Predicting the survival benefit of local surgery in patients aged 70 years or older with stage IV breast cancer: A population-based analysis

Yu-qi Chen a, b, Jia-wei Xu c, Xiao-fan Xu a, Xu-lin Wang a, Li-qun Huo a, Lu Wang a, Guo-hua Zhou b, **, Jun Gu a, **

a Research Institute of General Surgery, Affiliated Jingling Hospital, Medical School of Nanjing University /General Hospital of Eastern Theater Command, PLA, Nanjing, 210002, Jiangsu, China
b Clinical Pharmacology, Affiliated Jingling Hospital, Medical School of Nanjing University /General Hospital of Eastern Theater Command, PLA, Nanjing, 210002, Jiangsu, China

Purpose: The aim of this study was to establish individualized nomograms to predict survival outcomes in older female patients with stage IV breast cancer who did or did not undergo local surgery, and to determine which patients could benefit from surgery.

Methods: A total of 3,129 female patients with stage IV breast cancer aged ≥70 years between 2010 and 2015 were included in the Surveillance, Epidemiology, and End Results program. Multivariate Cox regression analysis was used to identify risk factors for overall survival (OS) and breast cancer-specific survival (BCSS). Survival analysis was performed using the Kaplan–Meier plot and log-rank test. Nomograms and risk stratification models were constructed.

Results: Patients who underwent surgery had better OS (HR = 0.751, 95% CI [0.668–0.843], P < 0.001) and BCSS (HR = 0.713, 95% CI [0.627–0.810], P < 0.001) than patients who did not undergo surgery. Patients with human epidermal growth factor receptor 2-positive, lung or liver metastases may not benefit from surgery. In the stratification model, low-risk patients benefited from surgery (OS, HR = 0.688, 95% CI [0.568–0.833], P < 0.001; BCSS, HR = 0.632, 95% CI [0.509–0.784], P < 0.001), while patients in the high-risk group had similar outcomes (OS, HR = 0.920, 95% CI [0.709–1.193], P = 0.509; BCSS, HR = 0.953, 95% CI [0.713–1.275], P = 0.737).

Conclusion: Older female patients with stage IV breast cancer who underwent surgery had better OS and BCSS than those who did not in each specific subgroup. Patients in low- or intermediate-risk-group benefit from surgery while those in the high-risk group do not.

© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Breast cancer (BC) is the most common cancer among women worldwide [1]. Approximately 3–25% of patients are diagnosed with stage IV BC at the initial diagnosis [2,3]. The treatment of stage IV BC is mainly systemic treatment, and the guidelines lack clear recommendations on the use of surgery in these patients.

A number of prospective and retrospective studies have explored the impact of local surgical treatment (LRT) on the prognosis of stage IV BC, and the results are still controversial [4–11]. The NCCN guidelines recommend that LRT for stage IV BC should be mainly used to solve local problems of the tumor such as ulcers, bleeding and pain, and also highlight that LRT is reasonable for a specific group of patients who benefit from systemic therapy [12]. Based on the results of a number of studies, patients with stage IV BC who tend to receive LRT or radiotherapy are younger; have smaller lesions, better molecular subtype, and less metastatic disease burden; and benefit from systemic treatment [14]. In general, LRT is only feasible when the tumor can be completely removed locally, and have no other immediately life-threatening pathology [12]. However, few studies have focused on the influence of LRT on the prognosis of older patients.

Although sub-groups analysis of the MF07-01 trial suggested
that most of the benefit was retained in patients with 55 years of age or less, not in patients older than 55 years [9], it is still meaningful to study whether older patients could benefit from surgery for the following reasons. In the MF07-01 trial, the mean age of patients in the LRT group was 51.8 ± 12.6 of which there were 59 patients aged ≥55 years, which may indicate a smaller number of older patients. In addition, breast cancer statistics have shown that the probability of a breast cancer diagnosis is highest for women in their 70s (4.1%), while breast cancer death is most likely among women in their 80s (1.0%), when divided into 10-year age groups [14]. Due to the aging trend of the population, the number of older patients with stage IV BC is likely to increase in the future. Therefore, it is valuable to explore multiple treatment methods for older patients with stage IV BC. Studying the influence of LRT on the prognosis of these patients may provide some references for future treatment methods.

Female patients with stage IV BC aged ≥70 years were selected from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015 to explore the effect of LRT on survival and prognosis.

2. Methods

2.1. Data source and patient selection

The SEER database 8.3.8 was queried for women aged ≥70 years that were diagnosed with stage IV BC with complete data from 2010 to 2015. The variables analyzed in this study included demographic characteristics (age at diagnosis, race, marital status, and benign or borderline tumor history), disease characteristics (laterality, tumor location, histological grade, molecular type, and TNM stage), treatment characteristics (breast surgery type, chemotherapy, and radiotherapy), and survival status (survival time and cause of death).

The detailed exclusion criteria are presented in Fig. 1. Patients with unknown or unspecified variable information were excluded.

