitary bone metastasis and an absence of chemotherapy presented a worse survival. Compared with the non-surgery group, the surgery group was associated with an markedly survival advantage

(BCSS: HR=0.542, 95% CI=0.499-0.589, p<0.001; OS: HR=0.555, 95% CI=0.512-0.601, p<0.001).

Stratified survival analysis

Furthermore, we performed a stratified analysis according to different variables. The Kaplan-Meier survival function was used to generate Figure 2 and Figure 3 in the hierarchical analysis, which represent the overall survival between surgery and non-surgery patients with different tumor size, nodal status, molecular subtypes and status of distant metastasis. The median survival time for hormone receptor positive HER2 negative (HR+HER2-) and triple negative (TNBC) subtype was 47 months (surgery) vs. 32 months (non-surgery) and 16 months (surgery) vs. 11 months (non-surgery) respectively. While for solitary bone metastasis and visceral metastasis patients, the median survival time was 52 months (surgery) vs. 36 months (non-surgery) and 36 months (surgery) vs. 22 months (non-surgery) respectively. Table 3 showed the hazards ratio (HR) and 95% confidence interval (CI) of the surgery group, which was determined by Cox regression analysis contrasted with that of the non-surgery group. Surgical treatment was indicated to significantly reduce mortality risk regardless of tumor size, nodal status, molecular subtype or status of distant metastasis. Similarly in other subgroups (Figure 4), surgery also presented a more favorable overall survival irrespective of age, race, histology grade or chemotherapy status.

Multivariate analysis for patients in the surgery group

We also performed a multivariate analysis by Cox proportional hazards model in the patients with surgical treatment. For both BCSS and OS, older age, more advanced T stage, higher histology grades, triple negative breast cancer, non-solitary bone metastasis and an

absence of chemotherapy presented a worse prognosis. N stage and type of surgery (masctomy or breast conserving surgery) remained irrelevant to the survival of this group of patients. While radiotherapy was identified to be a significantly favorable factor both in BCSS and OS (HR=0.819, 95% CI=0.694-0.966, p=0.018; HR=0.783, 95% CI=0.667- 0.920, p=0.003).

Discussion

In this large cohort of retrospective study, we sought to reveal the distinct outcomes of stage IV breast cancer with or without surgical intervention based on the SEER population-based data. Our findings indicated that the surgery group was associated with a better survival compared with the non-surgery group (BCSS: HR=0.542, 95% CI=0.499-0.589, p<0.001; OS: HR=0.555, 95% CI=0.512-0.601, p<0.001). Furthermore, this survival advantage persisted in all subgroups irrespective of age, race, tumor size, nodal status, histology grade, molecular subtype, chemotherapy status or status of distant metastasis.

Traditionally, it was considered that metastatic breast cancer was a systemic disease and local therapy would only have little impact on outcomes [17]. The primary aim of treatment is to alleviate symptoms, improve the quality of life and prolong survival. In clinical practice, the majority of patients with de novo stage IV breast cancer are recommended to receive systemic therapy including chemotherapy, anti-HER2 therapy or endocrine therapy. Surgery is mainly considered when there is tumor bleeding or ulceration [18]. Earlier studies also suggested that the growth of distant metastases could be stimulated by removal of primary tumor. Surgical intervention could reduce angiostatin secretion and stimulate the release of growth factors, thus accelerating metastatic growth and presenting an adverse effect on survival [14-16, 19]. However, other experimental studies indicated that although local surgery caused transient increase in tumor burden, it substantially reduced overall tumor burden and improved survival by inducing

177 immune suppression and restoring responsiveness [20-22]. Therefore, the utility of surgical
178 intervention in this population has long been debated. Multiple retrospective studies have
179 revealed the potential benefit with surgery [5-10, 23-27]. The most recent study based on the
180 SEER database (1998-2011) proposed a survival advantage with surgical intervention (median
181 overall survival, 34 months for surgery vs. 18 months for non-surgery) [28]. However, the data
182 about HER2 status in this study were incomplete and no stratified analysis was conducted. One
183 study based on NCDB database also noted a benefit for stage IV breast cancer patients with
184 surgery [9]. In a large cohort of 11,694 patients, an improved overall survival was observed for
185 the surgery group compared with the non-surgery group after propensity score matching
186 (HR=0.68, 95% CI=0.63-0.72, p<0.001). These conclusions are similar with the results in our
187 study, providing consistent evidence that well-selected patients with de novo stage IV breast
188 cancer who undergo surgical intervention could obtain a better survival.

