

Surgery of the primary tumor improves survival in women with stage IV breast cancer in Southwest China

A retrospective analysis

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Abstract

The International Consensus Guidelines for advanced breast cancer (ABC) considers that the surgery of the primary tumor for stage IV breast cancer patients does not usually improve the survival. However, studies have showed that resection of the primary tumor may benefit these patients. The correlation between surgery and survival remains unclear.

The impact of surgery and other clinical factors on overall survival (OS) of stage IV patients is investigated in West China Hospital. Female patients diagnosed with stage IV breast cancer between 1999 and 2014 were included (N=223). Univariate and multivariate analysis assessed the association between surgery and OS.

One hundred seventy-seven (79.4%) underwent surgery for the primary tumor, and 46 (20.6%) had no surgery. No significant differences were observed in age at diagnosis, T-stage, N-stage, histological grade, molecular subtype, hormone receptor (HR), and number of metastatic sites between 2 groups. Patients in the surgery group had dramatically longer OS (45.6 vs 21.3 months, log-rank $P < .001$). In univariate analysis, survival was associated with surgical treatment, residence, tumor size, lymph node, HR status, hormonal therapy, and radiotherapy. In multivariate analysis, surgery was an independent prognostic factor for OS [hazard ratio (HR), 0.569; 95% confidence interval (CI) 0.329–0.984, $P = .044$]. Additional independent prognostic factors were hormonal therapy (HR, 0.490; 95% CI 0.300–0.800) and radiotherapy (HR, 0.490; 95% CI 0.293–0.819). In addition, a favorable impact of surgery was observed by subgroup analysis.

Our study showed that surgery of the primary breast tumor has a positive impact on OS in with stage IV breast cancer patients.

Abbreviations: ABC = advanced breast cancer, CI = confidence interval, HER-2 = human epidermal growth factor receptor-2, HR = hazard ratio, HR = hormone receptor, OS = overall survival.

Keywords: overall survival, primary tumor, stage IV breast cancer, surgery

1. Introduction

Breast cancer is a significant health issue and is one of the most frequent types of cancers with rapidly increasing incidence rate

Editor: Yong Liu.

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The authors declare that they have no conflict of interest.

Supplemental Digital Content is available for this article.

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Medicine (2017) 96:22(e7048)

Received: 16 November 2016 / Received in final form: 2 May 2017 / Accepted: 6 May 2017

<http://dx.doi.org/10.1097/MD.0000000000007048>

both globally and within China. In 2012, nearly 190,000 cases were newly diagnosed with breast cancer in China and more than 47,000 deaths from the disease.^[1] The phenomenon of increasing breast cancer rates in China has been acknowledged for a number of years, and is a trend that is predicted to continue, with perhaps as many as 2,500,000 cases of breast cancer in China by 2021.^[2,3]

Of all the breast cancer patients, 5% to 10% patients had distant metastases at initial presentation.^[4–6] Metastatic breast cancer is still considered to be an incurable disease. Therefore, more attention should be paid for the treatment of metastatic breast cancer. According to the ABC guidelines, the standard treatment for stage IV breast cancer patients remains to be systemic palliative treatment, including chemotherapy, endocrine therapy, radiotherapy, and/or targeted therapy.^[7,8] Moreover, local therapy provided no survival advantages, and the primary goals of local treatment are the prevention or reduction of symptoms.^[9–11]

However, recent retrospective clinical studies have shown that resection of primary tumor was correlated with a significant increase in the survival rates of patients with primary metastatic breast cancer.^[12–16] In contrary, several studies have indicated that surgery in metastatic breast cancer does not translate into a significant survival benefit.^[17–21] Randomized clinical trials are now under way but have been slow to accrue and report.^[22,23] One study found that patients with stage IV breast cancer showed no significant survival benefit from surgical excision, even though they

were divided into hormone receptor (HR) positive and negative groups.^[24] Another 2 randomized trials presented only in an abstract form and were unable to show an overall survival (OS) benefit with the primary surgery.^[13] The ABC guidelines have been always concerned about the effect of resection of the primary tumor for stage IV breast cancer.^[7,8,25] According to the third international consensus, the breast tumor removal can be considered on an individual basis for selected patients, particularly to improve quality of life. And the approach is currently being investigated further in prospective clinical studies.^[8]

In China, the correlation between survival and surgery of the primary tumor in patients with stage IV disease still remains unclear, according to the Chinese Guideline for Advanced Breast Cancer 2015 (CABC 2015).^[26] The guideline only indicates that, if the patient with stage IV breast cancer decides to have surgery, the resection should be performed with clear margins and the axillary lymph nodes can be staged. Moreover, the precondition is that the patient has had good responses to initial systemic therapy before surgery. In addition, if the surgery can improve the patients' quality of life, it can also be considered.^[26] Thus, we conducted a retrospective analysis to explore the survival benefit of surgery in stage IV breast cancer using our Breast Cancer Information Management System (BCIMS).^[27-30] We also try to evaluate the effect of clinical parameters on surgery-related OS rates.

