Locoregional treatment of the primary tumor may improve overall survival and cancer-specific survival in breast cancer patients with bone metastases

Peng Deng (✉ 878686405@qq.com)  
Nanchang University Second Affiliated Hospital  
https://orcid.org/0000-0002-6838-1263

Anan Wang  
Nanchang University Second Affiliated Hospital

Lei Liu  
Nanchang University Second Affiliated Hospital

Zhiyang Liu  
Nanchang University Second Affiliated Hospital

Yonghui Luo  
Nanchang University Second Affiliated Hospital

Chenghao Yi  
Nanchang University Second Affiliated Hospital

Research article

Keywords: Stage Î breast cancer, Bone metastases, Locoregional treatment, Overall survival, Cancer-specific survival

DOI: https://doi.org/10.21203/rs.3.rs-455174/v1

License: ☑️ ① This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Aims: we sought to analyze data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program to conduct an epidemiologic study of the potential effect of surgery on survival in breast cancer patients with bone metastases.

Methods: Included in the analyses were histologically confirmed AJCC M1 breast cancer with bone metastasis who were diagnosed from January 2010 to December 2011. These patients were grouped according to whether or not they have undergone mastectomy. To account for differences in baseline characteristics, a propensity score was estimated to optimally adjust the data for the bias between the two groups.

Results: From a total of 1180 breast cancer patients with bone metastasis, 508 patients underwent mastectomy and 672 did not undergo mastectomy. The 3-, and 5-year overall survival rates for patients who underwent palliative mastectomy were 67.2%, and 45.8% compared with 49.5%, and 27.9% for patients who did not undergo mastectomy. The 3-, and 5-year cancer-specific survival rates for patients who underwent palliative mastectomy were 69.1%, and 49.2% compared with 52.4%, and 30.7% for patients who did not undergo mastectomy. Using the weights and strata obtained by the propensity score matching procedure, The 3-, and 5-year overall survival rates for patients who underwent palliative mastectomy were 68.1%, and 45.6% compared with 48.8%, and 28.7% for patients who did not undergo mastectomy. The 3-, and 5-year cancer-specific survival rates for patients who underwent palliative mastectomy were 70.2%, and 49.7% compared with 53.3%, and 31.9% for patients who did not undergo mastectomy.

Conclusions: Locoregional treatment was shown to be independently associated with improvement in survival in IV breast cancer patients with bone metastases. Therefore, surgical management for the primary tumor could be considered more actively in selected patients with stage IV breast cancer.

Introduction

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women. About 3–8% of patients with newly diagnosed disease have distant metastases at initial presentation. Bone is the most common metastatic site of breast cancer [1, 2]. Metastatic breast cancer is deemed an incurable disease with the main goals of treatment being prolongation of survival and palliation of symptoms. The mainstay of treatment is systemic therapy, which includes chemotherapy, endocrine therapy, and targeted drugs. An ongoing debate is the value of palliative mastectomy in selected patients. According to the current guidelines, mastectomy is advocated for symptomatic tumors in the palliative setting such as ulceration and bleeding, but not for asymptomatic tumors [3, 4].

The question of management of the primary tumor in women with de novo stage IV breast cancer has attracted significant interest, particularly as loss of control at the primary site can have a profound effect on the quality of life. Data from experiments in animal models of different cancers have suggested that surgical removal of the primary tumor could potentially increase metastatic spread[5]. By contrast, removal of the primary tumor was shown to improve survival in patients with metastatic renal cell carcinoma[4, 6]. Removal of the primary tumor could potentially improve the outcome in breast cancer by removing drug resistant clones of cancer cells. A number of recent studies have reported that surgery for stage breast cancer affects a patient's survival time.
Many of these retrospective studies indicated that surgery prolonged survival time. Several systematic reviews have reported significant differences in survival time[7]. These reviews are not without bias, and recently completed randomized trials do not support a significant survival benefit [8-10]. But in the subgroup analysis of the MF07-01 showed that local control benefits may exist in patients with bone metastases [8, 11]. Completion of ongoing trials is needed to reach a definitive conclusion regarding the merit of primary tumor resection for local control and survival.

To address this uncertainty, we sought to analyze data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program to conduct an epidemiologic study of the potential effect of surgery on survival in breast cancer patients with bone metastases.

