The role of adjuvant chemotherapy in stage I–III male breast cancer: a SEER-based analysis

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Abstract

Background and aims: Male breast cancer is an uncommon disease. The benefit of adjuvant chemotherapy in the treatment of male breast cancer patients has not been determined. The aim of this study was to explore the value of adjuvant chemotherapy in men with stage I–III breast cancer, and we hypothesized that some male patients may safely skip adjuvant chemotherapy.

Methods: Male breast cancer patients between 2010 and 2015 from the Surveillance Epidemiology and End Results database were included. Univariate and multivariate Cox analyses were used to analyse the factors associated with survival. The propensity score matching method was adopted to balance baseline characteristics. Kaplan–Meier curves were used to evaluate the impacts of adjuvant chemotherapy on survival. The primary endpoint was survival.

Results: We enrolled 514 patients for this study, including 257 patients treated with chemotherapy and 257 patients without. There was a significant difference in overall survival (OS) but not in breast cancer-specific survival (BCSS) between the two groups \( p < 0.001 \) for OS and \( p = 0.128 \) for BCSS, respectively. Compared with the non-chemotherapy group, the chemotherapy group had a higher 4-year OS rate (97.5% versus 95.2%, \( p < 0.001 \)), while 4-year BCSS was similar (98% versus 98.8%, \( p = 0.128 \)). The chemotherapy group had longer OS than the non-chemotherapy group among HR+, HER2–, tumour size > 2 cm, lymph node-positive male breast cancer patients \( p < 0.05 \). Regardless of tumour size, there were no differences in OS or BCSS between the chemotherapy and non-chemotherapy cohorts for lymph node-negative patients (OS: \( p > 0.05 \), BCSS: \( p > 0.05 \)). Adjuvant chemotherapy showed no significant effects on both OS and BCSS in patients with stage I (OS: \( p = 0.100 \), BCSS: \( p = 0.858 \)) and stage IIA breast cancer (OS: \( p > 0.05 \), BCSS: \( p > 0.05 \)).

Conclusion: For stage I and stage IIA patients, adjuvant chemotherapy could not improve OS and BCSS. Therefore, adjuvant chemotherapy might be skipped for stage I and stage IIA male breast cancer patients.

Keywords: chemotherapy, male breast cancer, prognosis, SEER, stage I–III

Introduction

Male breast cancer is an uncommon and rare malignancy, which accounts for only 1% of all breast cancer cases diagnosed worldwide and 1% of all male cancers.\(^1\,2\) In contrast to female patients, male breast cancer patients tend to have more frequent lymph node metastases and a higher percentage of oestrogen receptor-positive (ER+) or progesterone receptor-positive (PR+) tumours.\(^3\) Moreover, male breast cancer is more...
frequently associated with inherited mutations in the BRCA2 gene but less frequently with the BRCA1 gene than female breast cancer.4

According to epidemiology studies, approximately 25,000 male breast cancers are diagnosed annually in China and around 8000 men died of breast cancer each year, while in the United States, approximately 2670 cases of male breast cancer were newly diagnosed in 2019 and approximately 500 men died of breast cancer that year.5,6 The incidence of male breast cancer has been increasing in recent years, but it varies significantly by geographical region.7–9 Because of its rarity, few clinical trials specifically focus on how to treat male breast cancer. Therefore, clinicians have to extrapolate treatment strategies for male breast cancer from the data and treatment guidelines for female breast cancer.10

Several large clinical trials have shown that some women with breast tumour >1 cm may avoid adjuvant chemotherapy without reducing the overall survival rate.11 For example, the TAILORx trial12,13 was a prospective and randomized trial for women with hormone receptor-positive, human epidermal growth factor receptor 2-negative, stage T1–2, lymph node-negative and recurrence score (RS) of 11–25 breast cancers (HR+, HER2–, T1–2, N0, M0, RS 11–25), in which the patients received adjuvant endocrine therapy alone or adjuvant chemotherapy followed by endocrine therapy. The two groups had similar treatment efficacy and no significant differences in disease-free survival (DFS) or overall survival (OS). It has been suggested that female patients (HR+, HER2−, T1–2, N0, M0, RS <25) could be treated with endocrine therapy alone, which allows many women to avoid excessive adjuvant chemotherapy.