189 In spite of the evidence in several retrospective studies, supportive prospective analyses still
190 lacked. Fitzal's study (ABCSG-28 POSYTIVE) enrolled 90 previously untreated stage IV breast
191 cancer patients and randomly assigned them to surgical resection followed by systemic therapy
192 group or primary systemic therapy group [11]. This trial was stopped early due to poor
193 recruitment and the median overall survival for surgery and non-surgery group was 34.6 and 54.8
194 months respectively (HR=0.691, 95%CI= 0.358-1.333; p= 0.267). MF07-01 trial [12] is another
195 prospective, multicenter, phase III, randomized trial to focus on the impact of surgical treatment
196 on the survival of de novo stage IV BC patients. In this study, one group received sequential
197 systemic therapy after primary surgery and the other group only received systemic therapy alone.
198 Local surgery did not gained a survival advantage after 3 years of follow-up. But after 5 years of
199 follow-up, patients with local surgery achieved a better overall survival (HR=0.66, 95%CI=

0.49-0.88; p= 0.005). Unplanned subgroup analyses indicated that the survival benefit of surgical treatment presented in patients with younger age (<55 years), ER/PR positive, HER2 negative or solitary bone-only metastases. Although these findings identified the therapeutic value of surgical treatment and suggested several factors such as molecular subtype or metastatic site that should be taken into consideration, controversy still existed for the procedure of surgical resection followed by systemic therapy did not accord with the clinical practice now. The other prospective trial by Badwe et al. [13] randomly included 350 previously untreated de novo metastatic BC patients from India between 2005 to 2013. Median overall survival was 19.2 months (95% CI=15.98-22.46) in the surgery group and 20.5 months (16.96-23.98) in the non-surgery group (HR=1.04, 95%CI= 0.81-1.34; p= 0.79). The uncertain effect of surgery in this study might be attributed to the fact that only few patients enrolled received paclitaxel-based chemotherapy and most of HER2 positive patients did not take anti-HER2 therapy.

Our current study of the SEER database provided strong retrospective data of surgical treatment in stage IV breast cancer. It is expected that patients with lower disease burden and better prognostic factors such as ER+HER- subtype or solitary bone metastasis are more likely to undertake surgery, thereby resulting a better prognosis. In a matched paired retrospective analysis, it is noted that selection bias in stage IV breast cancer could affect the survival outcomes[29]. Therefore, propensity score matching analysis was applied in our study to balance covariates in different groups and reduce selection bias. The results of propensity score matching indicated that surgical intervention obtained a significant survival benefit. Furthermore, patients with surgery were shown to significantly reduce mortality risk in different subgroups, regardless of age, race, histology grade, tumor size, nodal status, molecular subtype, chemotherapy status or status of distant metastasis, suggesting that surgical treatment might have independent

therapeutic value to improve survival in stage IV breast cancer. However, one point that should be mentioned is a relatively poor survival for stage IV triple negative breast cancer (TNBC) patients. The median survival time for TNBC patients was 16 months (surgery) vs. 11 months (non-surgery) respectively. Although surgical intervention revealed a better survival outcome, whether these patients should received surgery required further discussion. For patients with surgical treatment, we also performed a multivariate analysis. Type of surgery (masctomy or breast conserving surgery) remained irrelevant to the survival, while radiotherapy was identified to be a significantly favorable factor both in BCSS and OS (HR=0.819, 95% CI=0.694-0.966, p=0.018; HR=0.783, 95% CI=0.667-0.920, p=0.003).