**Methods**

**Data Source**

We applied and obtained research files in Nov 2019 from National Cancer Institute's SEER database which was comprehensive source of population-based information covering 28% of the U.S. population. Strict quality control is maintained by the SEER Quality Improvement program that establishes standards for cancer registries and maintains them through continual monitoring, assessment, and education. We obtained the permission to access the SEER database with the ID number yich via Internet access method. Cases of breast cancer with bone metastasis reported to the SEER program between 2010 and 2011 were included in the study.

Included in the analyses were histologically confirmed AJCC M1 breast cancer with bone metastasis who were diagnosed from January 2010 to December 2011. As detailed in Figure 1, patients with multiple primaries, or patients lacking follow-up were excluded. Patients treated with local tumor excision or destruction alone (codes 19,99) as their first course of therapy were not included. Patients diagnosed with unknown subtypes and unknown metastatic sites/metastasis of other organs/ multiple organ metastasis were excluded. Patients who survival time is less than or equal to 3 months and unknown the cause of death were excluded. These patients were grouped according to whether or not they have undergone mastectomy.

**Classification of metastatic breast cancer**

Tumor grade was coded according to the International Classification of Diseases for Oncology (ICD-O), version 3. Tumor stage was coded according to the American Joint Committee on Cancer (AJCC) TNM staging system, 7th edition. ER, PR, and HER2 status were classified in the SEER registry according to immunohistochemistry (IHC) as well as fluorescence in situ hybridization (FISH) testing for HER2. Tumors were classified as ER+ or PR+ when 1% or more of the cells stained positive, although no additional information was available on the degree of ER or PR positivity. HER2 IHC was coded with the standard 0–3+ scoring system and considered borderline for 2+ IHC with an equivocal FISH result.

Demographic variables included age at diagnosis (≤39, 40–59, ≥60 years) and race (Caucasian, African American, API/AI). The cancer characteristics included grade (G1/well differentiated, G2/moderately differentiated, G3/poorly differentiated, G4/undifferentiated, unknown), and HR and HER2 status (positive, negative, unknown). Treatment characteristics included receipt of chemotherapy (no, yes.). The subtypes were
characterized according to the breast subtypes variable as HR+/HER2−, HR+/HER2+, HR−/HER2+ and triple negative. Metastatic sites included bone.

Statistical Analysis

One way ANOVA test with Student-Newman-Keuls post hoc test was used to compare the difference of continuous data. Chi-square test was used to compare the difference of categorical data. Multivariate Cox proportional hazard models identified factors associated with OS and CSS, with results reported using hazard ratios (HR) and 95% confidence intervals (CI). Subgroup analyses using multivariate Cox proportional hazard model estimated the HRs of locoregional treatment versus no locoregional treatment, and a forest plot was created to better present each prognostic factor’s effect on OS and CSS Kaplan–Meier curves were used to calculate 3-year and 5-year OS and CSS, with the log–rank test used to determine statistical differences across groups. Survival time, in months, was calculated from the date of diagnosis until the date of death. If the patient was alive, the patient was censored at the date of last contact.

To account for differences in baseline characteristics, a propensity score was estimated to optimally adjust the data for the bias between the two groups using the following predetermined factors: age at diagnosis, race, pathological grade, T stage, molecular subtype, chemotherapy type. All statistical analyses were performed using IBM SPSS software for Windows, version 25.0 (IBM Corporation, Armonk, New York). Comparative differences were considered significant at $P < 0.05$.

Results

Patient characteristics

From a total of 1180 breast cancer patients with bone metastasis, 508 patients underwent mastectomy and 672 did not undergo mastectomy. Table 1 summarizes the patient characteristics for both groups and outlines the significant differences between the two groups, thus indicating a relevant bias.

