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ORIGINAL ARTICLE

Surgery in initially metastatic breast cancer: prognosis is associated with patient characteristics and timing of surgery

Faling Xue[1]*, Liang Yu[2]*, Ying Lin[2], Zhongxing Wang[1], Songqi Li[2], Nan Shao[2], Fang Ye[1], Chen Gu[1], Xiaoxi Li[2]

[1]Department of Anesthesiology, the First Affiliated Hospital of Sun Yat-sen University, Guangdong, China; [2]Department of Breast Surgery, the First Affiliated Hospital of Sun Yat-sen University, Guangdong, China.

*These authors contributed equally to this work and should be considered co-first authors.

Summary

Purpose: *The role of surgery in patients with initially metastatic breast cancer (IMBC) is unclear. The purpose of this study was to determine if surgery improves the prognosis of patients with IMBC.*

Methods: *Data of patients with IMBC at the First Affiliated Hospital of Sun Yat-Sen University from 2000 to 2014 were retrospectively analyzed. The last follow-up was October 2015. Clinical characteristics and overall survival (OS) were compared and evaluated by univariate and multivariate analysis.*

Results: *Eighty-one patients were included in this study; 59 were operated and 22 were not. The median survival time was 28 months, 3-year survival rate was 32.5%, and 5-year survival rate was 8.4%. The OS of operated patients was significantly longer than those without surgery (34 vs. 23 months, p=0.002). Surgery (estimated hazard ratio [HR] =0.12, 95% confidence interval [CI]: 0.04-0.42) and endocrine therapy (HR=0.17, 95% CI: 0.06-0.54), were significantly associated with a better prognosis in the multivariate model. However, patients with surgery were younger, had fewer metastases, and a higher ratio of patients with Ki-67≤14%. Patients who were operated more than 3 months after diagnosis had better OS that those who had surgery less than 1 month (p=0.009). Stratified analyses of the surgery group found that younger age (HR 0.28, p=0.016), bone-only metastases (HR 0.24, p=0.006) and chemotherapy administration (HR 0.38, p=0.004) or endocrine therapy (HR 0.06, p=0.006) were favorable predictors of survival.*

Conclusion: *Surgery may prolong the OS of patients with IMBC, especially in certain of them, and in those who undergo surgery at a certain time.*

Key words: *initially metastatic breast cancer, prognosis, surgery*

Introduction

Initially metastatic breast cancer (IMBC) refers to patients with breast cancer with metastasis at the time of diagnosis. It has been reported that 0 to 11.2% of newly diagnosed breast cancer patients present with distant metastases [1-2]. These patients have a 5-year survival rate of approximately 20%, and overall survival (OS) ranges from 16 to 29 months [1,3].

IMBC has been considered an incurable disease, and the traditional principles of management were to prolong survival and improve quality of live. The first choice of treatment for these patients was systemic therapy based on prior studies and guidelines [3,4]. However, many of the studies for these patients are retrospective studies, and focused on both patients with recurrent metastatic

Correspondence to: Xiaoxi Li, MD,PhD. Department of Breast Surgery, the First Affiliated Hospital of Sun Yat-sen University, No.58 Zhongshan Rd, Guangzhou 510080, China.
Tel: +86 139 2606-9016, Fax: +86 20 87 33 0808, Email: lix2@21cn.com
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breast cancer (RMBC) and IMBC. In addition, National Comprehensive Cancer Network (NCCN) [4] and European Society for Medical Oncology guidelines [3] do not differentiate between patients with RMBC and IMBC.

Resection of the primary tumor was found to improve the OS in patients with initially metastatic gastric cancer and colon cancer, which suggested that aggressive local therapy might improve the prognosis of IMBC [5,6]. Over the 20 years, a large number of retrospective studies have been performed, and some of them found that aggressive local therapy might improve the prognosis in patients with IMBC [7-12]. Some studies, however, reported that primary resection did not improve outcomes of patients with IMBC [13,14]. Authors have suggested that most of the surgical benefit in IMBC patients might be due to obvious selection bias with patients who are younger, have fewer complications, single metastasis, simple bone metastases, smaller tumors, less lymph node involvement, better response to systemic therapy, and higher hormone receptor expression being more likely to accept surgery [7-12]. In addition, ESO-ESMO 2nd international consensus guidelines for advanced breast cancer pointed out that until there is more supporting evidence, it is not advocated to routinely perform aggressive surgery in IMBC patients [3].