Stage IV breast cancer is a group of highly heterogeneous disease. Advances in systemic treatment have greatly improved the control of metastases disease. Five-year disease special survival of de novo breast cancer has been improved from 28% (1990-1998) to 55% (2005-2010). Therefore, local treatment might play a more important role than conventionally considered in metastatic breast cancer patients. However, several limitations should also be mentioned in our study. Firstly, although propensity score matching analysis was utilized, selection bias might still exist regarding the retrospective design. Secondly, information about anti-HER2 targeted therapy and endocrine therapy is absent, while the regimen of chemotherapy and the exact site of radiotherapy (primary tumor or metastasis site such as bone) was also unavailable from the SEER database. Thirdly, we could not determine the timing of surgery for patients included, whether the surgical treatment was performed after systemic treatment or at initial diagnosis is also unknown.

In conclusion, our study provided additional evidence that patients with stage IV breast cancer could benefit from surgical treatment. Future multicenter, large-scale prospective studies with long-term follow-up are still warranted.

Acknowledgments

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Disclosures

The authors have declared that no competing interests exist.

Compliance with Ethical Standards

Ethical approval

This article does not contain any studies with human participants or animals conducted by any of the authors.

Informed consent

As this study contains data released by the SEER database which are publicly available and de-identified, informed consent was not needed.

Figure Captains

Figure 1. Kaplan-Meier curves of breast cancer specific survival (A) and overall survival (B) in the surgery and non-surgery groups after propensity score matching.

Figure 2. Kaplan-Meier curves of overall survival in the surgery and non-surgery groups stratified by different tumor size and nodal status. (A) T1+T2, (B) T3+T4, (C) N0+N1, (D) N2+N3.

Figure 3. Kaplan-Meier curves of overall survival in the surgery and non-surgery groups stratified by molecular subtypes and status of distant metastasis. (A) HR+HER2-, (B) TNBC, (C) solitary bone metastasis, (D) visceral metastasis.

Figure 4. Forest plot of overall survival in the surgery and non-surgery groups stratified by age, race, histology grade and chemotherapy status.

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Table 1(on next page)

Baseline Characteristics of stage IV patients with or without surgical treatment before and after PSM

Table 1: Baseline Characteristics of stage IV patients with or without surgical treatment before and after PSM

Characteristics	Before PSM					After PSM				
	Surgery (n=3883)		Non-Surgery (n=9151)		*P* [a]	Surgery (n=2269)		Non-Surgery (n=2269)		*P* [a]
	No	%	No	%		No	%	No	%	
Age (years)										
20-49	1163	30.0	1836	20.1	<0.001	604	26.6	600	26.4	0.893
50-79	2720	70.0	7315	79.9		1665	73.4	1669	73.6	
Race										
White	2841	73.2	6747	73.7	0.012	1643	72.4	1641	72.3	0.917
Black	685	17.6	1646	18.0		418	18.4	431	19.0	
Others	349	9.0	712	7.8		204	9.0	193	8.5	
Unknown	8	0.2	46	0.5		4	0.2	4	0.2	
T stage										
T1+T2	1903	49.0	3675	40.2	<0.001	1041	45.9	1059	46.7	0.592
T3+T4	1980	51.0	5476	59.8		1228	54.1	1210	53.3	
N stage										
N0+N1	2167	55.8	7201	78.7	<0.001	1426	62.8	1458	64.3	0.324
N2+N3	1716	44.2	1950	21.3		843	37.2	811	35.7	
Grade										
I+II	1314	33.8	4314	47.1	<0.001	827	36.5	847	37.3	0.196
III	2157	55.6	3860	42.2		1287	56.7	1296	57.1	
Unknown	412	10.6	977	10.7		155	6.8	126	5.6	
Histology										
IDC	2973	76.6	5745	62.8	<0.001	1673	73.7	1694	74.7	0.343
ILC	286	7.4	868	9.5		184	8.1	158	7.0	
Others	624	16.0	2538	27.7		412	18.2	417	18.3	
Molecular subtype										
HR+/HER-	1898	48.9	4524	49.4	<0.001	1085	47.8	1075	47.4	0.663
HR+/HER-	662	17.0	1320	14.4		387	17.1	393	17.3	
HR-/HER+	416	10.7	716	7.8		229	10.1	251	11.0	
TNBC	652	16.8	956	10.5		413	18.2	385	17.0	
Unknown	255	6.6	1635	17.9		155	6.8	165	7.3	
Chemotherapy status										
Yes	2875	74.0	4587	50.1	<0.001	1545	68.1	1532	67.5	0.680
No	1008	26.0	4564	49.9		724	31.9	737	32.5	
Radiation status										
Yes	1802	46.4	540	5.9	<0.001	405	17.8	438	19.3	0.208
No	2081	53.6	8611	94.1		1864	82.2	1831	80.7	
Solitary bone metastasis										