2.2. Statistical analysis

Percentage and stacked histograms were used to compare the change in the proportion of patients with stage IV BC who underwent LRT and the total number of patients from 2010 to 2015. All eligible patients were randomly divided into two groups at a ratio of 2:1 comprising a training set for survival analysis and construction of nomograms and a validation set for external validation, respectively. Propensity score matching (PSM) was performed using logistic regression with a caliper width of 0.01, without replacement to balance the clinical baseline. Pearson’s chi-squared test was used for categorical feature comparison, and Student’s t-test was used for continuous feature comparison.

The results of this study were breast cancer-specific survival (BCSS) and overall survival (OS). According to the cause of death...
classification in the SEER database, BCSS was defined as the time from the date of diagnosis to the date of death from breast cancer. OS was defined as the time from the date of diagnosis to death from any cause. The survival prognoses of the different groups were analyzed using Kaplan–Meier plots and log-rank tests. Univariate and multivariate Cox analyses were used to identify independent risk factors for prognosis. Subsequently, a subgroup analysis was performed to evaluate the survival benefit of surgery in each subgroup.

All independent risk factors were included in the nomogram. Internal validation was performed in the training set, and external validation was performed in the validation set to evaluate the

### Table 1
Comparison of the clinical baseline between the surgery and non-surgery groups in the training set before and after PSM.

|                | Before PSM | After PSM | P-value |
|----------------|------------|-----------|---------|
|                | Surgery (n = 845) n% | Non-surgery (n = 1503) n% | P-value |
|                | Surgery (n = 716) n% | Non-surgery (n = 1085) n% | P-value |
| Age (years)    | 0.013      | 0.411     |         |
| 70–79          | 522(61.8)  | 849(56.5) |         |
| ≥80            | 323(38.2)  | 654(43.5) |         |
| Race           | 0.141      | 0.858     |         |
| White          | 705(83.4)  | 1245(82.8) |         |
| Black          | 103(12.2)  | 165(11.0) |         |
| Other          | 37(4.4)    | 93(6.2)   |         |
| Site           | 0.507      | 0.739     |         |
| Outer          | 270(32.0)  | 507(33.7) |         |
| Inner          | 98(11.6)   | 185(12.3) |         |
| Other          | 477(56.4)  | 811(54.0) |         |
| Grade          | 0.000      | 0.129     |         |
| I–IIa          | 393(46.5)  | 930(61.9) |         |
| III–IVb        | 452(53.5)  | 573(38.1) |         |
| Laterality     | 0.526      | 0.738     |         |
| Left           | 427(50.5)  | 780(51.9) |         |
| Right          | 418(49.5)  | 723(48.1) |         |
| ICDO           | 0.525      | 0.128     |         |
| Duct           | 675(79.9)  | 1220(81.2) |         |
| Lobular        | 110(13.0)  | 172(11.4) |         |
| Other          | 60(7.1)    | 111(7.4)  |         |
| T              | 0.460      | 0.685     |         |
| T1–2           | 464(54.9)  | 849(56.5) |         |
| T3–4           | 381(45.1)  | 654(43.5) |         |
| N              | 0.000      | 0.672     |         |
| N0             | 215(25.4)  | 487(32.4) |         |
| N1–3           | 630(74.6)  | 1016(67.6) |         |
| Radiation      | 0.000      | 0.000     |         |
| Yes            | 280(33.1)  | 50(3.3)   |         |
| No             | 565(66.9)  | 1453(96.7) |         |
| Chemotherapy   | 0.000      | 0.334     |         |
| Yes            | 329(38.9)  | 462(30.7) |         |
| No/Unknown     | 516(61.1)  | 1041(69.3) |         |
| Bone           | 0.000      | 0.145     |         |
| Yes            | 472(55.9)  | 982(65.3) |         |
| No/Unknown     | 373(44.1)  | 521(34.7) |         |
| Brain          | 0.000      | 0.316     |         |
| Yes            | 18(2.1)    | 93(6.2)   |         |
| No/Unknown     | 827(97.9)  | 1410(93.8) |         |
| Liver          | 0.000      | 0.565     |         |
| Yes            | 143(16.9)  | 322(21.4) |         |
| No/Unknown     | 702(83.1)  | 1181(78.6) |         |
| Lung           | 0.000      | 0.388     |         |
| Yes            | 237(28.0)  | 552(36.7) |         |
| No/Unknown     | 608(72.0)  | 951(63.3) |         |
| subtype        | 0.000      | 0.544     |         |
| HR+/HER2–      | 531(62.8)  | 1028(68.4) |         |
| HR+/HER2+      | 103(12.2)  | 211(14.1) |         |
| TNBC           | 147(17.4)  | 169(11.2) |         |
| Marital status | 0.020      | 0.522     |         |
| Married        | 307(36.3)  | 475(31.6) |         |
| Unmarried      | 538(63.7)  | 1028(68.4) |         |
| History        | 0.003      | 0.483     |         |
| Yes            | 546(64.6)  | 1059(70.5) |         |
| No             | 298(35.4)  | 444(29.5) |         |

* In the SEER database, grade I means well differentiated, II means moderately differentiated, III means poorly differentiated, IV means undifferentiated.
accuracy of these nomograms. In addition, the concordance index (C-index) was used to measure the discrimination of the model. Through nomograms, older patients with stage IV breast cancer were classified into low-, intermediate- and high-risk groups to predict their prognosis. Analyses were conducted using SPSS statistical software (version 22.0; IBM Corp., Armonk, NY, USA) and packages (including rms, hmisc and survival) in R software (version 4.0.3; http://www.r-project.org). X-tile software was used to select the threshold for risk stratification. Statistical significance was determined using two-tailed P < 0.05.