2. Methods

2.1. Study design and patients

This was a retrospective study conducted in a cohort of female patients in Southwest China. Patients who were initially diagnosed with stage IV primary invasive breast cancer were registered in the BCIMS at West China Hospital, Sichuan University from 1999 to 2014 years. Ethical approval was issued by the Clinical Test and Biomedical Ethics Committee of West China Hospital, Sichuan University, for this study. The BCIMS recorded the patient characteristics, medical history, breast cancer diagnosis, laboratory results, tumor pathology reports, and treatments. These records were used to establish baseline diagnostic data. In our study, diagnosis of stage IV disease was made within 30 days of primary breast tumor resection. Patients with incomplete records were excluded from this study.

2.2. Patient data collection

The demographic information and tumor characteristics were collected, which included age at diagnosis, residence, menopause status, pathologic type, tumor stage, grade, molecular subtype, HR status, human epidermal growth factor receptor-2 (HER-2) expression, classification and number of metastatic sites. The use of therapy including chemotherapy, endocrine therapy, and radiation therapy were also recorded. OS was calculated from the time of diagnosis till the last follow-up (censored) or death due to any cause. Besides modified radical mastectomy and radical mastectomy, patients who underwent breast-conserving therapy or palliative surgery or mastectomy were included in the surgery group.

2.3. Statistical analysis

Baseline characteristics were compared using Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables between women who received therapeutic

surgery versus those who did not. Kaplan–Meier and log-rank analyses were used to evaluate the survival rates between the subgroups. A Cox proportional hazards model was used to determine the independent factors of survival based on the variables selected in univariate and multivariate analyses. All statistical tests were 2-tailed and *P* values less than .05 were considered to be statistically significant. Statistical analyses were done with SPSS 20.0 software (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

Female patients diagnosed with stage IV breast cancer between 1999 and 2014 were included (N=223). The median follow-up time was 24 months (1–178 months). Of these patients, 177 (79.4%) underwent surgery for the primary tumor (surgery group), while 46 (20.6%) had no surgical treatment (nonsurgery group). The clinical and pathological features of the study population are presented in Table 1 and Supplementary Table 1, <http://links.lww.com/MD/B715>. Patients in the surgery group were more likely to be from the urban area (*P*=.035), postmenopausal (*P*=.038) and have invasive ductal carcinoma (*P*<.001), HER-2 negative tumors (*P*<.001), fewer lung metastases (*P*=.024), and history of endocrine or radiation therapy (*P*<.001), than the nonsurgery group (Table 1). Furthermore, to understand the tumor responses to initial systemic therapy before surgery, the responses were compared between neoadjuvant chemotherapy and first chemotherapy, respectively, from the surgery group and nonsurgery group. Results showed that patients of surgery group had a better complete response or partial response in chemotherapy before surgery (*P*=.003). In addition, 35% of patients had surgical treatment directly in the surgery group (Table 1). No differences were found in both the groups on the basis of age at diagnosis, T-stage, N-stage, histological grade, molecular subtype, HR, number of metastatic sites, and chemotherapy (Supplementary Table 1, <http://links.lww.com/MD/B715>).

3.2. Effect of surgery on the overall survival rates

For the entire population, the median OS was 39 months. Patients who underwent surgery showed a longer median survival rates than those who did not (45.6 vs 21.3 months, log-rank *P*<.001) (Fig. 1A). Of the 177 patients in the surgery group, 115 had modified radical mastectomy and 57 had radical mastectomy, and 5 had other surgeries including breast-conserving surgery and mastectomy. No differences were found in the survival rates between the modified radical mastectomy group and the radical mastectomy group (Fig. 1B, log-rank *P*=.939). In addition, when compared the clinical characteristics of patients between the modified radical mastectomy and radical mastectomy groups, significant differences were observed in the number of lymph nodes between the 2 groups (Supplementary Table 2, <http://links.lww.com/MD/B715> *P*=.005).

3.3. Univariate and multivariate analysis of overall survival

Results of univariate analysis without any adjustment for potential confounders revealed an association between surgery and survival rates in stage IV breast cancer (Table 2, *P*<.001). Furthermore, patients living in urban (*P*=.001), with a smaller tumor (*P*=.024), lymph negative (*P*=.047), or HR positivity (*P*=.001), history of

Table 1
Patient characteristics who had significant statistical differences in the surgery group and nonsurgery group.