Yes	1506	38.8	2971	32.5	<0.001	768	33.8	780	34.4	0.707
No	2377	61.2	6180	67.5		1501	66.2	1489	65.6	

Abbreviations: PSM: propensity-score matching; MST, median survival time; IQR, inter quartile range; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

[a] The *P* value was calculated among all groups by the Chi-square test.

Table 2(on next page)

Multivariate Cox proportional hazard model for breast cancer-specific survival (BCSS) and overall survival (OS) after PSM in stage IV breast cancer

Table 2: Multivariate Cox proportional hazard model for breast cancer-specific survival (BCSS) and overall survival (OS) after PSM in stage IV breast cancer.

Variables	BCSS		OS	
	HR (95% CI)	*P* [a]	HR (95% CI)	*P* [a]
Age (years)				
20-49	Reference		Reference	
50-79	1.203 (1.095-1.303)	<0.001	1.257 (1.145-1.379)	<0.001
Race				
White	Reference		Reference	
Black	1.252 (1.134-1.382)	<0.001	1.286 (1.169-1.415)	<0.001
Others	0.887 (0.761-1.035)	0.127	0.879 (0.751-1.021)	0.092
Unknown	NA		NA	
T stage				
T1+T2	Reference		Reference	
T3+T4	1.408 (1.294-1.531)	<0.001	1.407 (1.297-1.526)	<0.001
Unknown	NA		NA	
N stage				
N0+N1	Reference		Reference	
N2+N3	1.091 (1.003-1.185)	0.042	1.098 (1.012-1.190)	0.024
Unknown	NA		NA	
Grade				
I+II	Reference		Reference	
III+IV	1.587 (1.436-1.753)	<0.001	1.517 (1.378-1.670)	<0.001
Unknown	1.279 (1.118-1.464)	<0.001	1.242 (1.090-1.414)	0.001
Molecular subtype				
HR+/HER2-	Reference		Reference	
HR+/HER2+	0.702 (0.612-0.805)	<0.001	0.714 (0.617-0.804)	<0.001
HR-/HER2+	0.923 (0.790-1.078)	0.311	0.936 (0.806-1.088)	0.388
TNBC	2.663 (2.373-2.988)	<0.001	2.603 (2.327-2.912)	<0.001
Unknown	1.485 (1.274-1.731)	<0.001	1.486 (1.282-1.722)	<0.001
Chemotherapy status				
Yes	Reference		Reference	
No	1.554 (1.412-1.710)	<0.001	1.577 (1.438-1.729)	<0.001
Solitary bone metastasis				
Yes	Reference		Reference	
No	1.390 (1.266-1.525)	<0.001	1.369 (1.252-1.498)	<0.001
Surgery status				
No	Reference		Reference	
Yes	0.542 (0.499-0.589)	<0.001	0.555 (0.512-0.601)	<0.001

Abbreviation: HR, hazard ratio; CI, confidence interval; BCSS, breast cancer-specific survival; OS, overall survival; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative

breast cancer.

