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Metastatic pattern discriminates survival benefit of primary surgery for de novo stage IV breast cancer: A real-world observational study

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ABSTRACT

Introduction: Role of surgery in the management of de novo stage IV breast cancer (BC) remains controversial. We aimed to determine the survival benefit of primary surgery on the basis of metastatic pattern.

Materials and methods: A retrospective cohort study based on the SEER database was conducted to identify patients with de novo stage IV BC diagnosed between 2010 and 2015. Patients were divided into surgery and non-surgery group, and propensity score weighting was used to balance clinicopathologic factors between groups.

Results: Of 8142 de novo stage IV BC patients, 1891 (23%) cases were managed with surgery and 6251 (77%) cases were managed without surgery. There were 3821 all-cause deaths and 3291 BC specific deaths over a median follow-up of 22 months. The weighted 3-year overall survival (OS) for the surgery group was 54.5%, compared to 47.7% ($P < 0.001$) for the non-surgery group. The magnitude of the survival difference with surgery was significantly correlated with metastatic patterns ($P_{\text{interaction}} < 0.05$). Significant survival improvements in surgery group compared with non-surgery group were observed in patients with bone-only metastasis (adjusted HR = 0.83, $P < 0.05$) or multiple metastases with bone involved (adjusted HR = 0.76, $P < 0.05$), whereas survival inferiority of surgery was found for patients with multiple visceral organs-only metastases (adjusted HR = 2.08, $P < 0.05$).

Conclusion: The survival benefit offered by surgery for de novo stage IV BC varies by metastatic patterns. Decisions for primary surgery of de novo stage IV BC patients should be tailored according to metastatic pattern.

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Introduction

Approximately 3–8% of breast cancer (BC) patients were first

Abbreviations: BC, breast cancer; OS, overall survival; BCSS, breast cancer specific survival; HR, hazard ratio; CI, confidence interval; SEER, Surveillance Epidemiology and End Results; NCI, National Cancer Institute; ESMO, European Society for Medical Oncology; AJCC, American Joint Committee on Cancer.

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diagnosed with distant metastases each year [1], and metastasis BC was traditionally deemed to be an incurable disease with a median overall survival (OS) of 2–3 years [2,3]. Nevertheless, recent series revealed metastatic BC patients improved survival over the past decade [2,4,5], and the definition of oligometastatic disease had been enlarged to encompass low volume metastatic disease and potentially amenable for local treatment to achieve a complete remission [6]. To date, the survival benefit of the removal of the primary tumor in patients with de novo stage IV BC had been found in retrospective cohort studies, but not validated in prospective trials [7–13].

Indeed, the difference of metastatic disease pattern among those debatable studies was considered as a possible reason for

inconsistent outcome. MF07-01 trial updated their results at 40 months median follow-up, a statistically significant improvement in OS was reported in favor of the surgery arm, which was also observed in subset of patients with bone only disease in their early follow-up of this trial (median follow-up: 21 months) [14]. Among two trials demonstrating no association between primary surgery for patients with de novo stage IV BC and improved survival, 28% and 37% of the participants with bone only disease were respectively identified in Indian Tata Memorial trial and ABCSG-28 POSITIVE trial [12,13], which was significantly lower than that in MF07-01 trial (47%) [14]. Of note, both trials suggested that primary surgery resulted in a significant detriment in distant progression free survival compared with that in the no locoregional treatment group [12,13], whose metastatic pattern including more than 60% visceral metastasis was comparable. Additionally, recent studies suggested patients with bone first metastasis have longer overall survival (OS) than patients with other first metastasis [15,16]. Expectedly, patients with visceral organs metastasis tended to have triple negative BC and poor survival [16,17], moreover, patients with multiple pulmonary and liver metastasis did marginally worse with an overall 3-year survival of 31% in the surgery group versus 67% for the systemic therapy group [11]. Despite evidence that the pattern of metastatic disease was prognostic relevant [14], existing retrospective cohort studies based on SEER database were often limited by ignoring this vital covariable [7,8,18].

The aim of this real-world observational study was to determine the survival benefit of primary surgery among de novo stage IV BC subpopulations stratified by metastatic patterns. We hypothesized that the local surgery may confer a survival benefit to patients with low metastatic tumor burden.

Material and methods

Study design and patients source

The Surveillance, Epidemiology, and End Results (SEER) database (<http://seer.cancer.gov/>) sponsored by the National Cancer Institute (NCI) covered 18 population-based registries, involving a large proportion (28%) of US people. We used the November 2017 SEER-18 submission for this retrospective longitudinal cohort study, which included patients from geographic regions covered as follows: Metropolitan Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Los Angeles, San Jose-Monterey, Utah, Rural and Greater Georgia, Alaska, Greater California, Kentucky, Louisiana, and New Jersey. We identified 17,595 patients over the age of 18 years who were first primarily diagnosed as IV stage BC between January 1, 2010, and December 31, 2015. We excluded patients only diagnosed by autopsy or death certifications, moreover, those cases without histological confirm were also excluded. Patient receiving surgery for metastatic sites or unknown sites as well as cases with unknown metastatic sites were excluded. Since SEER does not record the anatomic site of radiation therapy, patients were also excluded if they received radiation as part of initial therapy, as this could have been delivered to a distant site. Given that metastatic patients often had limited life expectancy, we excluded the patients dead within 6 months after diagnosis. At last, eligible 8142 de novo stage IV BC patients were included in this study, who were grouped according to whether they underwent primary tumor surgery (N = 1891) or not (N = 6251). Considering this study was reviewed and approved by the institutional review board at the First Affiliated hospital of Chongqing Medical university and determined to not be human participant research, patient consent was not involved.