Characteristics	All		Surgery		Nonsurgery		P
	N	%	N	%	N	%	
Residence	223		177	(79.4%)	46	(20.6%)	.035
Rural	75	(33.6%)	53	(29.9%)	22	(47.8%)	
Urban	147	(65.9%)	123	(69.5%)	24	(52.2%)	
Unknown	1	(0.05%)	1	(0.06%)	0	—	
Menopause							.038
No	125	(56.1%)	93	(52.5%)	32	(69.6%)	
Yes	98	(43.9%)	84	(47.5%)	14	(30.4%)	
Pathology							<.001
IDC	185	(83.0%)	155	(87.6%)	30	(65.2%)	
ILC	16	(7.2%)	15	(8.4%)	1	(2.2%)	
Others	22	(9.8%)	7	(4.0%)	15	(32.6%)	
HER2							<.001
Negative	142	(63.7%)	114	(64.4%)	28	(60.9%)	
Positive	56	(25.1%)	44	(24.9%)	12	(26.1%)	
Unknown	25	(11.2%)	19	(10.7%)	6	(13.0%)	
Metastatic sites							.024
Lung							
Yes	71	(31.8%)	50	(28.2%)	21	(45.7%)	
No	152	(68.2%)	127	(71.8%)	25	(54.3%)	
Hormonal therapy							<.001
No	118	(52.9%)	78	(44.1%)	40	(87.0%)	
Yes	103	(46.2%)	97	(54.8%)	6	(13.0%)	
Unknown	2	(0.9%)	2	(1.1%)	0	—	
Radiotherapy							<.001
No	142	(63.7%)	98	(55.4%)	44	(95.7%)	
Yes	75	(33.6%)	73	(41.2%)	2	(4.3%)	
Unknown	6	(2.7%)	6	(3.4%)	0	—	
Tumor response							.003*
CR/PR (NACT vs first CT)			90	(50.8%)	24	(52.2%)	
PD/SD (NACT vs first CT)			20	(11.3%)	18	(39.1%)	
Direct surgery			62	(35%)	—	—	
Unknown			5	(2.9%)	4	(8.7%)	

HER-2, CR = complete response, CT = Chemotherapy, human epidermal growth factor receptor-2, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, NACT = neoadjuvant chemotherapy, PD = progressive disease, PR = partial response, SD = stable disease.
 * P = .003 compared between the CR/PR group and PD/SD group.

hormonal therapy ($P < .001$), and radiotherapy ($P < .001$) showed a trend toward better survival rates (Table 2).

Results of multivariate analysis after adjustment for the possible confounding factors demonstrated that surgery was an independent prognostic factor associated with OS rate in stage IV breast cancer (HR, 0.569; 95% CI, 0.329–0.984, $P = .044$). Moreover, additional independent prognostic factors that correlated with prolonged survival rates were hormonal therapy (HR 0.490; 95%

CI 0.300–0.800, $P = .004$) and radiotherapy (HR 0.490; 95% CI 0.293–0.819, $P = .007$) summarized in Table 3.

3.4. Subgroup analysis of overall survival

Stratified analyses were based on age at diagnosis, menopause status, HR, HER-2 expression, and molecular subtype. Stratified analyses were conducted to explore the differences between the

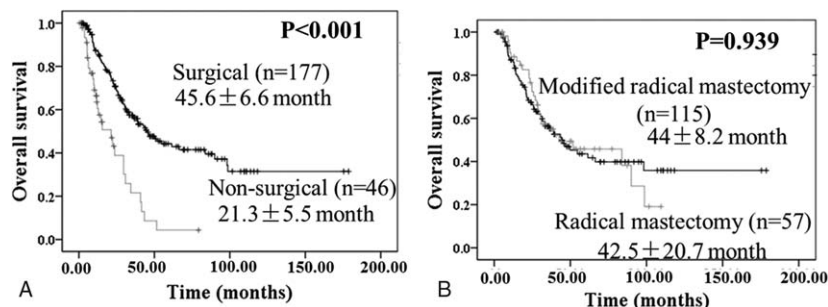


Figure 1. Overall survival of the patients by surgery status (A) and surgery approaches (B) in stage IV breast cancer patients.

Table 2

Univariate analysis of prognostic factors associated with OS in women with stage IV breast cancer.