[a] The *P* value was adjusted by the multivariate Cox proportional hazard regression model.

Table 3(on next page)

Multivariate Cox proportional hazard regression model of breast cancer-specific survival (BCSS) and overall survival (OS) for the 1:1 matched surgery and non-surgery groups, stratified by the T stage, N stage, breast subtype and metastasis status

Table 3: Multivariate Cox proportional hazard regression model of breast cancer-specific survival (BCSS) and overall survival (OS) for the 1:1 matched surgery and non-surgery groups, stratified by the T stage, N stage, breast subtype and metastasis status.

Variables [b]	Surgery vs. Non-surgery [a]			
	BCSS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
T stage				
T1+T2	0.492 (0.431-0.562)	<0.001	0.504 (0.443-0.572)	<0.001
T3+T4	0.580 (0.521-0.646)	<0.001	0.594 (0.535-0.659)	<0.001
N stage				
N0+N1	0.528 (0.475-0.587)	<0.001	0.538 (0.486-0.596)	<0.001
N2+N3	0.564 (0.493-0.646)	<0.001	0.585 (0.513-0.667)	<0.001
Breast subtype				
HR+/HER2-	0.554 (0.489-0.628)	<0.001	0.573 (0.508-0.646)	<0.001
HR+/HER2+	0.462 (0.361-0.592)	<0.001	0.473 (0.372-0.601)	<0.001
HR-/HER2+	0.459 (0.346-0.609)	<0.001	0.490 (0.374-0.643)	<0.001
TNBC	0.536 (0.455-0.631)	<0.001	0.534 (0.455-0.627)	<0.001
Metastasis status				
Solitary bone metastasis	0.495 (0.423-0.580)	<0.001	0.501 (0.431-0.583)	<0.001
Visceral metastasis	0.562 (0.510-0.619)	<0.001	0.568 (0.517-0.625)	<0.001

[a] Non-surgery as a reference.

[b] Adjusted by a multivariate Cox proportional model, including age, race, T stage, N stage, grade, molecular subtype, chemotherapy status, solitary bone or visceral metastasis where appropriate.

Table 4(on next page)

Multivariate analyses for breast cancer-specific survival (BCSS) and overall survival (OS) in stage IV breast cancer patients with surgical treatment

Table 4: Multivariate analyses for breast cancer-specific survival (BCSS) and overall survival (OS) in stage IV breast cancer patients with surgical treatment.

Variables	BCSS		OS	
	HR (95% CI)	*P* [a]	HR (95% CI)	*P* [a]
Age (years)				
20-49	Reference		Reference	
50-79	1.171 (1.017-1.348)	0.028	1.240 (1.081-1.423)	0.002
Race				
White	Reference		Reference	
Black	1.294 (1.115-1.501)	<0.001	1.372 (1.191-1.581)	<0.001
T stage				
T1+T2	Reference		Reference	
T3+T4	1.572 (1.382-1.787)	<0.001	1.568 (1.386-1.774)	<0.001
N stage				
N0+N1	Reference		Reference	
N2+N3	1.106 (0.975-1.255)	0.118	1.113 (0.985-1.257)	0.085
Grade				
I+II	Reference		Reference	
III+IV	1.625 (1.399-1.887)	<0.001	1.514 (1.314-1.745)	<0.001
Molecular subtype				
HR+/HER2-	Reference		Reference	
HR+/HER2+	0.580 (0.468-0.719)	<0.001	0.585 (0.476-0.719)	<0.001
HR-/HER2+	0.765 (0.599-0.978)	0.033	0.791 (0.626-0.999)	0.049
TNBC	2.486 (2.105-2.936)	<0.001	2.392 (2.036-2.812)	<0.001
Type of surgery				
Breast conserving surgery	Reference		Reference	
Masctomy	1.105 (0.965-1.267)	0.149	1.032 (0.913-1.235)	0.187
Chemotherapy status				
Yes	Reference		Reference	
No	1.500 (1.302-1.730)	<0.001	1.531 (1.336-1.754)	<0.001
Solitary bone metastasis				
Yes	Reference		Reference	
No	1.368 (1.189-1.594)	<0.001	1.370 (1.198-1.568)	<0.001
Radiation status				
No	Reference		Reference	
Yes	0.819 (0.694-0.966)	0.018	0.783 (0.667-0.920)	0.003