Identification of key variables

The SEER*Stat software (version 8.3.5) was used to extract relevant information, including patient identification, age of diagnosis, race/ethnicity, marital status, primary site, distant metastatic site, laterality, tumor size, regional node status, histology type, nuclear grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), surgery, chemotherapy, radiation therapy, cause-specific death classification, other cause of death classification and survival month. International Classification of Diseases for Oncology (ICD-O-3) [19] was used to identify the cancer site and histology type, and BC was selected by using the ICD-O-3 codes C500 to C506, 508 or 509. To investigate the benefit of primary surgery on the basis of metastasis patterns, the variable was categorized into single organ and multiple organs metastases. The single organ metastasis pattern was further classified into distant lymph nodes-only, bone-only, liver-only, lung-only and brain-only metastasis, and multiple organs metastasis pattern covered bone ± non-visceral organs ± visceral organs, non-visceral + visceral organs and visceral organs.

Outcome of interest

The primary endpoint of this study was overall survival (OS) and BC specific survival (BCSS), which was defined as an interval from time of diagnosis to overall death (BC specific death) or date of last contact and considered as censored statuses if patients were alive until date of last contact. SEER defines mortality data based on the International Classification of Diseases Revisions 8 to 10, which categorized the cause of death as BC specific death and other cause death.

Statistical analysis

We adopt the similar statistical analytic approaches with previous studies [20,21] that examined the benefit of interventions for BC subsets. Baseline patient, tumor and treatment characteristics were compared between non-surgery and surgery group using Pearson Chi-square and T test for categorical (ordinal) and continuous variables, respectively, which were reported as counts (percentage) and mean ± standard deviation. Multiple imputation of missing data was performed by a multivariate logistic regression model, and 10 cycles were repeated to produce a final data set (Table S1). Imputation model included these variables as follows: race (white, black, or others), marital status (single, separated and married), tumor size, regional lymph node status (no, yes and examined), nuclear grade (I,II,III), ER status, PR status and HER2 status.

The inverse probability propensity score weighting [22] was used to balance clinicopathological characteristics between surgery and non-surgery groups, and we calculated the propensity scores based on patient age, race, tumor size, regional lymph node status, nuclear grade, ER status, PR status, HER-2 status, marital status through a logistic regression model for receipt of surgery. Then, propensity score-weighted log-rank tests and Cox proportional hazards models were conducted to compare OS and BCSS between surgery and non-surgery groups, and hazard ratios (HRs) with 95% confidence interval (CI) of OS (BCSS) were calculated from multivariable models that adjusted for year of diagnosis, age, race, marital status, tumor size, regional lymph node status, histological type, nuclear grade, ER status, PR status, HER2 status and chemotherapy. Similar procedures were also performed among subgroups defined by metastatic pattern, and interaction tests were conducted using a likelihood ratio test to explore whether any survival benefit conferred by surgery varied across subgroups.

In addition, to assess the stability of our results, we conducted a series of sensitivity analyses. First, the entire analyses were

repeated after imputation unknown data using random survival forest methodology. Then, proportional subdistribution hazards model was used to calculate HR of BCSS between surgery and non-surgery group after adjusting competing events [23] such as death from other causes. Last, since the aims of primary surgery included palliative and therapeutic excision, we excluded the patients with AJCC 7th T4 carcinoma who often sought surgery to improve the quality of life.

All P values were calculated from 2-sided tests with threshold of 0.05 to evaluate statistical significance of survival benefit by surgery, and all statistical analyses were performed using R software (version 3.3.5).

Results

Patient characteristics

We identified 8142 eligible patients with de novo stage IV BC on the basis of our inclusion and exclusion criteria (Figure S1). Of this cohort, 1891 (23.2%) received the primary surgery, and 6251 (76.8%) patients were stratified into non-surgery group. Clinicopathologic factors and SEER cancer registries according to receipt of primary surgery were listed in Table 1 and Table S2, and the final data after multiple imputations was exhibited in Table 2. Balance in patient characteristics was achieved after propensity score adjustments for estimating average treatment effect, as shown in Table 2. All the

Table 1
Patient characteristics by receipt of primary surgery.