3. Results

3.1. Characteristics of eligible patients

From 2010 to 2015, there were a total of 454,990 older female breast cancer patients, of whom 75,698 were diagnosed with stage IV BC. The proportion of older patients with IV BC was approximately 16.64%. The number of these patients has been increasing annually; however, the proportion of patients undergoing surgery has been decreasing (Fig. 2). To study the prognosis of older patients with metastatic breast cancer, 3,129 patients were randomly divided into a training set (n = 2,348) and validation set (n = 781). There was no significant difference in the clinical baseline between the two groups (Supplementary Table 1). The clinical pathological differences in patients with or without surgery in the training set are shown in Table 1. Patients with higher grade, lymph node positivity, hormone receptor (HR)/human epidermal growth factor receptor 2 (HER2)+, triple-negative breast cancer (TNBC), bone metastases, married status, and no history of benign or borderline tumors preferred to undergo surgery (all P < 0.05).

3.2. Analysis of survival benefits from surgery

There was no significant difference in the clinical baseline between the surgery and non-surgery groups after PSM (Table 1). The median follow-up time was 16 months in the training set (interquartile range [IQR], 5–31 months) after PSM. As shown in the Kaplan–Meier plot (Fig. 3A and B), patients who underwent
surgery had better OS (HR = 0.751, 95% CI [0.668–0.843], P < 0.001) and BCSS (HR = 0.713, 95% CI [0.627–0.810], P < 0.001) than patients who did not undergo surgery. Patients aged over 80 years, who were black race, had poorly differentiated, did not undergo surgery, did not receive chemotherapy, were HR+/HER2−, had TNBC, and were unmarried had worse OS and BCSS (Fig. 3C).

### 3.3. Patients who benefit from surgery

Subgroup analysis in the training set after PSM was performed to explore which patient groups could benefit from surgery (Table 2). There was no significant difference in the prognosis of patients with liver or lung metastasis between the surgery and non-surgery groups. In addition, patients with HER2+ may not benefit from surgery.

### 3.4. Construction of nomograms and validation

According to the results of the multivariate Cox analysis (Table 3), nine variables (age, grade, T status, chemotherapy, bone metastasis, liver metastasis, subtype, marital status) were incorporated into nomograms to predict 3- and 5-year OS and BCSS for patients who underwent surgery (Fig. 4A and B). For patients who did not undergo surgery, eight variables (age, grade, chemotherapy, brain metastasis, liver metastasis, subtype, marital status and history of benign or borderline tumors) were included (Fig. 4C and D). The scores were assigned to each variable according to the point scale in each nomogram (Table 4). By evaluating the clinical factors of patients, the sum of the scores could predict the 3-year or 5-year OS and BCSS.

The credibility of the nomograms was judged through internal and external verification of the training and verification sets. The C-index of the four nomograms ranged from 0.653 to 0.705 in the internal validation and 0.684 to 0.713 in the external validation (Supplementary Table 2). Calibration curves for the 3-year and 5-year OS and BCSS predictions showed good coordination between the predictions of the model and observed outcomes (Fig. 5). Both the internal and external validations demonstrated sufficient accuracy of the models.

### 3.5. Survival benefit in risk stratification group

To better judge whether patients could benefit from surgery, a risk classification was constructed through the nomograms. A total of 1103 patients who underwent surgery and 2026 patients who did not were included in the study. After matching several independent prognostic factors, 976 patients were included in each group. There was no significant difference in clinicopathological factors between the two groups after PSM (Table 5). The score range in the risk stratification model was defined as low risk (total score 0–142), intermediate risk (total score 143–242), and high risk (total score >242) in the surgery group. In the non-surgery group, the score range in the risk stratification model was defined as low risk (total score 0–89), intermediate risk (total score 90–155), and high risk (total score >155). The prognosis of the three risk groups could be distinguished significantly by the model (Supplementary Fig. 1). As shown in the Kaplan–Meier plots (Fig. 6A–F), LRT significantly improved OS (HR = 0.688, 95% CI [0.568–0.833], P < 0.001) and BCSS (HR = 0.632, 95% CI [0.509–0.784], P < 0.001) in the low-risk group. Patients who underwent surgery in the intermediate group had better OS and BCSS than patients who did not undergo surgery.