Mastectomy as a prognostic factor for survival

The 3-, and 5-year overall survival rates for patients who underwent palliative mastectomy were 67.2%, and 45.8% compared with 49.5%, and 27.9% for patients who did not undergo mastectomy. The 3-, and 5-year cancer-specific survival rates for patients who underwent palliative mastectomy were 69.1%, and 49.2% compared with 52.4%, and 30.7% for patients who did not undergo mastectomy. The Kaplan–Meier-curves for overall survival and cancer-specific survival demonstrate longer. When the overall survival and cancer-specific survival are compared, the prognosis of patients who underwent mastectomy is generally better (Figure 2A, Figure 2B). These findings were confirmed by a multivariable risk adjustment of the Cox regression analysis in which mastectomy was a statistically significant protective factor for overall survival [hazard ratio for death (HR: 0.657, 95 % CI 0.562-0.769, $P<0.0001$) and cancer-specific survival (HR: 0.644, 95 % CI 0.547-0.759, $P<0.0001$) (Table 2 and Table 3).

Adjustment for patients’ characteristics with propensity score matching
To ensure that baseline differences in demographics and clinical characteristics across the two groups do not account for the outcome discrepancies, we carried out a 1:1 (patients who underwent mastectomy/patients who did not undergo mastectomy) matched case-control analysis using the propensity score matching method. During the propensity score matching, 522 patients who did not undergo mastectomy had to be excluded because they did not have a counterpart propensity score in the other group. A group of 658 patients were obtained, including 329 patients undergo mastectomy and 329 patients did not undergo mastectomy. The four rightmost columns in Table 1 summarize the patient characteristics obtained after propensity score weighting. No significant differences between the two groups after the propensity score matching.

**Propensity-score-matched prognostic factors for survival**

Using the weights and strata obtained by the propensity score matching procedure, the 3-, and 5-year overall survival rates for patients who underwent palliative mastectomy were 68.1%, and 45.6% compared with 48.8%, and 28.7% for patients who did not undergo mastectomy. The 3-, and 5-year cancer-specific survival rates for patients who underwent palliative mastectomy were 70.2%, and 49.7% compared with 53.3%, and 31.9% for patients who did not undergo mastectomy. The Kaplan–Meier-curves for overall survival demonstrate longer survival times for patients who underwent mastectomy (Figure 3A, Figure 3B).

When we performed a multivariable Cox regression analysis using the weights and strata obtained by the propensity score matching procedure, mastectomy was a persistent significant protective predictor for overall survival (HR 0.664, 95% CI 0.549-0.804, \( P < 0.0001 \)) and cancer-specific survival (HR: 0.651, 95% CI 0.532-0.796, \( P < 0.0001 \)). (Table 2 and Table 3).

**Subgroup analysis**

The number of deaths used in calculations of OS and CSS are summarized in Table S1 and Table S2 (detailed in the Supplement). Forest plots for the hazard ratios are summarized in Figure 4 and Figure 5. In these small subgroups, mastectomy was associated with more favorable OS compared with no mastectomy in older (\( \geq 49 \) y), Caucasian, higher tumor grades (G2-4), HR+/HER2-molecular subtype, and chemotherapy; was associated with more favorable CSS compared with no mastectomy in older (\( \geq 49 \) y), Caucasian, higher tumor grades (G3-4), HR+/HER2-molecular subtype, HR+/HER2+ molecular subtype and chemotherapy.

**Discussion**

Nowadays, breast cancer is the most commonly diagnosed cancer in women worldwide. The incidence rate has risen rapidly over the past few decades, with an annual growth rate of about 6.1% \[12, 13\]. It is estimated that in 2019 approximately over 150,000 women have stage IV breast cancer in the United States. In addition, about 6% of female breast cancer patients have distant metastasis at the time of diagnosis \[1, 14\]. Stage IV breast cancer is defined by metastasis from the breast and axilla to distant sites, most commonly the bone\[1\]. Traditionally, stage IV breast cancer is considered an incurable disease and the goal of treatment is to prolong life and reduce or prevent symptoms\[15\]. Previous knowledge has shown that the mainstay of treatment is systemic therapy, which includes chemotherapy, endocrine therapy, and targeted drugs, and so on. While surgery is reserved for symptomatic tumors bleeding or ulceration. Advances in systemic treatment have significantly improved the control of metastases and prolonged survival in IV breast cancer patients. In this
context, the role of mastectomy in survival has therefore become a question worth considering. Earlier studies had indicated that the growth of distant metastases could be stimulated by advanced local surgery[16]. Researchers pointed out that primary tumors can represent a source of antiangiogenic factors and growth factor inhibitors, suggesting that it can inhibit the growth of distant metastases. Surgical resection reduced angiostatin secretion and also stimulated the release of growth factors, which might promoted tumor growth[17-19]. In 2015, a randomized controlled trial on the effect of surgery for de novo stage IV breast cancer in India suggested that local surgery did not significantly improve overall survival [9]. Similarly, the initial reports from prospective studies by Badwe[20] et al and Soran [21] et al also failed to demonstrate a survival benefit among IV breast cancer patients who underwent surgical resection. However, these findings were criticized for a disproportionate inclusion of patients with advanced metastatic disease, insufficient systemic therapy regimens, and treatment sequences that did not match contemporary practices[22].