Characteristic	No. of Patients (%)		P*
	No-surgery group (N = 6251)	Surgery group (N = 1891)	
Year of diagnosis			
2010	914 (14.6)	359 (19.0)	<0.001
2011	1048 (16.8)	379 (20.0)	
2012	1076 (17.2)	389 (20.6)	
2013	1273 (20.4)	328 (17.3)	
2014	1309 (20.9)	280 (14.8)	
2015	631 (10.1)	156 (8.2)	
Age, years			
18–39	434 (6.9)	177 (9.4)	<0.001
40–44	333 (5.3)	125 (6.6)	
45–49	549 (8.8)	192 (10.2)	
50–54	747 (12.0)	261 (13.8)	
55–59	880 (14.1)	259 (13.7)	
60–64	904 (14.5)	241 (12.7)	
65–69	745 (11.9)	213 (11.3)	
70–74	594 (9.5)	144 (7.6)	
75–79	435 (7.0)	140 (7.4)	
80+	630 (10.1)	139 (7.4)	
Race/ethnic			
White	4724 (75.6)	1404 (74.2)	0.43
Black	1017 (16.3)	331 (17.5)	
Other ^a	484 (7.7)	148 (7.8)	
NA	26 (0.4)	8 (0.4)	
Marital status			
Single	1458 (23.3)	398 (21.0)	<0.001
Separated	1749 (28.0)	467 (24.7)	
Married	2697 (43.1)	909 (48.1)	
NA	347 (5.6)	117 (6.2)	
Tumor size (cm)			
<2 cm	794 (12.7)	252 (13.3)	<0.001
2–5 cm	2237 (35.8)	825 (43.6)	
>5 cm	1631 (26.1)	648 (34.3)	
NA	1589 (25.4)	166 (8.8)	
Regional node positive			
No	91 (1.5)	256 (13.5)	<0.001
Yes	1602 (25.6)	1281 (67.7)	
Not examined	4437 (71.0)	339 (17.9)	
NA	121 (1.9)	15 (0.8)	
Histological type			
Ductal	4169 (66.7)	1424 (75.3)	<0.001
Lobular	701 (11.2)	173 (9.1)	
Other	1381 (22.1)	294 (15.5)	
Grade			
I	436 (7.0)	108 (5.7)	<0.001
II	2188 (35.0)	616 (32.6)	
III	2038 (32.6)	1042 (55.1)	
NA	1589 (25.4)	125 (6.6)	
ER			
Negative	1080 (17.3)	546 (28.9)	<0.001
Positive	4847 (77.5)	1295 (68.5)	

Table 1 (continued)

Characteristic	No. of Patients (%)		P*
	No-surgery group (N = 6251)	Surgery group (N = 1891)	
NA	324 (5.2)	50 (2.6)	
PR			
Negative	1975 (31.6)	802 (42.4)	<0.001
Positive	3869 (61.9)	1029 (54.4)	
NA	407 (6.5)	60 (3.2)	
HER2			
Negative	4114 (65.8)	1263 (66.8)	0.004
Positive	1448 (23.2)	528 (27.9)	
NA	689 (11.0)	100 (5.3)	
Chemotherapy			
No	2882 (46.1)	614 (32.5)	<0.001
Yes	3369 (53.9)	1277 (67.5)	
Distant metastatic site			
Distant lymph nodes			
No	4833 (77.3)	1466 (77.5)	0.873
Yes	1418 (22.7)	425 (22.5)	
Bone			
No	1546 (24.7)	799 (42.3)	<0.001
Yes	4705 (75.3)	1092 (57.7)	
Lung			
No	4234 (67.7)	1343 (71.0)	0.008
Yes	2017 (32.3)	548 (29.0)	
Liver			
No	4581 (73.3)	1445 (76.4)	0.007
Yes	1670 (26.7)	446 (23.6)	
Brain			
No	5862 (93.8)	1864 (98.6)	<0.001
Yes	389 (6.2)	27 (1.4)	

Abbreviations: NA, not available; ER, estrogen-receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

^a American Indian/AK Native, Asian/Pacific Islander.

clinicopathologic factors except for race were statistically related to the receipt of primary surgery. Patients diagnosed during earlier years, younger patients, married patients, patients with larger tumor size, patients with regional lymph node metastasis, patients with ductal carcinoma, patients with high nuclear grade, ER/PR positive patients and HER2 negative patients were likely to receive the primary tumor removing.

Sites of distant metastases

A total of 12,737 sites of distant metastases were identified in the 8142 patients with de novo stage IV BC. The bone was the most common site of distant metastasis (5,797, 45.5%), followed by lung (2,565, 20.1%), liver (2,116, 16.6%), distant lymph nodes (1843, 14.5%) and brain (416, 3.3%) (Fig. 1). There are 4952 (60.8%) patients with single organ metastasis, and 3190 (39.2%) patients with multiple organs metastasis (Fig. 1). Metastatic patterns that weighted by propensity score according to receipt of surgery was shown in Table S3.