However, whether adjuvant chemotherapy is necessary for all men with breast cancer is unclear. We hypothesized that there are some male patients with stage I–III breast cancer who could avoid adjuvant chemotherapy, similar to female patients. To verify this hypothesis, we conducted this study by using the Surveillance Epidemiology and End Results (SEER) database to explore the relationship between adjuvant chemotherapy and survival outcomes in stage I–III male breast cancer patients and to determine whether any male patient could safely skip adjuvant chemotherapy.

Materials and methods

Database
We used the SEER database, which is the population-based registry for incident cancers in the United States and is broadly representative of the nation as a whole.14 SEER-based estimates of breast-cancer mortality are virtually identical to those ascertained from US mortality data,15 and the SEER programme has had virtually complete case ascertainment and reporting for decades. We obtained data from the SEER*Stat software, version 8.3.6. This study was exempted by the ethics committee of the Guangdong Provincial People’s Hospital because our data were from the SEER database, which is open to the public.

Study population
We first identified 1395 male breast cancer patients from 2010 to 2015 according to the following criteria: male breast cancer patients aged over 18 years old; only primary cancer; ductal and/or lobular carcinoma; detailed information about grade, stages, ER status, PR status and HER2 status was available; and detailed data about survival was available (Figure 1). We used propensity score matching (PSM) to reduce the imbalance between the two groups and the final cohort consisted of 514 patients, including 257 patients treated with chemotherapy and 257 patients without.

Statistical analysis
We used IBM SPSS Statistics 24.0 software to analyse all of the data. The chi-squared test was used to compare categorical variables across the chemotherapy and non-chemotherapy groups. Our outcome of interest was survival, including OS and breast cancer-specific survival (BCSS). OS was defined as the time from the diagnosis of breast cancer to the date of death from any cause; and BCSS was defined as the survival time from the diagnosis of breast cancer to the date of death caused by breast cancer.16 OS and BCSS between the chemotherapy and non-chemotherapy groups were compared with Kaplan–Meier plots, which were generated to determine differences in their survival. Subgroup analysis of the effects of various factors on OS and BCSS between the two groups was conducted using the Kaplan–Meier curves. Univariate and multivariate analysis to identify factors associated with survival
were conducted using Cox proportional hazards regression models. We included the variables that had $p<0.05$ in the univariate analysis or were considered clinically worth exploring in the multivariate analysis. To balance the differences and impacts of the baseline characteristics, a 1:1 paired match, by the PSM method, was also carried out. All tests were two-sided, and $p<0.05$ in the statistical test results was considered statistically significant.

**Results**

**Patient baseline characteristics**

We first analysed 1395 patients, including 567 with chemotherapy and 828 without chemotherapy. In our study, the median follow-up period was 38 months (range: 0–83 months). The majority of patients in the chemotherapy group were younger than 65 years old, while they were more likely to be over 65 years old in the non-chemotherapy group. Patients younger than 65 years old in the chemotherapy group and patients older than 65 years old in the non-chemotherapy group were 60.7% and 65.5%, respectively. In our cohort, 97.8% were positive for the oestrogen receptor, 91.8% were positive for the progesterone receptor and 87.8% were negative for the human epidermal growth factor receptor 2.

Before matching, the chi-squared test results showed that significant differences between the two groups were observed for age ($p<0.001$), grade ($p<0.001$), AJCC stage ($p<0.001$), tumour size ($p<0.001$), lymph node (LN) status ($p<0.001$), ER status ($p=0.011$), PR status ($p=0.012$), HER2 status ($p<0.001$) and radiation ($p<0.001$). To minimize the disturbance of confounding factors and to reduce the imbalance
between the two groups, we used a 1:1 (chemotherapy/non-chemotherapy) matched analysis with a caliper of 0.001 by PSM. Ten variables were included in the PSM, including age, grade, AJCC stage, tumour size, LN status, ER status, PR status, HER2 status and radiation. Because of the imbalance in these variables in the two groups (all \( p < 0.05 \)), we used the PSM for these variables in order to minimize the selection bias. After matching, no statistically significant differences (\( p > 0.05 \)) were found for all of the characteristics between the two groups, thus indicating that the variables were well balanced. Finally, 514 patients were obtained in the study, including 257 patients in the chemotherapy group and 257 patients in the non-chemotherapy group. The demographics and clinicopathological characteristics of the enrolled patients before and after PSM are listed in Table 1.