### Table 2 Subgroup analyses of OS and BCSS outcomes. All HRs refer to surgery vs. non-surgery in the subgroup analysis.

| Factor             | OS            | P-value | BCSS         | P-value |
|--------------------|---------------|---------|--------------|---------|
| Age (years)        |               |         |              |         |
| 70–79              | 0.673(0.574,0.789) | 0.000   | 0.625(0.525,0.745) | 0.000   |
| ≥80                | 0.781(0.659,0.926) | 0.004   | 0.780(0.645,0.944) | 0.011   |
| Race               |               |         |              |         |
| White              | 0.715(0.629,0.813) | 0.000   | 0.688(0.597,0.794) | 0.000   |
| Black              | 0.718(0.518,0.996) | 0.047   | 0.684(0.476,0.982) | 0.040   |
| Site               | 0.639(0.386,1.059) | 0.082   | 0.612(0.357,1.047) | 0.073   |
| Site               | 0.725(0.592,0.888) | 0.002   | 0.708(0.565,0.887) | 0.003   |
| Other              | 0.658(0.458,0.945) | 0.023   | 0.638(0.429,0.949) | 0.026   |
| Other              | 0.719(0.616,0.838) | 0.000   | 0.682(0.574,0.809) | 0.000   |
| Grade              |               |         |              |         |
| I–II               | 0.617(0.521,0.730) | 0.000   | 0.539(0.444,0.655) | 0.000   |
| III–IV             | 0.785(0.668,0.923) | 0.003   | 0.802(0.674,0.954) | 0.013   |
| Marital status     |               |         |              |         |
| Left               | 0.762(0.648,0.896) | 0.001   | 0.786(0.658,0.938) | 0.008   |
| Right              | 0.663(0.561,0.783) | 0.000   | 0.586(0.485,0.708) | 0.000   |
| Chemotherapy       |               |         |              |         |
| Yes                | 0.685(0.554,0.847) | 0.000   | 0.667(0.530,0.840) | 0.001   |
| No/Unknown         | 0.729(0.635,0.837) | 0.000   | 0.695(0.595,0.813) | 0.000   |
| Bone               |               |         |              |         |
| Yes                | 0.649(0.558,0.754) | 0.000   | 0.646(0.548,0.763) | 0.000   |
| No/Unknown         | 0.800(0.666,0.961) | 0.017   | 0.730(0.593,0.897) | 0.003   |
| Brain              |               |         |              |         |
| Yes                | 0.494(0.246,0.992) | 0.047   | 0.480(0.217,1.060) | 0.069   |
| No/Unknown         | 0.720(0.640,0.810) | 0.000   | 0.690(0.605,0.787) | 0.000   |
| Liver              |               |         |              |         |
| Yes                | 0.879(0.685,1.127) | 0.309   | 0.851(0.651,1.112) | 0.236   |
| No/Unknown         | 0.673(0.590,0.767) | 0.000   | 0.642(0.554,0.744) | 0.000   |
| Lymph node         |               |         |              |         |
| Yes                | 0.934(0.765,1.140) | 0.502   | 0.921(0.740,1.145) | 0.458   |
| No/Unknown         | 0.631(0.547,0.728) | 0.000   | 0.595(0.507,0.699) | 0.000   |
| Subtype            |               |         |              |         |
| HR+/HER2−          | 0.668(0.577,0.773) | 0.000   | 0.619(0.525,0.731) | 0.000   |
| HR+/HER2+          | 0.822(0.591,1.145) | 0.247   | 0.770(0.541,1.095) | 0.145   |
| TNBC               | 0.675(0.432,1.056) | 0.085   | 0.725(0.446,1.179) | 0.195   |
| Marital status     |               |         |              |         |
| Married            | 0.699(0.563,0.868) | 0.001   | 0.699(0.552,0.886) | 0.003   |
| Unmarried          | 0.715(0.623,0.821) | 0.000   | 0.675(0.579,0.788) | 0.000   |
| History            |               |         |              |         |
| No                 | 0.743(0.646,0.854) | 0.000   | 0.694(0.595,0.809) | 0.000   |
| Yes                | 0.658(0.535,0.810) | 0.000   | 0.673(0.531,0.854) | 0.001   |
(HR = 0.842, 95% CI [0.711–0.998], P = 0.043) and similar BCSS (HR = 0.857, 95% CI [0.710–1.031], P = 0.099). However, there were no significant differences in OS (HR = 0.920, 95% CI [0.709–1.193], P = 0.509) and BCSS (HR = 0.953, 95% CI [0.713–1.275], P = 0.737) between patients who did and did not undergo surgery in the high-risk group.

4. Discussion

A large sample of older female patients with stage IV BC was selected from the SEER database to explore the effect of LRT on prognosis in this study. The total number of these patients has been increasing annually, which may be related to the increase in the size of...
of the older population, and to the higher incidence of BC in women of this age [14]. The proportion of patients who choose LRT has declined, which may be due to the development of systemic treatments, including paclitaxel-based chemotherapy, molecular targeted therapy, endocrine therapy, and immunotherapy [15–17].