Abbreviation: HR, hazard ratio; CI, confidence interval; BCSS, breast cancer-specific survival; OS, overall survival; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

[a] The *P* value was adjusted by the multivariate Cox proportional hazard regression model.

Figure 1

Kaplan-Meier curves of breast cancer specific survival (A) and overall survival (B) in the surgery and non-surgery groups after propensity score matching

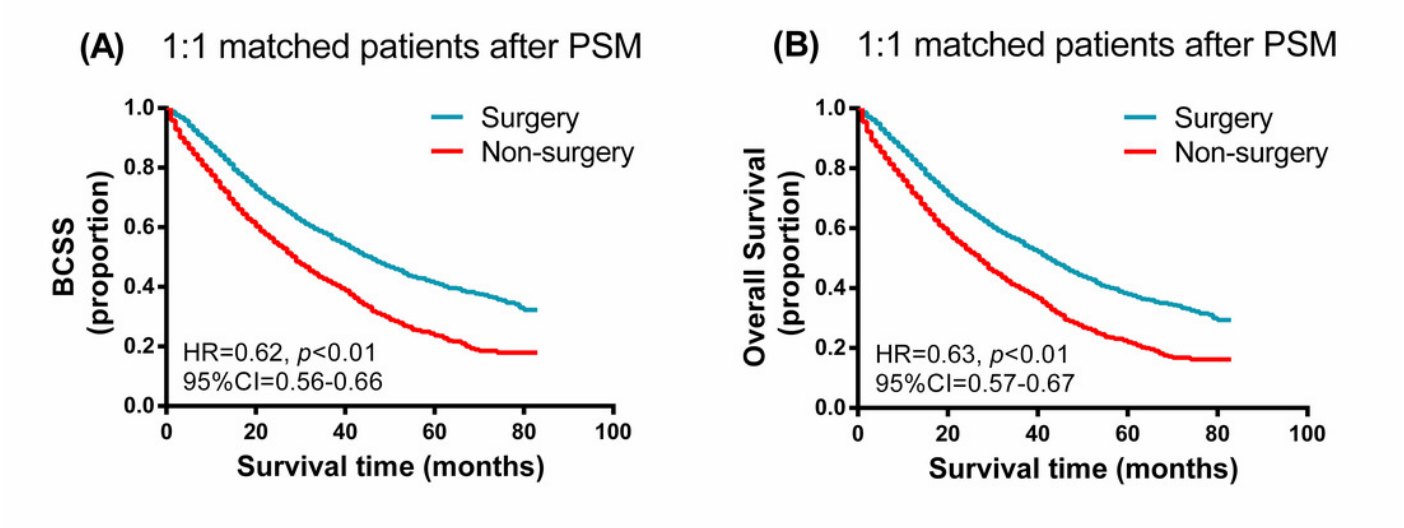

Figure 2

Kaplan-Meier curves of overall survival in the surgery and non-surgery groups stratified by different tumor size and nodal status. (A) T1+T2, (B) T3+T4, (C) N0+N1, (D) N2+N3