**Survival analysis for all stage I–III patients**

We used the Kaplan–Meier method to evaluate the OS and BCSS of the chemotherapy and non-chemotherapy groups. The median follow-up was 40 months (range: 1–83 months) versus 36 months (range: 1–82 months) in the chemotherapy group and non-chemotherapy group, respectively. In general, adjuvant chemotherapy could significantly improve OS (before PSM: \( p = 0.001 \); after PSM: \( p < 0.001 \)) but not BCSS (before PSM: \( p = 0.083 \); after PSM: \( p = 0.128 \)) (Figure 2). As shown in Table 2, the 4-year OS was 97.5% in the chemotherapy group and 95.2% in the non-chemotherapy group (\( p < 0.001 \)), while the 4-year BCSS of the chemotherapy group was similar to the non-chemotherapy group, which was 98% versus 98.8% (\( p = 0.128 \)).

**Survival analysis stratified by clinical characteristics**

We further constructed Kaplan–Meier survival curves and conducted a pair-wise comparison among different receptors status, stage, tumour size and LN status to explore the different effects of these factors on the chemotherapy group and non-chemotherapy group. We found that chemotherapy was a better prognostic indicator for OS in patients with HR+ (\( p < 0.001 \); Figure 3A) and HER2− (\( p < 0.001 \); Figure 3E) and grade I–III (\( p < 0.05 \); Figure 4A–C), but not for BCSS (\( p > 0.05 \); Figure 3C, D, G, H; Figure 4D, E). A better prognostic value of adjuvant chemotherapy for OS also existed for patients with stage II (\( p = 0.003 \); Figure 5B) and stage III breast cancer (\( p = 0.006 \); Figure 5C). Adjuvant chemotherapy showed no significant effects on both OS and BCSS in patients with stage I breast cancer (5-year OS: 91.8% versus 83.1%, \( p = 0.100 \); 5-year BCSS: 93.1% versus 95.9%, \( p = 0.858 \)). Since most of the male breast cancer patients were HR+/HER2−, we further investigated the effects of tumour size and LN status in HR+/HER2− cases between the two groups. There were no OS or BCSS differences for the chemotherapy and the non-chemotherapy cohorts among LN-negative patients (OS: \( p > 0.05 \); BCSS: \( p > 0.05 \); Figure 6A–F). The chemotherapy group had a longer OS than the non-chemotherapy group for HR+, HER2−, tumour size >2 cm, LN-positive male breast cancer (\( p < 0.05 \); Figure 6H and I), but it had no difference for BCSS (Figure 6J–L).

**Subgroup analysis for all stage I–III breast cancer patients**

In the univariate analysis, age, marital status, stage, tumour size, LN status, HER status, surgery and chemotherapy (all \( p < 0.05 \)) were associated with OS, while the significant predictors of BCSS in patients were marital status, stage, tumour size and surgery (all \( p < 0.05 \)) (Table 3). After multivariate analysis, age, marital status, stage, tumour size, LN status, surgery, and chemotherapy were significant independent predictors of OS (all \( p < 0.05 \)), and only marital status was significantly independent predictors of BCSS (\( p < 0.05 \) (Table 4).