Stage IV BC patients aged 70–79 years, with poorly differentiated or undifferentiated tumor, with lymph node-positive disease, who received chemotherapy, with TNBC, with married status, or with a history of benign or borderline tumors were more likely to receive LRT, which is consistent with the results of multiple retrospective analyses that patients who choose surgery may be younger, have a higher histological grade, and have fewer metastases or only have bone metastases [13]. After adjusting for confounding factors, the prognosis of the surgery group was better than that of the non-surgery group (OS, HR = 0.751, 95% CI [0.668–0.843], P < 0.001. BCSS, HR = 0.713, 95% CI [0.627–0.810], P < 0.001). Subgroup analysis found that patients with liver or lung metastases did not benefit from surgery as well as HER2+ patients.

Although a number of retrospective analyses have recognized that LRT is beneficial to the prognosis of specific patients [18–21], there are still inconsistencies in which patients could benefit. A retrospective analysis from the Epidemiological Strategy and Medical Economics (EMSE) database suggested that patients with visceral metastases can also benefit from surgery, but patients with TNBC cannot [18]. Another retrospective analysis from EMSE proposed that LRT can improve the prognosis of all patients with stage IV BC, except those with TNBC [19]. A retrospective analysis from the National Cancer Database of America found that both HR+ and HER2+ patients could benefit from surgery and that it was better to

Fig. 4. Nomograms for predicting 3- and 5-year OS and BCSS in older patients with stage IV BC. (A) OS for patients who underwent surgery. (B) BCSS for patients who underwent surgery. (C) OS for patients who did not undergo surgery. (D) BCSS for patients who did not undergo surgery.

Table 4
Clinical variable scores in each nomogram.

| Variable        | Surgery OS | Surgery BCSS | Non-surgery OS | Non-surgery BCSS |
|-----------------|------------|--------------|----------------|------------------|
| Age (years)     | 0 0        | 38 36        | 70–79          | 0 0              |
| Grade I–II      | 0 0        | 23 42        | I–II           | 0 0              |
| T1–2            | 0 0        | 21 28        | HR+/HER2−/TNBC | 0 0              |
| Chemotherapy    | 0 0        | 5 0          | Brain          | 0 0              |
| Marital status  | 0 0        | 5 0          | Yes            | 0 0              |
| Bone            | 66 58      | 5 0          | HR+/HER2−/TNBC | 0 0              |
| Liver           | 0 0        | 3 0          | HR+/HER2+      | 0 0              |
| Tumor type      | 0 0        | 100 100      | HR+/HER2−/TNBC | 0 0              |
| Marital status  | 0 0        | 15 16        | HR+/HER2+      | 0 0              |
| Lung            | 50 59      | 24 24        | HR+/HER2−/TNBC | 0 0              |
| Subtype         | 0 0        | 82 88        | Marital status | 0 0              |
| Marital status  | 0 0        | 28 28        | Married        | 0 0              |
| History         | 0 0        | 0 0          | Unmarried      | 0 0              |

Y.-q. Chen, J.-w. Xu, X.-f. Xu et al. The Breast 59 (2021) 124–134
undergo neoadjuvant therapy before surgery [20]. The existence of these differences may be due to the inconsistent clinical factors in the population included in each analysis, including age, treatment methods, reasons for choosing surgery, diagnostic criteria in various regions, and subjective factors of clinicians.

Thus, high-quality prospective studies may provide valuable conclusions. The TATA trial found that LRT did not improve the prognosis of patients with stage IV BC who were sensitive to systemic treatment, although LRT can reduce local progression, it may also lead to distant metastasis [8]. The TCRRC 013 trial also found that surgery did not improve OS in patients with stage IV BC who benefited from systemic therapy [22]. In the E2018 trial, patients who benefitted from systemic treatment had similar three-year OS and progression-free survival between the surgery and nonsurgery groups [23]. In the ABCSG 28 trial, it was found that surgery did not affect the prognosis of untreated stage IV BC patients and would reduce the quality of life of these patients [10]. All of the above four prospective studies had negative results. However, due to the shortcomings of these trials, such as the baseline imbalance in the TRCBR 013 trial, the imbalance in the HER2-targeted therapy

Fig. 5. Calibration curves for nomograms in training set (A) and validation set (B). The 45° blue dotted line represents the ideal reference, which means the nomograms-predicted survival probabilities (x-axis) exactly match the actual survival proportions (y-axis). Red dots represent nomogram-predicted probabilities for each group, and blue error bars represent the 95% CIs of these estimates.
Table 5  
Comparison of baseline between surgery and non-surgery groups after PSM.