Survival benefit of primary surgery

After a median follow-up time of 22 months from diagnosis (interquartile range, 12–34 months), 3391 BC specific deaths (41.6%), 430 deaths from other cancer causes (5.3%). The 3-year OS rate weighted by inverse propensity score was 54.5% in the surgery group and 47.7% in the non-surgery group (log-rank test, $P < 0.001$; HR, 0.82; 95% CI, 0.78 to 0.86). The 3-year BCSS rate weighted by inverse propensity score was 58.5% in the surgery group and 51.8% in the non-surgery group (log-rank test, $P < 0.001$; HR, 0.79; 95% CI, 0.76 to 0.83). Statistically significant difference from the proportional hazard assumption in the Cox regression hazard model

adjusting for age, race, marital status, tumor size, regional lymph node status, nuclear grade, histological type, chemotherapy and metastasis sites ($P < 0.001$; adjusted HR for OS, 0.83; 95% CI, 0.79 to 0.87; $P < 0.001$; adjusted HR for BCSS, 0.79; 95% CI, 0.75 to 0.84). After adjusting for other clinical factors and considering propensity score, single organ metastasis pattern (i.e. distant lymph node-only, bone-only, liver-only, lung-only and brain-only metastasis) ($P = 0.002$) and multiple organs metastases pattern (i.e. bone \pm non-visceral organs \pm visceral organs, non-visceral + visceral organs, visceral organs) ($P = 0.005$) were respectively identified as statistically significant effect modifiers of surgery for BC specific deaths among patients with single organ metastasis and multiple organs metastases.

Survival benefit of surgery according to metastasis pattern

Single organ metastasis

Among 4952 patients with single organ metastasis, there are 3113 patients with bone metastasis, 704 patients with lung metastasis, 581 patients with liver metastasis, 477 patients with distant lymph node metastasis, and remaining 50 patients with brain metastasis. Patients with single organ metastasis had survival benefit of primary surgery compared with non-surgery group (OS: absolute difference, 5.4%, HR, 0.87, 95% CI, 0.82 to 0.93, $P < 0.001$; BCSS: absolute difference, 5.9%, HR, 0.83, 95% CI, 0.77 to 0.89, $P < 0.001$, Fig. 2). The magnitude of improved survival among patients receiving primary surgery was significantly correlated with the metastatic site ($P_{\text{interaction for OS}} = 0.02$; $P_{\text{interaction for BCSS}} < 0.001$). When examining the benefit of primary surgery stratified by metastatic site, we found that the survival for the primary surgery group was significantly better than that observed in the non-

Table 2
Patient characteristics by weighted by propensity score.

Characteristic	No. of Patients (%)	
	No-surgery group (N = 6251)	Surgery group (N = 1891)
Year of diagnosis		
2010	959 (15.3)	288 (15.3)
2011	1079 (17.3)	327 (17.3)
2012	1121 (17.9)	401 (21.2)
2013	1235 (19.8)	363 (19.2)
2014	1249 (20.0)	325 (17.2)
2015	608 (9.7)	187 (9.9)
Age, years		
18–39	449 (7.2)	167 (8.8)
40–44	362 (5.8)	109 (5.8)
45–49	545 (8.7)	169 (8.9)
50–54	759 (12.1)	241 (12.7)
55–59	876 (14.0)	285 (15.1)
60–64	894 (14.3)	231 (12.2)
65–69	770 (12.3)	224 (11.9)
70–74	564 (9.0)	144 (7.6)
75–79	426 (6.8)	162 (8.6)
80+	607 (9.7)	160 (8.5)
Race/ethnic		
White	4709 (75.3)	1399 (74.0)
Black	1051 (16.8)	330 (17.5)
Other ^a	491 (7.9)	162 (8.6)
Marital status		
Single	1522 (24.3)	465 (24.6)
Separated	1820 (29.1)	521 (27.6)
Married	2910 (46.6)	905 (47.9)
Tumor size (cm)		
<2 cm	1054 (16.9)	341 (18.0)
2–5 cm	2859 (45.7)	842 (44.5)
>5 cm	2338 (37.4)	709 (37.5)
Regional node positive		
No	431 (6.9)	74 (3.9)
Yes	2097 (33.5)	783 (41.4)
Not examined	3723 (59.6)	1034 (54.7)
Histological type		
Ductal	4323 (69.2)	1379 (72.9)
Lobular	643 (10.3)	190 (10.0)
Other	1285 (20.6)	323 (17.1)
Grade		
I	555 (8.9)	208 (11.0)
II	2810 (45.0)	747 (39.5)
III	2886 (46.2)	936 (49.5)
ER		
Negative	1348 (21.6)	480 (25.4)
Positive	4903 (78.4)	1411 (74.6)
PR		
Negative	2278 (36.5)	726 (38.4)
Positive	3973 (63.6)	1165 (61.6)
HER 2		
Negative	4605 (73.7)	1391 (73.5)
Positive	1646 (26.3)	500 (26.5)
Chemotherapy		
No	2696 (43.1)	741 (39.2)
Yes	3555 (56.9)	1150 (60.8)
Distant metastatic site		
Distant lymph nodes		
No	4832 (77.3)	1436 (75.9)
Yes	1419 (22.7)	455 (24.1)
Bone		
No	1831 (29.3)	605 (32.0)
Yes	4420 (70.7)	1286 (68.0)
Lung		
No	4241 (67.9)	1242 (65.7)
Yes	2010 (32.2)	649 (34.3)
Liver		
No	4646 (74.3)	1406 (74.4)
Yes	1605 (25.7)	485 (25.6)
Brain		
No	5934 (94.9)	1823 (96.4)
Yes	317 (5.1)	68 (3.6)