Although other series reported similar results, the effectiveness of mastectomy in IV breast cancer remains uncertain. It has been suggested that although surgical resection of the primary tumor may cause transient increase in tumor burden, it substantially reduced overall tumor burden and improved survival by restoring immune responsiveness and enhancing sensitivity to chemotherapy[23, 24]. In recent years, some observational studies have shown that 35%-60% of breast cancer patients with stage IV received surgical resection and this treatment was associated with a survival advantage [4, 15, 25, 26]. Similarly, survival advantage with surgery for the intact breast primary in stage IV breast cancer has also been demonstrated in several studies. In 2012, Petrelli et al. [27] reported that the first meta-analysis compared survival outcomes in patients with stage IV breast cancer who received PTR or no PTR. They analyzed 15 observational studies and found that PTR provided survival benefits for stage IV breast cancer patients (HR=0.69; 95% CI: 0.63-0.77; \(P<0.001\)). A completed trial (NCT00557986) in Turkey showed that surgery did not achieve a survival benefit after 3 years of follow-up, but after 5 years follow-up, patients with surgery achieved a better survival, especially in patients with bone metastases alone. The same result was also shown in another report. Rapiti et al [28] reported that complete surgical excision of the primary tumor led to a 40% reduction in the risk of death from breast cancer and was most pronounced for women with bone-only metastatic disease can benefit from initial surgical treatment. The question of management of the primary tumor in women with de novo stage IV breast cancer has caused us great concern, particularly in patients with bone-only metastases. It is undeniable that these retrospective studies may have limitations, including the inability to control selective bias. To explore the potential impact of surgery on the survival of patients with bone metastases, we selected a total of 1180 breast cancer patients histologically confirmed AJCC M1 breast cancer with bone metastases in National Cancer Institute's SEER database, which was diagnosed between January 2010 and December 2011. In this large, nationally representative study of more than 1180 breast cancer patients, we analyzed the data and confirmed that patients who underwent palliative mastectomy showed better survival than individuals who did not undergo mastectomy. On multivariate Cox regression analysis to control for the effect of known covariates including age at diagnosis, race, pathological grade, molecular subtype, and chemotherapy type, palliative mastectomy for de novo stage IV breast cancer remained an independent factor associated with better survival. Although a survival advantage of fewer prognostic factors, such as T stage, has not yet been clearly demonstrated in our study. Comprehensive local therapy, including surgery for the intact breast primary, may improve locoregional control outcomes for IV breast cancer, particularly in IBC [6]. In contrast, chemotherapy was significantly related to better OS (HR=0.704, 95%CI (0.570-0.870), \(P<0.0001\)) and CSS (HR=0.730, 95%CI (0.585-0.911), \(P=0.005\)) for all IV breast cancer patients (Table 2, Table 3). This result is in agreement with other
reports. In Soran et al.'s MF07-01 trial, among the 274 patients that could be evaluated, the results showed that OS was significantly longer in the patients who received surgery followed by chemotherapy [29]. Consequently, primary tumor mastectomy may improve survival of patients with stage IV breast cancer when used in conjunction with chemotherapy.

Through subgroup analysis, we found that primary tumor removal was significant associated with improvement in survival in most subgroups. Therefore, surgical management for the primary tumor could be considered more actively in patients with stage IV breast cancer. In addition, the availability of chemotherapy and adjuvant therapy for the treatment of IV breast cancer is already commonly used and showed significant OS and CSS. Therefore, patients with metastatic breast cancer will develop a durable long-term response and improved survival outcome with coordinated multidisciplinary therapy[15]. Joint efforts from surgeons, pathologists, oncologists and radiologists have been made to better personalized approach to patient management on an individualized basis.