|          | Surgery (n = 976) n% | Non-surgery (n = 976) n% | P-value |
|----------|----------------------|--------------------------|---------|
| Age(years) |                      |                          |         |
| 70–79    | 595(61.0)            | 579(59.3)                | 0.460   |
| ≥80      | 381(40.0)            | 397(40.7)                |         |
| Race     |                      |                          |         |
| White    | 805(82.5)            | 822(84.2)                | 0.069   |
| Black    | 130(13.3)            | 101(10.4)                |         |
| Other    | 41(4.2)              | 53(5.4)                  |         |
| Site     |                      |                          |         |
| Outer    | 316(32.4)            | 310(31.8)                | 0.868   |
| Inner    | 110(11.2)            | 105(10.8)                |         |
| Other    | 550(56.4)            | 561(57.4)                |         |
| Grade    |                      |                          |         |
| I–II     | 497(50.9)            | 515(52.8)                | 0.415   |
| III–IV   | 479(49.1)            | 461(47.2)                |         |
| Laterality |                    |                          |         |
| Left     | 482(49.4)            | 515(52.8)                | 0.133   |
| Right    | 494(50.6)            | 461(47.2)                |         |
| ICDO     |                      |                          |         |
| Duct     | 778(79.7)            | 798(81.8)                | 0.062   |
| Lobular  | 137(14.0)            | 105(10.8)                |         |
| Other    | 61(6.3)              | 73(7.5)                  |         |
| T        |                      |                          |         |
| T1–2     | 528(54.1)            | 518(53.1)                | 0.650   |
| T3–4     | 448(45.9)            | 458(46.9)                |         |
| N        |                      |                          |         |
| N0       | 250(25.6)            | 310(31.8)                | 0.001   |
| N1–3     | 726(74.4)            | 666(68.2)                |         |
| Radiation|                      |                          |         |
| Yes      | 311(31.9)            | 38(3.9)                  | 0.000   |
| No       | 665(68.1)            | 938(96.1)                |         |
| Chemotherapy |            |                          |         |
| Yes      | 346(35.5)            | 332(34.0)                | 0.506   |
| No/Unknown|                  |                          |         |
| Bone     | 630(64.5)            | 644(66.0)                | 0.357   |
| No/Unknown|                  |                          |         |
| Brain    | 587(60.1)            | 567(58.1)                |         |
| No/Unknown|                  |                          |         |
| Yes      | 389(39.9)            | 409(41.9)                | 0.089   |
| No       | 26(2.7)              | 27(2.8)                  |         |
| No/Unknown|                  |                          |         |
| Liver    | 950(97.3)            | 949(97.2)                | 0.858   |
| No/Unknown|                  |                          |         |
| Yes      | 170(17.4)            | 173(17.7)                | 0.488   |
| No       | 806(82.6)            | 803(82.3)                |         |
| Lung     |                      |                          |         |
| Yes      | 296(30.3)            | 282(28.9)                | 0.137   |
| No/Unknown|                  |                          |         |
| No/Unknown|                  |                          |         |
| No/Unknown|                  |                          |         |
| HR−/HER2− | 648(66.4)            | 637(65.3)                | 0.569   |
| HR+/HER2+ |                  |                          |         |
| TNBC     | 104(10.6)            | 130(13.3)                |         |
| Marital status | |                  |         |
| Married  | 347(35.6)            | 335(34.3)                | 0.569   |
| Unmarried| 629(64.4)            | 641(65.7)                |         |
| History  |                      |                          |         |
| No       | 649(66.5)            | 643(65.9)                | 0.774   |
| Yes      | 327(33.5)            | 333(34.1)                |         |

In this study, nomograms were constructed to predict the prognosis of stage IV BC patients after 3 or 5 years, which may be used as a reference for clinicians to decide whether to perform surgery in these patients. However, for older patients with metastatic tumors, the survival prognosis may not be the key to their well-being compared with other endpoints, such as functional status, quality of life and complications with standard therapy options [24,25]. Unfortunately, no relevant data were recorded in the SEER database. In the MF07 trial, patients were found to have similar physical or mental states, regardless of whether they received LRT [26]. Similarly, the ABCSG 28 trial also supported that LRT did not improve quality of life [27]. According to the E2018 trial, although surgery reduced the proportion patients with local regional recurrence or progression in three years, it did not improve health-related quality of life [23]. However, a retrospective analysis from China suggested that the quality of life in patients with de novo stage IV BC can be improved by reducing the incidence of local symptoms through primary tumor surgery [28]. Several cases have reported that LRT could solve local problems, improve the quality of life of patients, and reduce the psychological pressure of advanced BC [29]. However, the populations of the above-mentioned studies were not older patients, and the research in each region has certain biases, such as diagnostic criteria and health status assessment criteria. In addition, the factors affecting the quality of life in patients with BC is complex, including education, age, social support, smoking, and the presence or absence of children [30], which may lead to difficulties in assessment. Therefore, more relevant prospective studies are required.