Abbreviations: ER, estrogen-receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

^a American Indian/AK Native, Asian/Pacific Islander.

surgery group for patients with bone metastasis (OS: absolute difference, 10.5%, HR, 0.83; 95% CI, 0.76 to 0.9, $P < 0.001$; BCSS: absolute difference, 9.9%, HR, 0.8; 95% CI, 0.73 to 0.87; $P < 0.001$, Fig. 1). Patients with moderate tumor burden (i.e. distant lymph node, lung or brain metastasis) demonstrated no significant difference in OS or BCSS (distant lymph node: OS, absolute difference, 0.6%, HR, 0.96, 95% CI, 0.77 to 1.19, $P = 0.71$; BCSS, absolute difference, -6.0% , HR, 1.16; 95% CI, 0.92 to 1.47, $P = 0.20$; lung: OS, absolute difference, 6.1%, HR, 0.9; 95% CI, 0.77 to 1.05; $P = 0.19$; brain, BCSS, absolute difference, -4.4% , HR, 0.52, 95% CI, 0.25 to 1.08, $P = 0.08$, Fig. 2), whereas patients with liver metastasis who received tumor removing were marginally associated with worse prognosis than those without primary surgery (OS: absolute difference, -2.5% , HR, 1.16; 95% CI, 0.96 to 1.4; $P = 0.14$; BCSS: absolute difference, -2.3% , HR, 1.13; 95% CI, 0.92 to 1.39; $P = 0.23$, Fig. 2).

Multiple organ metastasis

We also observed the OS and BCSS benefit of primary surgery for de novo stage IV BC patients with multiple organs metastases (OS: absolute difference, 18.3%, HR, 0.8, 95% CI, 0.74 to 0.86, $P < 0.001$; BCSS: absolute difference, 7.7%, HR, 0.78, 95% CI, 0.72 to 0.84, $P < 0.001$, Fig. 3), which significantly varied across metastatic patterns (i.e. bone \pm non-visceral \pm visceral organs, non-visceral \pm visceral organs, visceral organs) ($P_{\text{interaction for OS}} < 0.001$, $P_{\text{interaction for BCSS}} < 0.001$). Surgery benefit was observed in the subjects with bone and additional non-visceral/visceral metastases compared with non-surgery group (OS: HR, 0.76; 95% CI, 0.70 to 0.83, $P < 0.001$, BCSS: HR, 0.74; 95% CI, 0.68 to 0.81, $P < 0.001$). However, patients with distant metastases simultaneously in liver and lung, who saw near one-fold increment in overall deaths (OS: absolute difference, -8.1% ; HR, 2.08; 95% CI, 1.39 to 3.11, $P < 0.001$, Fig. 3).

In sensitivity analyses performed after the exclusion of patients with T4 stage, after restriction of patients within SEER 9, after repeating analyses using the proportional subdistribution hazards model, and after exclusion of patients diagnosed after 2015, we observed similar findings.

Discussion

In this large population-based cohort study, we observed lower overall and BC specific mortality in de novo stage IV BC patients managed with surgery than individuals without surgery, and this finding based on the real-world study controlling metastatic patterns is consistent with prior studies [7–10,18,24,25]. Moreover, we suggest a possible heterogeneous treatment effect of primary surgery that may be most important when metastatic pattern varied. Our findings indicated that definitive local surgery of only-bone metastasis de novo stage IV BC patients offers a significant survival advantage over non-operative management, but no significant survival improvement for surgery was observed in other single organ metastasis BC patients. For subjects with multiple distant organs involved, surgery can also improve survival in subjects with high tumor burden accompanied by bone metastasis, whereas surgery plays a risk role for patients only with simultaneous lung and liver metastases. These results suggest that individualized decisions for primary surgery of de novo stage IV breast cancer patients could be tailored on the basis of metastatic pattern.