**Discussion**

As male breast cancer is a rare disease, there is a lack of treatment guidelines and clinical trials specially focused on male breast cancer patients. In the present study, tumour stage, grade and ER status were independent prognostic factors for OS. Therefore, to further understand the association between adjuvant chemotherapy and the survival of stage I–III male breast cancer patients, we stratified the patients by tumour grade, surgery and receptor status, tumour size and LN status. The data of HER2 status were available only after 2010 due to limitations in the SEER database. We enrolled data between 2010 and 2015 in order to ensure the accuracy of the data and ensure that the follow-up time was more than 5 years. The patients’ median age was 65.5 years, approximately 5–10 years older than the average age at diagnosis for women, which may be...
| Variables     | Data before PSM | Data after PSM |
|---------------|-----------------|----------------|
|               | Chemotherapy     | Non-chemotherapy |       | Chemotherapy     | Non-chemotherapy |
|               | \(n = 567\)     | \(n = 828\)    |       | \(n = 257\)     | \(n = 257\)     |
|               | \(p\) value     | \(p\) value    |       | \(p\) value     | \(p\) value    |
| Age [%]       |                 |                 |       |                 |                 |
| < 65 years    | 344 (60.7)      | 286 (34.5)      | <0.001 | 114 (44.4)      | 112 (43.6)      | 0.859           |
| ≥ 65 years    | 223 (39.3)      | 542 (65.5)      |       | 143 (55.6)      | 145 (56.4)      |                 |
| Marital status [%] | 0.599            |               |       | 0.158           |                 |
| Married       | 372 (65.6)      | 549 (66.3)      |       | 175 (68.1)      | 167 (65.0)      |                 |
| Unmarried     | 166 (29.3)      | 228 (27.5)      |       | 71 (27.6)       | 85 (33.1)       |                 |
| Unknown       | 29 (5.1)        | 51 (6.2)        |       | 11 (4.3)        | 5 (1.9)         |                 |
| Race [%]      |                 |                 |       |                 |                 |
| White         | 447 (78.8)      | 665 (80.3)      |       | 211 (82.1)      | 217 (84.4)      | 0.772           |
| Black         | 83 (14.6)       | 115 (13.9)      |       | 37 (14.4)       | 31 (12.1)       | 0.736           |
| Other         | 37 (6.5)        | 48 (5.8)        |       | 9 (3.5)         | 9 (3.5)         |                 |
| Grade [%]     |                 |                 | <0.001 |                 |                 |
| I             | 29 (5.1)        | 118 (14.3)      |       | 14 (5.4)        | 16 (6.2)        | 0.707           |
| II            | 268 (47.3)      | 480 (58.0)      |       | 131 (51.0)      | 138 (53.7)      |                 |
| III           | 270 (47.6)      | 230 (27.8)      |       | 112 (43.6)      | 103 (40.1)      |                 |
| Laterality [%]|                 |                 |       |                 |                 |
| Left          | 320 (56.4)      | 439 (53.0)      |       | 141 (54.9)      | 130 (50.6)      | 0.208           |
| Right         | 247 (43.6)      | 389 (47.0)      |       | 116 (45.1)      | 127 (49.4)      | 0.331           |
| Stage [%]     |                 |                 | <0.001 |                 |                 |
| I             | 90 (15.9)       | 387 (46.7)      |       | 74 (28.8)       | 69 (26.8)       | 0.632           |
| II            | 292 (51.5)      | 364 (44.0)      |       | 142 (55.3)      | 139 (54.1)      |                 |
| III           | 185 (32.6)      | 77 (9.3)        |       | 41 (16.0)       | 49 (19.1)       |                 |
| Tumour size [%]|                 |                 | <0.001 |                 |                 |
| T \(\leq 2\) cm | 194 (34.2)   | 4445 (53.7)    |       | 96 (37.4)       | 105 (40.9)      | 0.669           |
| 2 < T \(\leq 5\) cm | 292 (51.5) | 335 (40.5)    |       | 136 (52.9)      | 126 (49.0)      |                 |
| T > 5 cm      | 81 (14.3)       | 48 (5.8)        |       | 25 (9.7)        | 26 (10.1)       |                 |
| LN status [%] |                 |                 | <0.001 |                 |                 |
| Positive      | 180 (31.7)      | 602 (72.7)      |       | 124 (48.2)      | 131 (51.0)      | 0.537           |
| Negative      | 387 (48.3)      | 226 (27.3)      |       | 133 (51.8)      | 126 (49.0)      |                 |
explained by men’s general lack of awareness of this rare disease and the ignorance of the related risk factors causing male breast cancer. Our study found that most male breast cancers are ER-positive and HER2 negative, which is consistent with that of a previous study. Previous studies have evaluated the effect of adjuvant chemotherapy on survival in male breast cancer.
Wang et al. stated that whether to apply radiation or chemotherapy or not should be carefully considered for ER+ HER2– male patients.\textsuperscript{21} In addition, a retrospective study\textsuperscript{22} of 134 male breast cancer patients in Zhejiang Cancer Hospital in China showed that the chemotherapy group had similar DFS as the non-chemotherapy group, but OS in the chemotherapy group was superior to that of the non-chemotherapy group, indicating that male breast cancer patients may benefit from chemotherapy. The retrospective study by Goss et al. of 229 male breast cancer patients recommended chemotherapy if the patient has a positive LN. However, these studies did not further