However, we have noticed that some studies have suggested that certain patients, such as those who are younger and have bone-only metastasis, may benefit from surgery [9,12]. A study has also suggested that the timing of surgery may also influence the prognosis [15]. Danna et al. [16] used a mouse model of metastatic breast cancer, and found that surgical resection of the primary lesion reduced cellular immunity and anti-tumor antibody production induced by the primary tumor. Rashid et al. [17] also using a mouse model, found that removal of the primary lesion could reduce the overall tumor burden.

Thus, the purpose of this study was to determine if surgery, and/or the timing of surgery, affects the OS of patients with IMBC, and to examine if patient clinical characteristics define certain patients who may benefit more from surgery.

Methods

Patients

We retrospectively reviewed the medical records of patients with IMBC who were treated at the First Affiliated Hospital of Sun Yat-Sen University from January 1, 2000 to December 31, 2014. Patients were included in the analysis if they met the following criteria: (1) identified with metastases by clinical or radiological evidence at the time of, or within 3 months of being diagnosed with breast cancer [7,15]; (2) metastases were identified according to the American Joint Commission of Cancer (AJCC) 7th edition staging criteria [18]; (3) did not receive any prior treatment; (4) had follow-up of more than 3 months. Patients with recurrent metastases were excluded. The study was approved by the local Clinical Research Ethics Committees, and written informed consent was waived due to the retrospective nature of the study.

Data collection

Information extracted from the clinical records included age, sex, year of diagnosis, menopause status, tumor size, lymph node (LN) metastasis, number and types of metastases, Ki-67 index, hormone receptor and HER2 expression, chemotherapy, endocrine therapy, trastuzumab, surgery and time of surgery, length of follow-up and death. Tumor size, LN involvement, and distant metastasis were staged according to the AJCC 7th edition on tumor staging system [18]. Expression of estrogen (ER) and progesterone receptors (PR) and HER2 were defined according to immunohistochemistry detection guidelines of ER and PR published in 2010 [19] and HER2 detection guidelines published in 2013 [20]. As information of progression-free survival were not intact, the study outcome was OS, defined as days from diagnosis to last clinic visit day or day of death. Surgical interval was defined as the day from diagnosis to the day of surgery.

Statistics

All analyses were performed using IBM SPSS software version 20 (IBM Corporation, Somers, New York). Continuous variables were reported as mean ± standard deviation and compared by Mann-Whitney U test between the surgery and non-surgery groups because normality was not assumed. Categorical variables were analyzed by chi-square test or Fisher's exact test if expected value ≤5 was found. The statistical significance level for all the tests was set at a 2-tailed value of $p<0.05$. Univariate and multivariate Cox regression models were used to investigate the associations between independent variables and OS. If a variable reached a significance level of $p<0.10$ in univariate analysis, it was included in the multivariate model. Kaplan-Meier survival analysis and log-rank test were used to estimate and compare the OS with respect to associated factors.

Results

Patient characteristics

A total of 81 IMBC patients met the study criteria and were included in the analysis. Of the patients 71 (87.65%) received chemotherapy, and in 77.5% the chemotherapy drugs were anthracycline-taxane. Approximately 48% of HER2+ patients received targeted treatment. Of the patients, 59

(72.83%) were operated and 22 (27.16%) were not. In the surgery group, 42 underwent radical mastectomy and axillary lymphadenectomy, 10 were subjected to breast and pectoral muscle resection and axillary LN dissection, 5 underwent mastectomy alone, and 2 lumpectomy alone.