Knowledge of metastatic pattern of BC, especially the prognostic value of distant metastasis site was widely studied [4,5,16,17,26,27]. It was well known that the most common metastasis sites were bones, lung, liver, brain and the distant lymph nodes [28], and bone-only metastasis was the most common subset and had the

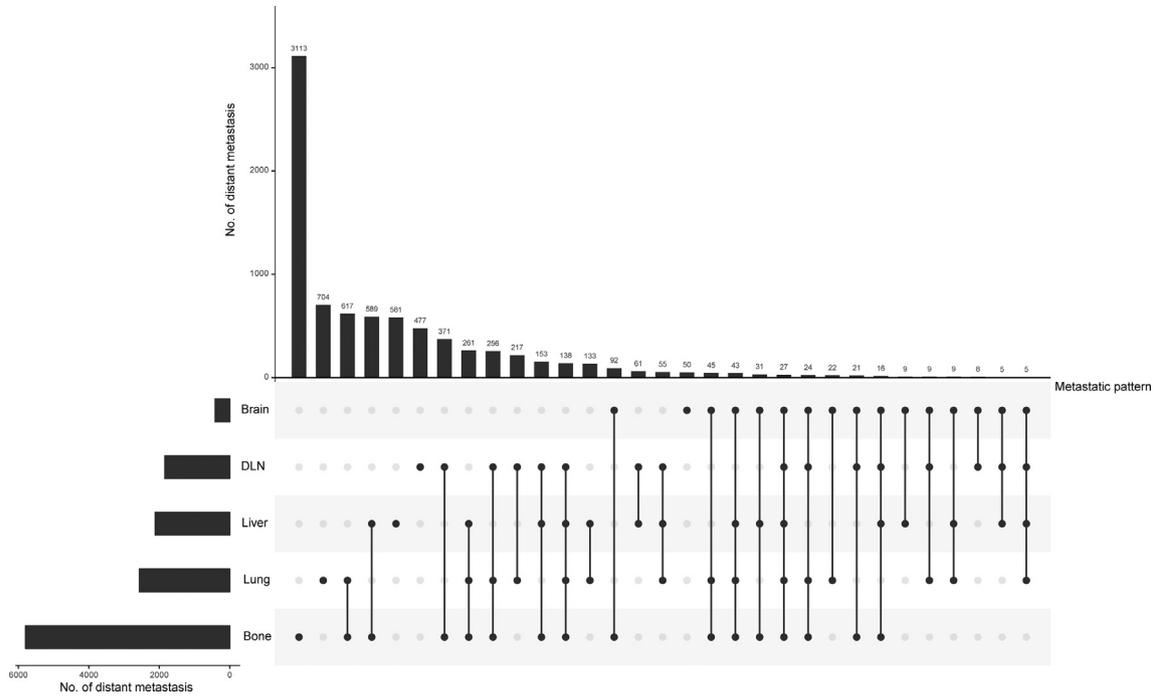


Fig. 1. The distribution of metastatic patterns in de novo stage IV breast cancer patients.

Site of distant metastasis	No. of Patients		Weighed 3-year OS (%)		Weighed Multivariable *† HR of OS	p	Weighed 3-year BCSS (%)		Weighed Multivariable *† HR of BCSS	P
	Non-surgery group	Surgery group	Non-surgery group	Surgery group			Non-surgery group	Surgery group		
Distant Lymph nodes	285	192	54.8	55.4	0.96	0.71	64.4	58.4	1.16	0.2
Bone	2,409	704	53.6	64.1	0.83	<0.001	57.4	67.3	0.8	<0.001
Brain	34	16	14.7	9.2	0.42	0.013	19.2	14.8	0.52	0.08
Lung	434	270	46.4	52.5	0.90	0.19	50.4	59.6	0.75	0.001
Liver	378	203	53.3	50.7	1.16	0.14	57.6	55.3	1.13	0.23
Total	3,540	1,385	52.3	58	0.87	<0.001	56.6	62.5	0.83	<0.001

$P_{interaction} = 0.02$ $P_{interaction} < 0.001$

Fig. 2. Hazard ratio comparing OS/BCSS between surgery group and non-surgery group according to metastatic site for patients with single organ metastasis. (*) Weighted by inverse propensity score. (†) Multivariate analysis adjusted by age of patients, year of diagnosis, race, marital status, nuclear grade, histologic type, tumor size, ER, PR, HER2 status, chemotherapy. Abbreviations: OS, overall survival; BCSS, breast cancer specific survival; HR, hazard ratio; ER, estrogen-receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

best OS [17,26,29–31]. These findings were mirrored in our analysis, 37.7% and 71.2% of the whole cohort reported bone and bone-only metastasis at initial diagnosis, the latter had best survival. Recent studies [4,16] consistently observed that a constant time trend of improvement in prognosis of metastatic BC patients, but this effect is confined to HER2-positive cases. Importantly, subtypes of BC showed preferential site of relapse [32–34], for example, both HER2-positive and triple negative tumors are at risk of developing

visceral and brain metastases despite active systemic treatment [26], and luminal A tumors often tend to metastasis to bone [27]. It was highlighted that metastatic pattern and its subtypes of BC would help to personalize therapeutic options and follow-up examinations of cancer patients [26,27,33].