| Group                  | Before matching | After matching |
|------------------------|----------------|---------------|
|                        | 4-year OS      | 4-year BCSS   | 4-year OS | 4-year BCSS |
| Chemotherapy           | 98.6%          | 99.3%         | 97.5%     | 98.8%       |
| Non-chemotherapy       | 96.6%          | 99.4%         | 95.2%     | 98.8%       |
| \(p\) value           | 0.001          | 0.083         | <0.001    | 0.128       |
| Total                  | 98.2%          | 99.4%         | 97%       | 99%         |

BCSS, breast cancer-specific survival; OS, overall survival.

**Figure 3.** Kaplan–Meier survival curves of the effect of chemotherapy on OS (A, B, E, F) and BCSS (C, D, G, H) by HR+ or HER2 status.

BCSS, breast cancer-specific survival; HR, hormone receptor; HER2, human epidermal growth factor receptor-2; OS, overall survival.
Figure 4. Kaplan–Meier survival curves of the effect of chemotherapy on OS (A–C) and BCSS (D, E) by tumour grade. BCSS, breast cancer-specific survival; OS, overall survival.

Figure 5. Kaplan–Meier survival curves of the effect of chemotherapy on OS (A–C) and BCSS (D–F) by stage. BCSS, breast cancer-specific survival; OS, overall survival.
identify any association between adjuvant chemotherapy and survival by stratifying patients by tumour grade, stage, tumour size or other clinical characteristics. Whether all men should receive adjuvant chemotherapy is still unclear.

Regardless of matching patients by baseline characteristics, adjuvant chemotherapy was significantly associated with OS but not with BCSS, consistent with the results of the previous studies.\textsuperscript{21,23} Furthermore, our study showed that adjuvant chemotherapy was not associated with BCSS in patients stratified by grade, stage, receptors status, tumour size and LN status. This means that adjuvant chemotherapy could reduce the risk of dying from all causes but not the risk of dying from breast cancer.

In our study, 76 of 514 patients died (21 patients in the chemotherapy group and 55 patients in the non-chemotherapy group). The causes of mortality were categorized as breast cancer (6.4%), heart diseases (2.9%), diabetes mellitus (0.8%), chronic obstructive pulmonary disease and allied conditions (0.6%), accidents and adverse effects (0.4%), Alzheimer’s disease (0.2%), hypertension without heart disease (0.2%), lung and bronchus disease (0.2%), other infectious and parasitic diseases including HIV infection (0.2%) and septicaemia (0.2%), and other causes of death (2.7%). However, there was an OS benefit but no BCSS benefit between the two groups in patients with stage IIB and stage III disease. We found that the BCSS survival curve of the chemotherapy group was above that of the non-chemotherapy group among patients with stage T2 and T3 disease. Therefore, the failure to improve the BCSS may be associated with the small sample size. This phenomenon has also been reported previously. The result from Yu \textit{et al.}\textsuperscript{22} showed that the chemotherapy group had better OS ($p=0.026$) but not DFS ($p=0.165$) than those of the non-chemotherapy group among male patients with breast cancer.