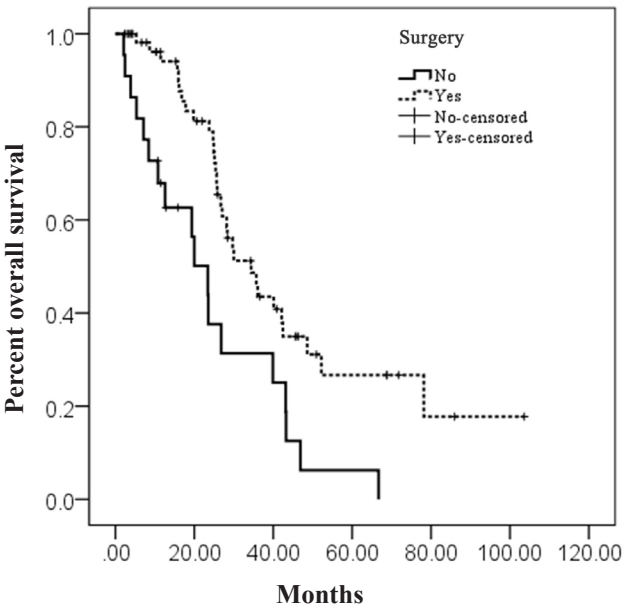

Figure 1. Kaplan-Meier curves of overall survival for patients with initially metastatic breast cancer who were operated or not (overall survival: 34 months vs. 23 months). Censored: patients who were alive by the end of the follow-up or lost to followed-up. Log-rank test, p=0.002.

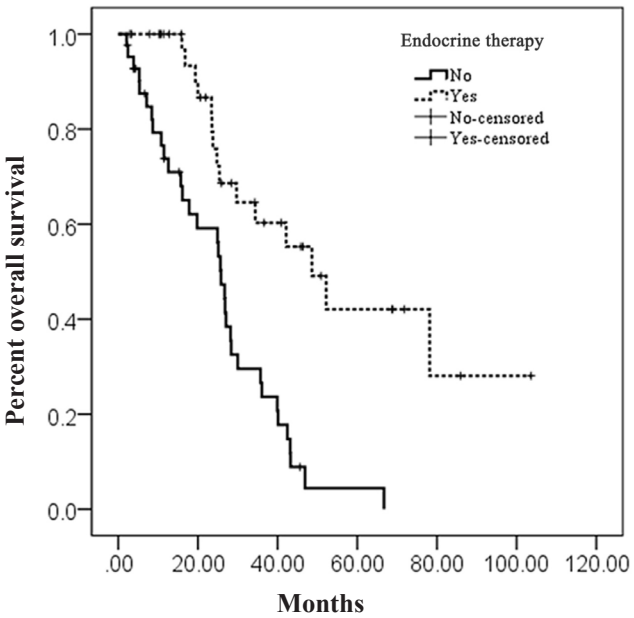

Figure 2. Kaplan-Meier curves of overall survival for patients with initially metastatic breast cancer who received or not endocrine therapy. Censored: patients who were alive by the end of the follow-up or lost to followed-up. Log-rank test, p<0.001.

The characteristics of patients in the surgery and non-surgery groups are shown and compared in Tables 1 and 2. Patients in the surgery group were significantly younger (47.78±10.53 vs. 57.95±12.33 years, p=0.001), and had a lower number of metastasis and a higher ratio with a Ki-67 index ≤14%. A higher percentage of patients in the surgery group received endocrine therapy, but the difference was not significant (54.24 vs. 31.82%, p=0.085). There was no significant difference between the two groups in tumor size, stage and type of metastasis, hormone receptor positivity, and HER2 expression (all, p>0.05).

Follow-up and factors associated with OS

At the last follow-up, 49 patients had died, 19 were still alive, and 13 were lost to follow-up. The shortest survival was 2 months and the longest was 104 months, with a median survival time of 28 months. The 3-year survival rate was 32.5% and the 5-year survival rate was 8.4%. As indicated in Table 3, age, menopause, metastasis number, ER, PR, Ki-67, surgery and endocrine therapy were found to have p values<0.10 in univariate analysis, and thus entered into the multivariate model. In multivari-