Recently released 4th ESO (European School of Oncology)-ESMO (European Society of Medical Oncology) international consensus guidelines [6] for advanced breast cancer (ABC4), suggested that a

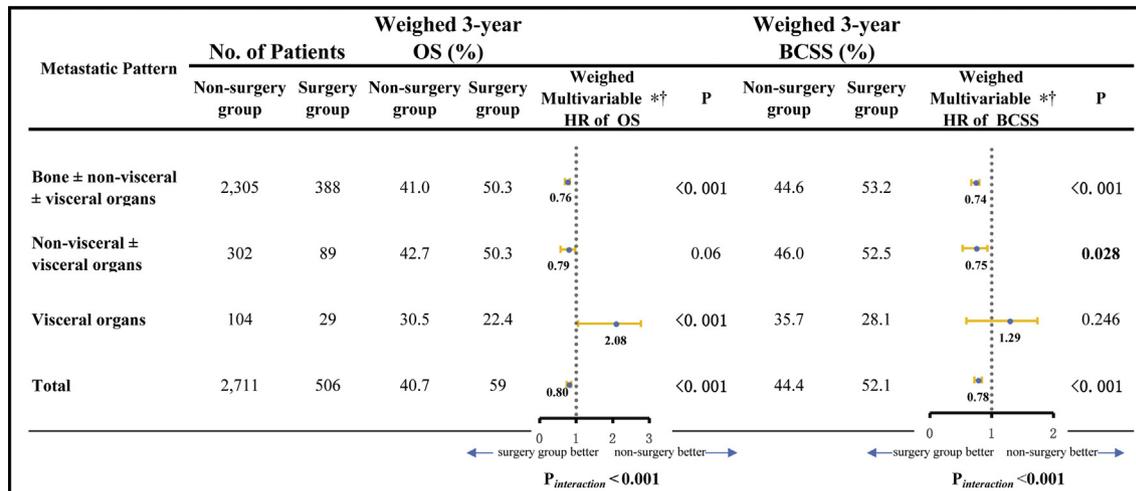


Fig. 3. Hazard ratio comparing OS/BCSS between surgery group and non-surgery group according to metastatic pattern for patients with multiple organs metastasis. (*) Weighted by inverse propensity score. (†) Multivariate analysis adjusted by age of patients, year of diagnosis, race, marital status, nuclear grade, histologic type, tumor size, ER, PR, HER2 status, chemotherapy. Abbreviations: OS, overall survival; BCSS, breast cancer specific survival; HR, hazard ratio; ER, estrogen-receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

multimodal approach, including local-regional treatments with curative intent, should be considered for these selected metastasis BC patients. Additionally, oligometastatic disease is defined as low volume metastatic disease with limited number and size of metastatic lesions [6], which also represents an intermediate stage of metastatic disease associated with an indolent disease course and prolonged survival [35]. In this regard, it was reported that pre-treatment count of circulating tumor cells (CTCs) can provide valuable prognostic information in metastatic BC [36–40]. Obviously, identifying those cases with a lower propensity to metastatic spreading based on CTC risk stratification might further help in selecting subjects eligible for local surgery. Accordingly, ongoing randomized controlled trial ECOG 2018 (ClinicalTrials.gov Identifier: NCT01242800) will hopefully address this issue that whether a subset of patients with stage IV BC will benefit from local surgery, remarkably, absolute value of CTCs burden was evaluated throughout participants. Given the evidence that the 21-gene risk score was independently prognostic for survival in ER-positive/HER2-negative de novo stage IV breast cancer [41], but the trail TBCRC 013 [24] suggested 21-gene risk score was not a stratification factor in local management of metastatic BC patients.

Available randomized controlled trails that releasing results comprised different metastatic patterns, and 28%, 37%, 38% and 46% participants were respectively identified bone-only metastasis in TATA [13], TBCRC 013 [24], POSYTIME [12] and MF07-01 [42] trail, only the last one observed surgery benefit for de novo stage IV BC. Still, only patients in MF07-01 trail received operation before systemic therapies, and delaying adjuvant therapy was likely to be weakened but enlarge the effect of local therapy. Suitable candidates and best timing of surgery are currently ongoing studied. A randomized phase III trial ECOG 2018 (NCT01242800) is studying early surgery and radiotherapy to see how well it works compared to standard palliative therapy in treating patients with stage IV breast cancer. The SUBMIT study (NCT01392586) is a randomized controlled trial that will provide evidence on whether or not surgery of the primary tumor in breast cancer patients with metastatic disease at initial presentation results in an improved survival, while it was terminated due to low accrual rate [43]. Another ongoing Japanese study is being conducted to confirm the superiority, in terms of overall survival, of primary tumor resection plus systemic therapy to systemic therapy alone in untreated breast cancer

patients with metastatic lesions who are not refractory to conventional primary systemic therapy [44].