There were some limitations to this study. For example, the SEER database did not collect information such as Ki67 status, chemotherapy regimen, use of molecular targeted therapy, and endocrine therapy which may influence prognosis. In addition, patients' health status, comorbid disease and complications were not collected, which may lead to the possibility that some patients with better health status may choose surgery and obtain a better prognosis. Because of the complex underlying disease and low tolerance to complications, it is important for clinicians to assess whether older patients can withstand the stress of surgery. A full geriatric population in the TATA trial, and the poor recruitment of the ABCSG 28 trial, the results should be discussed objectively. The MF07 study found that patients younger than 55 years old, with HR−, HER2− status and bone metastases alone can benefit from surgery [9]. This trial aimed to perform surgery before systemic treatment, and did not pay attention to the effect of systemic treatment, which may indicate that surgery that reduces tumor burden may have a positive effect on subsequent comprehensive treatments and may also reduce the number of drug-resistant tumor cells. However, MF07 also had a problem with imbalanced clinical pathological factors between the two groups, especially HR status. More prospective trials are needed to clarify the value of LRT, such as the JCOG1017 trial in Japan, the NCT01392586 trial in the Netherlands, and NCT01242800 trial in the United States.
assessment is needed for all older patients with tumors when developing individual treatment plans, including functional status, psychological health, polypharmacy, comorbidities, nutrition, social support, and cognitive ability [24]. In addition, the possibility of late diagnosis of metastatic disease could also affect the interpretation of the results (for the SEER database, initial de novo breast cancer is defined if metastases are diagnosed within the first four months after diagnosis). In addition, the nomograms constructed in this study still lack verification in real-world patients. The existence of these shortcomings may lead to certain limitations in the research results, and more relevant high-quality prospective studies are needed.

5. Conclusion

Older female patients with stage IV BC who underwent surgery had better OS and BCSS than those without in a specific subgroup. Nomograms may be used as an auxiliary method to help clinicians judge whether it is appropriate to perform LRT.

Author contributions

YQC: formal analysis, investigation, visualization, writing—original draft and writing—review and editing. JWX: formal analysis, data curation, methodology, supervision, and validation. XFX, LQH and LW: writing—review and editing, data curation. GJ, GHZ: conceptualization, funding acquisition, project administration, resources, supervision, writing, review, and editing. All authors read and approved the final manuscript.

Availability of data and materials

Please contact the author for data requests.
Consent for publication
Not applicable.

Funding
This work was supported by grants from the Jiangsu Province Science and Technology Project of China (No. 2017726 for Jun Gu).

Declaration of competing interest
None.

Acknowledgments
We would like to thank the researchers and study participants for their contributions.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.06.007.