Variable	HR	Univariate analyses	
		95% CI	P
Local therapy			
Nonsurgery vs surgery	0.332	0.216–0.509	<.001
Age, y			
≤50 vs ≥50	0.946	0.656–1.365	.766
Residence			
Urban vs rural	1.848	1.268–2.692	.001
Menopause			
Yes vs no	1.000	0.693–1.441	.999
T-stage			
≤2 vs > 2	2.831	1.150–6.969	.024
N-stage			
Negative vs positive	1.936	1.009–3.712	.047
HR			
Negative vs positive	0.532	0.361–0.785	.001
HER-2			
Negative vs positive	1.423	0.938–2.159	.097
Hormonal therapy			
No vs yes	0.307	0.207–0.454	<.001
Radiotherapy			
No vs yes	0.421	0.280–0.633	<.001

CI = confidence interval, HER-2 = human epidermal growth factor receptor-2, HR = hazard ratio, HR = hormone receptor, OS = overall survival.

surgery and nonsurgery groups, and also to determine which group of patients would benefit the most from surgery. The survival results of each subgroup are summarized in Table 4. Favorable and significant impact with surgical resection was observed in most of the patients in the subgroup, which was performed according to age at diagnosis, menopause status, HR,

Table 3

Multivariate analysis of prognostic factors associated with OS in women with stage IV breast cancer.

Variable	HR	Multivariate analysis	
		95% CI	P
Local therapy			
Nonsurgery vs surgery	0.569	0.329–0.984	.044
Age, y			
≤50 vs ≥50	1.168	0.609–2.243	.640
Residence			
Urban vs rural	1.165	0.748–1.814	.499
Menopause			
Yes vs no	1.267	0.645–2.490	.491
T-stage			
≤2 vs >2	2.576	0.927–7.156	.069
N-stage			
Negative vs positive	1.818	0.893–3.701	.099
HR			
Negative vs positive	0.626	0.379–1.033	.067
HER-2			
Negative vs. positive	1.022	0.635–1.645	.929
Hormonal therapy			
No vs yes	0.490	0.300–0.800	.004
Radiotherapy			
No vs yes	0.490	0.293–0.819	.007

CI = confidence interval, HER-2 = human epidermal growth factor receptor-2, HR = hazard ratio, HR = hormone receptor, OS = overall survival.

Table 4

Stratified analyses results of median overall survival in month.

Variance	All	Surgery	Nonsurgery	P
Full sample	39.0	45.6	21.3	<.001
Age, y				
≤50	39.0	45.6	22.2	.001
>50	39.0	46.0	15.4	<.001
Residence				
Rural	27.0	28.5	21.3	.180
Urban	46.0	66.4	15.4	<.001
Menopause				
Premenopause	40.7	46.5	22.1	<.001
Postmenopause	39.2	46.0	21.3	.001
HR				
Negative	21.4	24.7	11.8	.018
Positive	43.4	54.7	22.2	<.001
HER-2				
Negative	43.3	54.7	15.4	<.001
Positive	26.0	30.7	12.8	.009
Molecular subtype				
Nontriple negative	41.5	50.0	21.3	<.001
Triple negative	18.4	21.4	7.2	.039

HER-2 = human epidermal growth factor receptor-2, HR = hormone receptor.

HER-2 expression, and molecular subtype. However, female only in urban showed a survival advantage after receiving the surgical treatment (66.4 vs 15.4 months, log-rank $P < .001$; Table 4). Moreover, patients from urban showed an additional survival of 20.8 months with surgery. In addition, both women with HR positive (log-rank $P < .001$) and HER-2 negative (log-rank $P < .001$) saw an additional improvement in survival of 9.1 months in the surgery group.

4. Discussion

To the best of our knowledge, this is the first single-center cohort study that focused on exploring the association between survival and therapeutic surgery in women with stage IV breast cancer in Southwest China.

As in previous study, a large fraction (37–57%) of these women had undergone breast surgery.^[31] Surprisingly, in our study, 79.4% of these patients underwent surgery for the primary tumor, whereas only 20.6% had no surgical treatment. However, few data from China focused on this issue, a small study showed a high fraction rate (75.8%) of stage IV breast cancer women who underwent surgical resection.^[32] More retrospective studies and large meta-analysis suggested that breast surgery showed a favorable effect on the OS of patients with stage IV breast cancer.^[13,14,32–36] The ABC guidelines also reported available data regarding the value of removal of the primary tumor in patients with stage IV.^[7,21,37] Our findings are in accordance with these reports analyzing the impact of surgery on survival.