It was estimated that bone-only metastasis occurred in 17–37% of women with BC [31,34,45], and bone was the first site of distant disease in 25–40% of patient with metastatic breast cancer [46]. Interestingly, an unpublished study announced survival comparison results between patients with bone-only first metastasis and other-only first metastasis, suggesting the former experienced the better OS [15]. Indeed, during the course of the disease, a prospective study revealed that less one third of bone-only metastasis patients further developed visceral organs metastases after 30 months follow-up [17]. ESMO international consensus guidelines [6] as well as a large amount of studies [11,25,47] suggested that the subset of patients with bone-only disease would benefit from removal of the primary tumor. This large-scale retrospective study further verified prior results, moreover, we found de novo stage IV breast cancer patients with high distant tumor burden accompanied by bone metastasis could also improve survival from local surgery, which was paradoxical with previous studies [12,13]. Of note, according to preclinical evidence supporting the hypothesis of better survival among bone-first metastasis breast cancer, those individuals with high metastatic burden who yielded survival advantage from surgery may be due to inclusion of lots of bone-first metastasis patients. Provocatively speaking, whether surgical subjects can be extended to patients with bone-first metastasis needs additional prospective clinical trials evaluating the value of those candidates. On the other hand, surgery is also deemed to reduce BC stem cells, as at least 10% of breast cancer cells existed in the primary tumor, which may be associated with distant metastases [48].

Interestingly, we found that patients with simultaneous liver and lung metastases suffered from local surgery, suggesting the importance to select subsets in surgical procedure. A Netherlandish study performed disease specific survival analysis of surgery versus no surgery stratified by type of metastasis, patients after surgery with only visceral type referring to metastasis to brain, lung, pleura, liver yielded survival advantage in univariate analysis, but not in multivariate analysis [49]. Moreover, prior clinical trail MF07-01 also suggested that patients with visceral involvement may suffer from surgery [14,42]. It was reported that primary tumor can represent a source of antiangiogenic factors and growth factor

inhibitors, suggesting that its removal may lead to an accelerated relapse [50,51]. Surgical procedure and anesthesia could induce the additional release of growth factors associated with surgical wounding and immunosuppression [52,53]. Indeed, both TATA and POSYITIVE trial identified a trend toward worse oncological outcome like distant progression-free survival after surgery [12,13], although POSYITIVE study was not recruiting anymore and the trial was stopped early due to poor recruitment. Therefore, future prospective studies should be designed to determine if local surgery would be contraindicated in certain subsets.

It was well known that primary systematic treatment remains the standard approach for metastatic breast cancer patients. To date, advanced systematic therapies also provide us comprehensive insights into treatment choices for de novo stage IV BC patients, and a series of factors like ER/PR/HER status, tumor burden, biological age, physical score, comorbidities, menopausal status, need for a rapid disease/symptom control, socio-economic and psychological factors and so on should be taken into account [6]. Besides conventional systematic therapies, a German study indicated that the OS of advanced BC patients with bone metastasis receiving bone-targeted agents varied among the types of metastasis ranging from 54 months, 38 months–28 months for patients with bone-only metastases, non-visceral with or without bone metastases and visceral with or without bone metastases respectively [17]. Their results are very similar with our study, suggesting that both local and systematic treatment could be tailored according to tumor burdens.

This is the first comprehensive study to evaluate the surgery benefit varied by metastatic pattern for de novo stage IV BC, but several limitations should be noted. Besides the extent and site of metastatic disease, additional effect modifiers such as surgical resection margins, timing of surgery, type of systemic treatment administered prior to surgery, and coding errors may influence the effect of surgery [25,54–56]. We were not able to control these potential modifier effects in this retrospective study due to lack of the information of those variables in the SEER database, such as the information of endocrine, anti-HER2, denosumab or zoledronic acid therapies. Despite propensity score matching used in this study, it is worth nothing that selection bias, such as younger age, better performance status, smaller size of primary tumor, and good response to prior systemic therapy may have influenced the decision to perform surgery, which can affect reliability of this retrospective study. Additionally, the SEER program only included five site-specific distant metastases at the initial diagnosis, and we could not obtain further details concerning the other sites of distant metastases.

In conclusion, survival benefit offered by surgery for de novo stage IV BC varies by metastatic patterns. Local surgery for patients with bone-only metastasis or high metastatic burden accompanied by bone metastasis offers a significant survival advantage over non-operative management, whereas the opposite effect is observed among simultaneous liver and lung metastasis patients. Decisions for primary surgery of de novo stage IV BC patients should be tailored according to metastatic pattern, and mechanisms of bone/visceral organs-only/first metastasis BC are needed further understanding.

Author contributions

Conception or design: Kang W, Hong-Yuan L. Acquisition, analysis, or interpretation of data: Kang W, Zhu-Yue L, Yang S, Ye-Lei X, Jie L, Xiang Z, Hong-Yuan L. Drafting of the manuscript: Kang W. Critical revision of the manuscript for important intellectual content: Kang W, Zhu-Yue L, Yang S, Ye-Lei X, Jie L, Xiang Z, Hong-Yuan L. Statistical analysis: Kang W, Yang S. Supervision: Hong-Yuan L. All

authors have given final approval of the manuscript for submission and publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejso.2019.02.013>.

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