**Limitation and strength**

We would like to acknowledge some certain limitations of this study. Undoubtedly, a relevant selection bias cannot be excluded since younger and healthier patients with less comorbidity and metastases have a higher propensity of being operated on, whereas the older, sicker patients with multiple metastases are less likely to undergo surgery. Nevertheless, the advantage of the present analysis of the SEER database is the high power of a large cohort and the potential to mirror outcomes in the daily clinical routine.

These results of the present study shed light on the role of surgery and potential benefit in solitary bone metastases of breast cancer. We hope that the ongoing trials will help to clarify the effects of palliative mastectomy of patients with metastatic breast cancer.

**Conclusion**

In our study, the locoregional treatment group had significantly higher 3- and 5-year cancer-specific survival rates and 3- and 5-year overall survival rates than the none locoregional treatment group. Therefore, surgical management for the primary tumor could be considered more actively in selected patients with stage IV breast cancer.

**Declarations**

**Acknowledgements**

Not applicable.

**Funding**

The study was supported by The National Natural Science Foundation of China (grant no. 81860466).

**Availability of data and materials**
These data are publicly available for use in accordance with a limited use agreement for SEER research data: SEER Program (https://seer.cancer.gov) SEER*Stat Database: Incidence-SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying) - Linked To County Attributes - Total U.S., 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission.

**Authors’ contributions**

CHY, PD, YHL and AAW conceived and designed the study. All authors contributed to the Collection and assembly of data. PD, CHY and AAW analysed the data. PD and CHY wrote the manuscript. All authors made Figures and tables. The authors read and approved the final manuscript.

**Ethics approval and consent to participate**

The study was reviewed by the Institutional Review Board of the Second Affiliated Hospital of Nanchang University. It was determined to be a retrospective analysis of publicly available, de-identified data and was determined to be exempt from requiring written informed consent.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A, Siegel RL: *Breast cancer statistics, 2019*. CA Cancer J Clin 2019, 69(6):438-451.

2. Siegel RL, Miller KD, Fuchs HE, Jemal A: *Cancer Statistics, 2021*. CA Cancer J Clin 2021, 71(1):7-33.

3. Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, Bergh J, Bhattacharyya G, Biganzoli L, Cardoso MJ et al: *3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3)*. Annals of oncology : official journal of the European Society for Medical Oncology 2017.

4. Li X, Huang R, Ma L, Liu S, Zong X: *Locoregional surgical treatment improves the prognosis in primary metastatic breast cancer patients with a single distant metastasis except for brain metastasis*. Breast 2019, 45:104-112.

5. Demicheli R, Retsky MW, Swartzendruber DE, Bonadonna G: *Proposal for a new model of breast cancer metastatic development*. Annals of oncology : official journal of the European Society for Medical Oncology 1997, 8(11):1075-1080.

6. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R: *Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial*. Lancet 2001, 358(9286):966-970.
7. Ruiterkamp J, Voogd AC, Bosscha K, Tjan-Heijnen VC, Ernst MF: Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature. *Breast cancer research and treatment* 2010, 120(1):9-16.

8. Soran A, Ozbas S, Kelsey SF, Gulluoglu BM: Randomized trial comparing locoregional resection of primary tumor with no surgery in stage IV breast cancer at the presentation (Protocol MF07-01): a study of Turkish Federation of the National Societies for Breast Diseases. *The breast journal* 2009, 15(4):399-403.

9. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, Budrukkar A, Mittra I, Gupta S: Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *The Lancet Oncology* 2015, 16(13):1380-1388.

10. King TA, Lyman JP, Gonen M, Voci A, De Brot M, Boafo C, Sing AP, Hwang ES, Alvarado MD, Liu MC et al: Prognostic Impact of 21-Gene Recurrence Score in Patients With Stage IV Breast Cancer: TBCRC 013. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2016, 34(20):2359-2365.

11. Yu Y, Hong H, Wang Y, Fu T, Chen Y, Zhao J, Chen P, Cai R, Tan Y, He Z et al: Clinical Evidence for Locoregional Surgery of the Primary Tumor in Patients with De Novo Stage IV Breast Cancer. *Ann Surg Oncol* 2021.

12. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer* 2015, 136(5):E359-386.

13. Park EH, Min SY, Kim Z, Yoon CS, Jung KW, Nam SJ, Oh SJ, Lee S, Park BW, Lim W et al: Basic Facts of Breast Cancer in Korea in 2014: The 10-Year Overall Survival Progress. *Journal of breast cancer* 2017, 20(1):1-11.

14. Siegel RL, Miller KD, Jemal A: *Cancer statistics, 2018*. *CA: a cancer journal for clinicians* 2018, 68(1):7-30.

15. Lane WO, Thomas SM, Blitzblau RC, Plichta JK, Rosenberger LH, Fayanju OM, Hyslop T, Hwang ES, Greenup RA: Surgical Resection of the Primary Tumor in Women With De Novo Stage IV Breast Cancer: Contemporary Practice Patterns and Survival Analysis. *Ann Surg* 2017.

16. Pan H, Zhang K, Wang M, Ling L, Zhou W, Wang S: Palliative Local Surgery for Locally Advanced Breast Cancer Depending on Hormone Receptor Status in Elderly Patients. *Clin Breast Cancer* 2019, 19(1):e247-e260.

17. Fisher ER, Fisher B: Experimental Studies of Factors Influencing the Development of Hepatic Metastases. Xiii. Effect of Hepatic Trauma in Parabiotic Pairs. *Cancer Res* 1963, 23:896-900.

18. Folkman J: New perspectives in clinical oncology from angiogenesis research. *Eur J Cancer* 1996, 32A(14):2534-2539.

19. Al-Sahaf O, Wang JH, Browne TJ, Cotter TG, Redmond HP: Surgical injury enhances the expression of genes that mediate breast cancer metastasis to the lung. *Ann Surg* 2010, 252(6):1037-1043.

20. Badwe R, Parmar V, Hawaldar R, Nair N, Kaushik R, Siddique S, Navale A, Budrukkar A, Mittra I, Gupta S: Abstract S2-02: Surgical removal of primary tumor and axillary lymph nodes in women with metastatic breast cancer at first presentation: A randomized controlled trial. *Cancer Research* 2013, 73:S2-02-S02-02.

21. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslimanoglu M, Igci A, Canturk Z, Utkan Z, Ozaslan C, Evrensel T: Abstract S2-03: Early follow up of a randomized trial evaluating resection of the primary breast tumor in
women presenting with de novo stage IV breast cancer, Turkish study (protocol MF07-01). Cancer Research 2013, 73(24 Supplement):S2-S03.

22. Shien T, Doihara H: Resection of the primary tumor in stage IV breast cancer. World J Clin Oncol 2014, 5(2):82-85.

23. Danna EA, Sinha P, Gilbert M, Clements VK, Pulasaki BA, Ostrand-Rosenberg S: Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Res 2004, 64(6):2205-2211.

24. Rashid OM, Nagahashi M, Ramachandran S, Graham L, Yamada A, Spiegel S, Bear HD, Takabe K: Resection of the primary tumor improves survival in metastatic breast cancer by reducing overall tumor burden. Surgery 2013, 153(6):771-778.

25. Warschkow R, Guller U, Tarantino I, Cerny T, Schmied BM, Thuerlimann B, Joerger M: Improved Survival After Primary Tumor Surgery in Metastatic Breast Cancer: A Propensity-adjusted, Population-based SEER Trend Analysis. Ann Surg 2016, 263(6):1188-1198.

26. Thomas A, Khan SA, Chrischilles EA, Schroeder MC: Initial Surgery and Survival in Stage IV Breast Cancer in the United States, 1988-2011. JAMA Surg 2016, 151(5):424-431.

27. Petrelli F, Barni S: Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. Med Oncol 2012, 29(5):3282-3290.

28. Rapiti E, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP, Chappuis PO, Bouchardy C: Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 2006, 24(18):2743-2749.

29. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, Canturk Z, Utkan Z, Ozaslan C, Evrensel T et al: Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. Annals of surgical oncology 2018, 25(11):3141-3149.