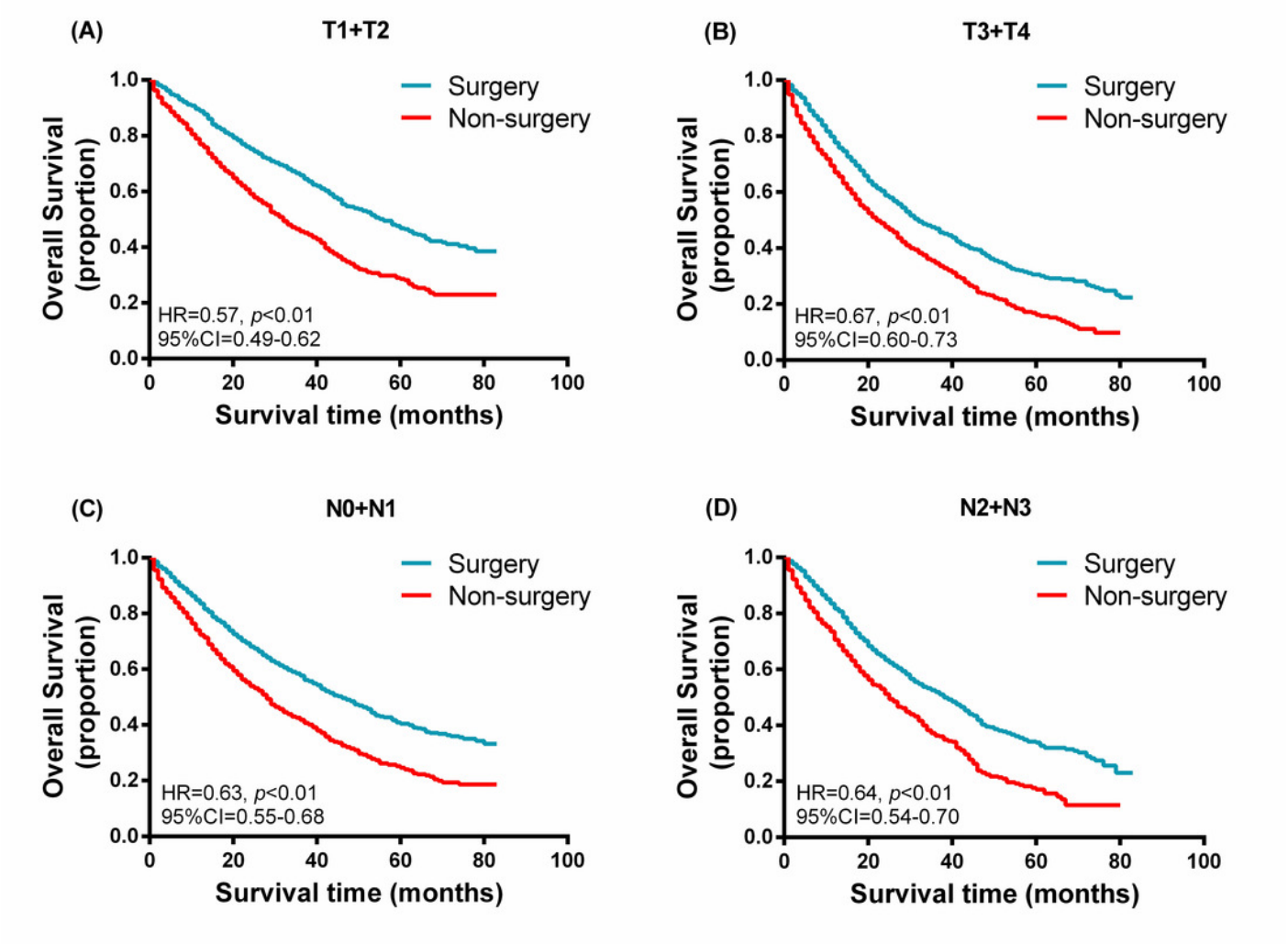

Figure 3

Kaplan-Meier curves of overall survival in the surgery and non-surgery groups stratified by molecular subtypes and status of distant metastasis. (A) HR+HER2-, (B) TNBC, (C) solitary bone metastasis, (D) visceral metastasis