However, some studies were not in favor of the above-suggested beneficial effects of surgery and also suggested that this might be associated with the patient selection bias.^[4,31,38,39] Furthermore, in most clinical practices, women with stage IV breast cancer who underwent surgery may frequently tend to be younger and healthier, or had more modest tumor or disease burdens, or had good responses to initial systemic therapy. Otherwise, surgery would be done only to address wound healing concerns or palliative locally extensive tumor. These clinical factors may contribute to the observed and improved survival in patients who

underwent surgery for metastatic breast cancer.^[13,31] Practically, it is hard to set up a standard “response” that will lead to a benefit from surgery. Nevertheless, in the present study, 79.4% patients with primary metastatic breast cancer underwent surgical treatment. Patients with surgery had dramatically longer OS than those without surgery. No differences were found in the patient characteristics between surgery and nonsurgery groups (such as age at diagnosis, T-stage, N-stage, histological grade, molecular subtype, HR, and number of metastatic sites). Although our findings showed that patients of surgery group had a better response in neoadjuvant chemotherapy before surgery, we still had 35% patients to direct surgical treatment in that group. These suggested that the restrictions, such as younger and healthier patients, patients with more modest tumor or disease burdens, or had good responses to initial systemic therapy, are not essential and more patients can benefit from the primary surgery. Without doubt, more research needs to be implemented to confirm the significant indicators that guide in the surgical selection.

Moreover, importantly, technology and knowledge have advanced at a breathless pace. The discovery of stage IV breast cancer becomes earlier, diagnoses of the disease are likewise more precise, and even the scope and trauma of surgery is getting smaller. Thus, many patients diagnosed with stage IV breast cancer today have a lower tumor or disease burden rates than their counterparts from the earlier eras.^[13] These all lead to a lower survival load and are capable of benefiting from the surgical treatment in stage IV breast cancer patients. Recent research in a small population of patients with solitary bone metastases showed a significant improvement in the survival followed by complete excision of the primary breast tumor and regional nodes.^[13] More prospective studies are to be carried out to delineate the effect of surgery in stage IV breast cancer.

Surgery with free surgical margins caused a larger difference in the OS.^[4] In the present study, we found that modified radical mastectomy or radical mastectomy could not affect the OS, which suggested that modified radical mastectomy instead of radical operation may act as the primary surgical selection for stage IV breast cancer. However, due to the differences in the number of involving lymph node between the 2 groups in our study, more researches should be conducted to confirm the hypothesis. In the subgroup analysis, we found that women living in urban could gain a survival benefit from surgery compared with those living in rural. This might be associated with lack of disease awareness, psychological recognition, and comprehensive geriatric assessment in the rural areas where women suffered a short survival period, regardless of surgical treatment (28.5 months in surgery group vs 21.3 months in nonsurgery group). Our previous study also demonstrated that OS and progression-free survival were significantly lower for rural patients than urban patients who were diagnosed with breast cancer at West China Hospital.^[28] Thus, efforts should be made to ensure that all patients receive the optimal treatment regardless of where they live. However, longer survival by surgical resection for patients was not affected by subgroup analysis, according to age at diagnosis, menopause status, HR, HER-2 expression, and molecular subtypes.

Our data showed that surgery seemed to be an independent prognostic factor for OS in patients with stage IV breast cancer, by adjusting other clinical factors such as age, tumor type and burden, and systemic therapy. To some extent, this attempted to neutralize the clinical selection bias, although selection bias has yet to be a significant factor that affects the survival benefit in our cohort.

Local therapy is well established as an important palliative intervention for breast cancer patients.^[40–42] Hopefully, we

believe that surgery of primary tumor for women with initial metastatic breast cancer should be part of the regimens to effectively prolong the survival in the near future. More studies and better patient selection are necessary to resolve this question. By confirming good prognostic biomarkers for surgery patients with stage IV breast cancer, we may guide and select the appropriate patients for surgery and improve their survival; also try to avoid the surgery selection for population who cannot benefit from this choice.

There were several limitations in the present study. This was a single-center study with a small number of patients, which only represented the patients in Southwest China. Selection bias still played a confusing role in the survival–benefit ratio. Notably, we were unable to account for the use and time of delivery for chemotherapy, hormonal therapy, radiotherapy, or targeted therapy in our cohort. Patients who had a good response to systemic therapy may be identified as having a more controllable disease and require a subsequent surgery by chance.

5. Conclusions

Our study shows that surgery of the primary breast tumor in patients with initial stage IV disease had a positive impact on survival rates. After adjusting for the clinical factors, it has been demonstrated that surgery was also independently associated with improved survival rates. This work will support and add evidence to the critical concepts in the care of women with advanced breast cancer disease.

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