Tables
| variables | Patient characteristics in raw data | Patient characteristics after propensity score weighting |
|-----------|-----------------------------------|--------------------------------------------------------|
|           | Total (n=1180) | No Surgery (n=672) | Surgery (n=508) | P value | Total (n=658) | No Surgery (n=329) | Surgery (n=329) | P value |
| Age       |                   |                   |                   |         |                   |                   |                   |         |
| ≤39       | 95                | 48                | 47                | 0.023   | 45                | 19                | 26                | 0.533   |
| 40-59     | 528               | 284               | 244               |         | 289               | 148               | 141               |         |
| ≥60       | 557               | 340               | 217               |         | 324               | 162               | 162               |         |
| Race      |                   |                   |                   |         |                   |                   |                   |         |
| Caucasian | 932               | 520               | 412               | 0.088   | 554               | 279               | 275               | 0.146   |
| African American | 167 | 108 | 59 |         | 74 | 40 | 34 |         |
| API/AI    | 79                | 42                | 37                |         | 30                | 10                | 20                |         |
| Unknown   | 2                 | 2                 | 0                 |         | 0                 | 0                 | 0                 |         |
| T stage   |                   |                   |                   |         |                   |                   |                   |         |
| T1        | 143               | 79                | 64                | 0.0001  | 71                | 36                | 35                | 0.99    |
| T2        | 403               | 185               | 218               |         | 239               | 117               | 122               |         |
| T3        | 189               | 97                | 92                |         | 117               | 58                | 59                |         |
| T4        | 303               | 187               | 116               |         | 199               | 101               | 98                |         |
| Tx        | 142               | 124               | 18                |         | 32                | 17                | 15                |         |
| Grade     |                   |                   |                   |         |                   |                   |                   |         |
| G1        | 101               | 57                | 44                | 0.0001  | 49                | 24                | 25                | 0.428   |
| G2        | 494               | 281               | 213               |         | 314               | 164               | 150               |         |
| G3/4      | 373               | 158               | 215               |         | 233               | 107               | 126               |         |
| Gx        | 212               | 176               | 36                |         | 62                | 34                | 28                |         |
| Subtype   |                   |                   |                   |         |                   |                   |                   |         |
| HR+/HER2- | 888               | 523               | 365               | 0.033   | 516               | 255               | 261               | 0.897   |
| HR-/HER2+ | 152               | 85                | 67                |         | 78                | 42                | 36                |         |
| HR+/HER2+ | 55                | 26                | 29                |         | 25                | 13                | 12                |         |
| Triple negative | 85 | 38 | 47 |         | 39 | 19 | 20 |         |
| chemotherapy | yes | 629 | 300 | 329 | 0.0001 | 360 | 180 | 180 | 1 |
| no        | 551               | 372               | 179               |         | 298               | 149               | 149               |         |
| Variables     | Full-model Cox regression analysis | Propensity-score-adjusted Cox regression analysis |
|---------------|-----------------------------------|-----------------------------------------------|
|               | HR(95%CI) | P value  | HR(95%CI)  | P value  |
| Age           |           |          |            |          |
| ≤39           | reference |          | reference  |          |
| 40-59         | 0.945(0.718-1.242) | 0.683 | 0.973(0.639-1.482) | 0.899 |
| ≥60           | 1.163(0.883-1.533) | 0.283 | 1.326(0.872-2.015) | 0.187 |
| Race          |           |          |            |          |
| Caucasian     | reference |          | reference  |          |
| African American | 1.488(1.226-1.806) | 0.0001 | 1.438(1.069-1.934) | 0.016 |
| API/AI        | 0.846(0.633-1.129) | 0.256 | 0.611(0.366-1.022) | 0.06  |
| Unknown       | 1.289(0.180-9.250) | 0.8  | N/A         | N/A    |
| T stage       |           |          |            |          |
| T1            | reference |          | reference  |          |
| T2            | 1.504(1.162-1.946) | 0.002 | 1.471(1.026-2.108) | 0.036 |
| T3            | 1.623(1.222-2.156) | 0.001 | 1.768(1.194-2.617) | 0.004 |
| T4            | 2.004(1.544-2.601) | 0.0001 | 2.162(1.498-3.119) | 0.0001 |
| Tx            | 1.536(1.135-2.077) | 0.005 | 1.287(0.724-2.288) | 0.389 |
| Grade         |           |          |            |          |
| G1            | reference |          | reference  |          |
| G2            | 1.069(0.817-1.398) | 0.629 | 1.422(0.957-2.113) | 0.081 |
| G3/4          | 1.391(1.047-1.847) | 0.023 | 1.734(1.144-2.629) | 0.01  |
| Gx            | 1.122(0.833-1.511) | 0.45  | 1.784(1.113-2.858) | 0.016 |
| Subtype       |           |          |            |          |
| HR+/HER2-     | reference |          | reference  |          |
| HR+/HER2+     | 0.683(0.537-0.869) | 0.002 | 0.708(0.503-0.995) | 0.047 |
| HR-/HER2+     | 0.771(0.519-1.146) | 0.199 | 0.622(0.357-1.229) | 0.192 |
| Triple negative | 2.139(1.635-2.798) | 0.0001 | 2.189(1.456-3.290) | 0.0001 |
| chemotherapy  |           |          |            |          |
| yes           | 0.742(0.635-1.129) | 0.0001 | 0.704(0.570-0.870) | 0.001 |
| no            | reference |          | reference  |          |
| Surgery of the primary | | | | |
| yes           | 0.657(0.562-0.769) | 0.0001 | 0.664(0.549-0.804) | 0.0001 |
| no            | reference |          | reference  |          |
Table 3 Prognostic factors for cause-specific death classification