References
[1] Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2020;70:7e30. https://doi.org/10.3322/caac.21590.
[2] Arciero C, Liu Y, Gillespie T, Subbedar P. Surgery and survival in patients with stage IV breast cancer. Breast J 2019;25:644-653. https://doi.org/10.1111/tbj.13296.
[3] Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2019;69:7-34. https://doi.org/10.3322/caac.21551.
[4] Lane WD, Thomas SM, Blitzblau RC, Plichia JK, Rosenberger LH, Fayanju OM, et al. Surgical resection of the primary tumor in women with de novo stage IV breast cancer: contemporary practice patterns and survival analysis. Ann Surg 2019;269:337-44. https://doi.org/10.1097/SLA.0000000000002821.
[5] 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;45:104-12. https://doi.org/10.1016/j.breast.2019.03.006.
[6] Choi SH, Kim JW, Choi J, Sohn J, Kim SI, Park S, et al. Locoregional treatment of the primary tumor in patients with de novo stage IV breast cancer: a radiation oncologist’s perspective. Clin Breast Can 2018;18:e167–78. https://doi.org/10.1002/cbc2.10002.
[7] Xiao W, Zou Y, Zheng S, Hu X, Liu P, Xie X, et al. Primary tumor resection in stage IV breast cancer: a systematic review and meta-analysis. Eur J Surg Oncol 2018;44:1504–12. https://doi.org/10.1016/j.ejso.2018.08.002.
[8] Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, et al. Locoregional treatment versus no treatment of the primary tumor in patients with metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol 2015;16:1380–8. https://doi.org/10.1016/S1470-2045(15)00135-7.
[9] Soran A, Ozmen V, Ozbas S, Karkanik H, Muslimanoglu M, Iigo AA, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: protocol MF07-01q. Ann Surg Oncol 2018;25:3141–9. https://doi.org/10.1245/s10434-018-6494-6.
[10] Fitzal F, Bjelic-Radisic V, Knauer M, Steger G, Hubalek M, Balic M, et al. Impact of breast surgery in primary metastasized breast cancer: outcomes of the prospective randomized phase III ABCSG-28 POSITIVE trial. Ann Surg Oncol 2019;26:1163–9. https://doi.org/10.1245/s10434-00002271.
[11] Ma L, Mi Y, Cui S, Wang H, Jiang Z. Role of locoregional surgery in patients with de novo stage IV breast cancer: analysis of real-world data from China. Sci Rep 2020;10:1832. https://doi.org/10.1038/s41598-020-75119-0.
[12] Matthew P, William J, Benjamin O, Abraham J, Aft Rebecca, Kimberly H, et al. NCCN guidelines insights: breast cancer. Version 3.2018. J Natl Compr Canc Netw 2019;17:118–26. https://doi.org/10.6004/jnccn.2019.0009.
[13] Gera R, Chehade H, Wazir U, Tayeh S, Mokbel K. Locoregional therapy of the primary tumour in de novo stage IV breast cancer in 216 066 patients: a meta-analysis. Sci Rep 2020;10:2952. https://doi.org/10.1038/s41598-020-59908-1.
[14] Desantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Sauer AG, et al. Breast cancer statistics, 2019. CA A Cancer Journal for Clinicians 2019;69:438–51. https://doi.org/10.3332/caac.21583.
[15] Tyagi NK, Dhsey-Thind S. Clinical practice guidelines in breast cancer. Curr Oncol 2018;25:5315–60. https://doi.org/10.3747/cj.25.3.729.
[16] Harbeck N, Grant M. Breast cancer. Lancet 2017;389:1134–50. https://doi.org/10.1016/S0140-6736(16)31891-8.
[17] Peng F, Li J, Mu S, Cai L, Hu Y. Epidemiological features of primary breast lymphoma patients and development of a nomogram to predict survival. Breast 2021;57:49–61. https://doi.org/10.1016/j.breast.2021.03.006.
[18] Hotton Lusque A, Leufflen L, Campone M, Levy C, Honart JF, et al. Early locoregional breast surgery and survival in de novo metastatic breast cancer in the multicenter national exem cohort. Ann Surg 2021. https://doi.org/10.1097/SLA.00000000000004776.
[19] Pons-Tostivint E, Kirova Y, Lusque A, Campone M, Geffrotel J, Mazzoni C, et al. Survival impact of locoregional treatment of the primary tumor in de novo metastatic breast cancers in a large multicentric cohort study: a propensity score-matched analysis. Ann Surg Oncol 2018;26:356–65. https://doi.org/10.1245/s10434-018-6831-9.
[20] Stahl K, Wong W, Dodge D, Brooks A, Shen C. Benefits of surgical treatment of stage IV breast cancer for patients with known hormone receptor and her2 status. Ann Surg Oncol 2020;28:2646–58. https://doi.org/10.1245/s10434-020-09244-5.
[21] Lin Y, Huang K, Zeng Z, Zhang J, Song C. Impact of breast surgery on survival of patients with stage IV breast cancer: a seer population-based propensity score matching analysis. PeerJ 2020;8:e8694. https://doi.org/10.7717/peerj.8694.
[22] King TA, Lyman G, Gonen M, Reyes S, Hwang E, Rugo HS, et al. A prospective analysis of surgery and survival in stage IV breast cancer (bcem 013). J Clin Oncol 2016;34:1006. https://doi.org/10.1200/JCO.2016.34.15_suppl.1006.
[23] Khan Seema Ahsan, Zhao Fengmin, Solin Lawrence J, Goldstein Lori J, Cella David, Basik Mark, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: a trial of the ECOG-ACRIN Research Group (E2188). J Clin Oncol 2020;38:18LB2. https://doi.org/10.1200/JCO.2020.38.18_suppl.18LB2.
[24] Loh KP, Soto-Perez-De-Celis E, Hsu T, De Glas NA, Battisti N, Baldini C, et al. What every oncologist should know about geriatric assessment for older patients with cancer: young international society of geriatric oncology position papers. Journal of Oncology Practice 2018;14:85. https://doi.org/10.1200/JOP.2017.026435.
[25] Matthys MB, Dempsey AM, Melisko ME, Dreher N, Che ML, Veer LJ, et al. Incorporation of patient-reported outcomes measurement information system to assess quality of life among patients with breast cancer initiating care at an academic center. Cancer; 2021.https://doi.org/10.1002/cncr.33496.
[26] Soran A, Soyder A, Ozbas S, Ozmen V, Seginz E. The role of loco-regional treatment in long-term quality of life in de novo stage IV breast cancer patients: protocol M07-01q. Support Care Canc 2020;28:1025. https://doi.org/10.1186/s12885-020-06894-2.
[27] Si Y, Yuan P, Hu N, Wang X, Xu B. Primary tumor surgery for patients with de novo stage iv breast cancer can decrease local symptoms and improve quality of life. Ann Surg Oncol 2020;27:1025–33. https://doi.org/10.1245/s10434-019-09092-2.
[28] Kai M, Kubo M, Kawai H, Kurata K, Mori H, Yamada M, et al. Qel-enhancing surgery for patients with her2-positive metastatic breast cancer. BMJ Support Palliat Care 2019;9:151–4. https://doi.org/10.1136/bmjspcare-2018-001622.
[29] Larrea-Baz N, Pérez-Gómez B, Guerrero-Zotano Ángel, Casas AM, Pollán M. Primary breast cancer and health related quality of life in Spanish women: the epigescan case-control study. Sci Rep 2020;10:7741. https://doi.org/10.1038/s41598-020-63637-w.