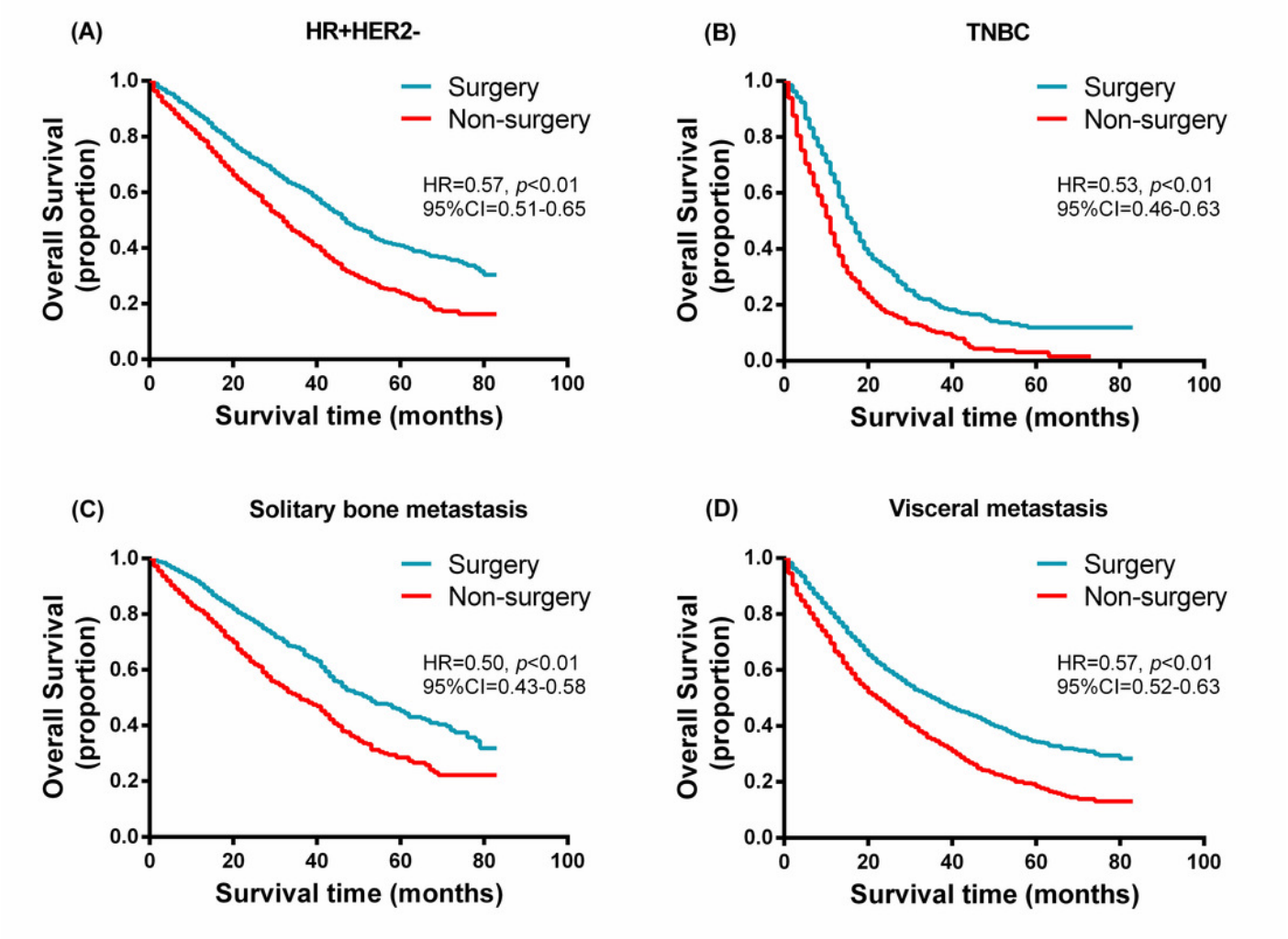

Figure 4

Forest plot of overall survival in the surgery and non-surgery groups stratified by age, race, histology grade and chemotherapy status