| variables          | Full-model Cox regression analysis | Propensity-score-adjusted Cox regression analysis |
|--------------------|------------------------------------|--------------------------------------------------|
|                    | HR(95%CI)                           | P value                                          |
|                    |                                    | HR(95%CI)                                        | P value                                          |
| **Age**            |                                    |                                                  |
| ≤39                | reference                           |                                                  |
| 40-59              | 0.919(0.695-1.215)                  | 0.554                                            |
| ≥60                | 1.094(0.825-1.450)                  | 0.433                                            |
| **Race**           |                                    |                                                  |
| Caucasian          | reference                           |                                                  |
| African American   | 1.463(1.195-1.792)                  | 0.000                                            |
| API/AI             | 0.913(0.683-1.221)                  | 0.541                                            |
| Unknown            | 1.370(0.191-9.839)                  | 0.754                                            |
| **T stage**        |                                    |                                                  |
| T1                 | reference                           |                                                  |
| T2                 | 1.521(1.161-1.991)                  | 0.002                                            |
| T3                 | 1.629(1.210-2.194)                  | 0.001                                            |
| T4                 | 1.990(1.514-2.616)                  | 0.000                                            |
| Tx                 | 1.648(1.206-2.251)                  | 0.002                                            |
| **Grade**          |                                    |                                                  |
| G1                 | reference                           |                                                  |
| G2                 | 1.068(0.804-1.420)                  | 0.649                                            |
| G3/4               | 1.445(1.072-1.948)                  | 0.016                                            |
| Gx                 | 1.162(0.850-1.589)                  | 0.347                                            |
| **Subtype**        |                                    |                                                  |
| HR+/HER2-          | reference                           |                                                  |
| HR+/HER2+          | 0.687(0.536-0.881)                  | 0.003                                            |
| HR-/HER2+          | 0.795(0.530-1.192)                  | 0.268                                            |
| Triple negative    | 2.236(1.700-2.941)                  | 0.000                                            |
| **chemotherapy**   |                                    |                                                  |
| yes                | 0.757(0.643-0.891)                  | 0.001                                            |
| no                 | reference                           |                                                  |
| **Surgery of the primary** |                |                                                  |
| yes                | 0.644(0.547-0.759)                  | <0.0001                                          |
| no                 | reference                           |                                                  |

Figures
**Figure 1**

Patient Selection Flow Sheet.
Figure 2
Kaplan-Meier plot of overall survival and cancer-specific survival.
Figure 3

Kaplan-Meier plot of overall survival and cancer-specific survival after propensity score weighting.
**Figure 4**

Forest plot of overall survival subgroup analyses
Figure 5

Forest plot of cancer-specific survival subgroup analyses.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.pdf
- TableS2.pdf