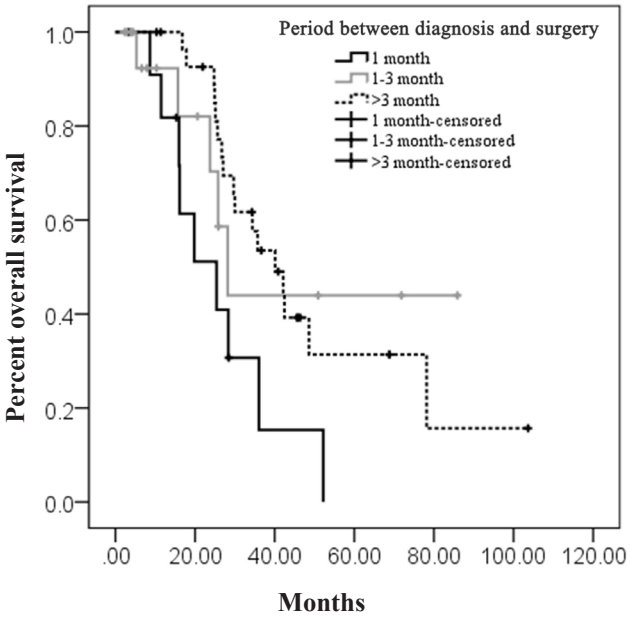

Figure 3. The effect of the timing of surgical intervention at the primary tumor site on overall survival in the surgery group. Patients with different preoperative interval had a significantly different prognosis (log-rank test, p=0.039). Patients who underwent surgery more than 3 months (group 3) after diagnosis had improved overall survival than those who had surgery less than 1 month (group 1) (p=0.009). However, the overall survival difference between group 1 and group 2, and between group 2 and group 3 did not reach statistical significance (log-rank test, p=0.168 and p=0.947, respectively).

ate analysis, surgery and endocrine therapy were significantly associated with improved OS (both, p<0.05). The hazard ratio (HR) for surgery was 0.12 (95% confidence interval [CI]: 0.04-0.42) and the HR for endocrine therapy was 0.17 (95% CI: 0.06-0.54).

Kaplan-Meier survival estimate

Kaplan-Meier analysis was used to compare the OS between groups who received surgery and endocrine therapy. The estimated 3-year survival rates of surgery and non-surgery groups were 56.09% and 31.33%, respectively, and the rates of those with or without endocrine therapy were 60.27% and 23.65%, respectively (Figure 1 and 2; both, p<0.01).

Further analysis of OS of the surgery group was performed based on the time between diagnosis and surgery: less than 1 month (group 1), 1 to 3 months (group 2), and more than 3 months (group 3). Patients who underwent surgery more than 3 months (group 3) after diagnosis had improved OS compared to those that received surgery less than 1 month (group 1) (p=0.009). There was no significant difference in OS between group 1 and group 2, or between group 2 and group 3 (log-rank test, p=0.168 and p=0.947, respectively).

Stratified analyses of surgery group for factors associated with OS

Further analysis was performed to identify factors associated with OS in operated patients. As indicated in Table 4, age ≤50 years, pre-menopause, higher tumor stage (T3/T4 or N2/N3), bone metastasis-only, number of metastases≥3, ER+, PR+, HER2-, Ki-67 index >14%, underwent chemotherapy or endocrine therapy, and did not receive targeted therapy were associated with better OS (all, p<0.05, hazard ratios [HR] HR <1). However, some of the non significant results might also be due to the limitation of small sample size.

Discussion

We examined the survival outcomes of IMBC patients with and without surgery, and we found that OS of patients who underwent surgery was significantly longer than those who did not.

Whether or not surgery improves the OS of IMBC patients is still controversial. Because there is large heterogeneity in IMBC patients, to a certain degree prognosis is hard to predict [21]. Several factors like younger age, smaller primary tumor, and having just one metastatic site might contribute to better OS [22]. Studies have also suggested that effective chemotherapy drugs and targeted drug therapy could increase the OS of patients with IMBC [23,24]. Uyeturk et al. [25]https://paperpile.com/c/UyqodL/Nqk99 found that chemotherapy and bisphosphonate therapy were prognosis-related factors in IMBC patients by analyzing the outcomes of 102 patients with IMBC at a single center. A recent study showed that locoregional treatment, including radiotherapy, together with systemic therapies might be an important option for IMBC patients [26]. In our study, the OS of patients who received chemotherapy and trastuzumab was longer compared to those who did not receive these treatments, but the difference was not statistically significant, which might due to the small sample and a certain number of censored data. In addition, patients in the surgery group were younger and more likely to receive endocrine therapy; moreover, endocrine therapy was also an independent factor related to OS in the multivariate Cox regression analysis.

Six randomized controlled clinical trials are currently being performed, and preliminary results of 2 trials have been reported. In the study by Badwe et al. [13] 350 patients with IMBC were randomly divided into a surgery or non-surgery group after 6 cycles of chemotherapy. The initial results showed that there was no statistically significant difference in the survival time between the 2 groups (19.2 vs. 20.5 months, HR=1.04, 95% CI 0.81-1.34, p=0.79). Similarly, there was no significant difference in the prognosis of the 2 groups after stratification analysis. Moreover, local progression-free time in the surgical group was shorter than that in the non-surgery group. In the study by Soran et al. [27] patients received appropriate systemic therapy after surgery. Preliminary results showed that surgery did not improve the prognosis of patients with IMBC, but subgroup analysis showed that bone-only metastasis patients achieved a survival benefit from surgery. A multi-center prospective registry study by King et al. reported that surgery was associated with improved OS in patients with IMBC [28]. Compared to King's study, patients included in Badwe's study [13] might discontinue chemotherapy and re-initiate it after recurrence and most HER-2 positive patients did not receive targeted therapy. Patients in our study were significantly more likely to have systemic treatment than those in Badwe's prospective study, and the survival time of patients who underwent primary resection was significantly longer than that of patients who did not have surgery. Although there may be some bias in the current evidence, it seems clear that surgical treatment of IMBC patients does not deteriorate their prognosis. Removal of the local tumor may enhance a patient's confidence in treatment, and to

some extent reduce the tumor burden. With respect to the timing of surgery, a study of young patients with breast cancer found that 5-year survival rates were significantly different in patients with preoperative intervals of 6 weeks and less than 2 weeks (80% vs. 90%, p=0.005); the longer the waiting time before surgery, the poorer the prognosis [29]. Ruiterkamp et al. [30] found that there was no difference in OS between IMBC patients who had surgery before or after the diagnosis of the metastases. By analyzing 75 IMBC patients who underwent surgery, Rao et al. [15] found that progression-free survival was longer in patients with longer preoperative intervals (>3 months) than in patients with shorter preoperative intervals, while OS was not affected. The authors speculated that patients with longer preoperative intervals may have an opportunity to receive preoperative chemotherapy and thus respond well to complete local remission of the tumor. Our study found a significant OS difference between patients in whom the interval were >3 months and <1 month. It was not the sooner the better if IMBC patients were operated, maybe the timing of surgery was another point to be focused.

A recent study showed that select patients (>N2, >T3, or T2N1) were more likely to benefit from surgery [26].

Another study showed that patients with favorable characteristics, such as young age and no comorbidities, had the most benefit from surgery [9]. In our study, the rate of surgery of IMBC patients was relatively high, but most patients received systemic treatment simultaneously, and patients who were operated had a longer OS. We also found that some characteristics such as bone-only metastases, ER+, PR+, age <50 years, and received chemotherapy or endocrine therapy were associated with a survival benefit in patient that were subjected to surgery. In a large retrospective cohort study 21,372 IMBC patients from 1988 to 2011, Thomas et al. [10] found that the rate of surgery significantly declined from 67.8% in 1988 to 25.1% in 2011; however, surgery was found to prolong survival, especially in select patients. Soran et al. [27] also found that only bone-only metastasis was associated with a survival benefit from surgery.

The median OS of IMBC patients in the current study was 28 months, which is longer than that of a prospective study in India where the median OS was 19.2 months [13]. Our patients received more aggressive treatment, however. For example, 46.9% of HER2+ patients at our center received trastuzumab, and 77.5% received anthracycline-taxane, while in the Indian study in 96% of cases the chemotherapy drug was anthracycline only, and only 2% of HER2+ patients received targeted treatment [13]. The patients with the shortest and longest survival in our study were both bone-only metastases; the former were triple negative subtype and the latter were luminal A subtype. The former refused all systemic and local treatment and tried Chinese medicine, and the latter received systemic and local therapy, and the preoperative interval was more than 3 months.

Although it is difficult to make a conclusion that resection of the primary tumor could improve the prognosis in IMBC patients because patients in the surgery group were younger than those in non-surgery group, and this was a retrospective study, it was clear that surgery did not worsen the prognosis. This is one of the few studies that aimed to analyse the impact of surgery on survival for IMBC patients in an Asian population. Compared to the other studies, the timing of surgery was also considered in our study, and we found that a suitable preoperative interval might lead to a better prognosis. Moreover, patients with certain characteristics, such as younger age, bone-only metastases, chemotherapy or hormonotherapy administration, might enjoy a greater benefit from surgery.

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Conflict of interests

The authors declare no conflict of interests.

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