In the results, we found that adjuvant chemotherapy had no significant effects on both OS and BCSS in male patients with stage I male breast cancer (OS: $p=0.100$, BCSS: $p=0.858$) compared with the non-chemotherapy group. Besides, in patients with LN-negative breast cancer, neither OS nor BCSS were significant between the chemotherapy and non-chemotherapy groups. Furthermore, the chemotherapy group did not have longer OS or BCSS than the non-chemotherapy group among male patients with HR\textsuperscript{+}, HER2\textsuperscript{−}, $T\leq2$ cm and LN-positive breast cancer. This means that patients with T1N0M0, T2N0M0 and T1N1M0, who have clinical stage I or IIA disease, may not benefit from adjuvant chemotherapy. Therefore, we concluded that adjuvant
Table 3. Univariate and multivariate Cox regression model analysis of overall survival between the chemotherapy group and the non-chemotherapy group.

| Characteristics | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|----------------------|
|                 | p value             | Hazard ratio         | 95.0% CI for Exp(B) | p value | Hazard ratio | 95.0% CI for Exp(B) |
|                 |                     | 95.0% CI for Exp(B)  |                     |         |             |                     |
| **Age**         |                     |                      |                     |         |             |                     |
| <65 years       | Reference           |                      | Reference           |         |             |                     |
| ≥65 years       | **0.004**           | 2.056                | 1.252–3.378         | **0.049** | 1.688       | 1.002–2.844         |
| **Marital status** |                     |                      |                     |         |             |                     |
| Married         | Reference           |                      | Reference           |         |             |                     |
| Unmarried       | **0.006**           | 1.891                | 1.195–2.993         | **0.024** | 1.740       | 1.076–2.814         |
| Unknown         | 0.920               | 1.076                | 0.260–4.452         | 0.353   | 1.980       | 0.469–8.369         |
| **Race**        |                     |                      |                     |         |             |                     |
| White           | Reference           |                      | Reference           |         |             |                     |
| Black           | 0.936               | 1.026                | 0.540–1.950         |         |             |                     |
| Other           | 0.759               | 1.199                | 0.376–3.823         |         |             |                     |
| **Grade**       |                     |                      |                     |         |             |                     |
| I               | Reference           |                      | Reference           |         |             |                     |
| II              | 0.639               | 1.327                | 0.407–4.324         |         |             |                     |
| III             | 0.267               | 1.945                | 0.601–6.296         |         |             |                     |
| **Laterality**  |                     |                      |                     |         |             |                     |
| Left            | Reference           |                      | Reference           |         |             |                     |
| Right           | 0.559               | 1.144                | 0.729–1.796         |         |             |                     |
| **Stage**       |                     |                      |                     |         |             |                     |
| I               | Reference           |                      | Reference           |         |             |                     |
| II              | 0.328               | 1.086                | 0.584–2.020         | 0.523   | 0.711       | 0.249–2.028         |
| III             | <**0.001**          | 3.340                | 1.759–6.345         | 0.879   | 0.903       | 0.241–3.382         |
| **Tumour size** |                     |                      |                     |         |             |                     |
| T ≤2 cm         | Reference           |                      | Reference           |         |             |                     |
| 2 cm < T ≤5 cm  | 0.120               | 1.527                | 0.895–2.605         | 0.236   | 1.732       | 0.698–4.297         |
| T >5 cm         | <**0.001**          | 3.955                | 2.084–7.504         | 0.062   | 2.951       | 0.947–9.197         |
| **LN status**   |                     |                      |                     |         |             |                     |
| Positive        | Reference           |                      | Reference           |         |             |                     |
| Negative        | **0.026**           | 1.690                | 1.066–2.680         | 0.300   | 1.352       | 0.764–2.390         |

(Continued)
chemotherapy may not improve the prognosis of male patients with stage I–IIA disease.

Our results should be considered within the context of the study limitations. First, family history is one of the strongest risk factors for breast cancer, but relevant information on family history is not available from the SEER database. Second, since HER2 status was not registered until 2010, we included only patients diagnosed from 2010 to 2015. Third, data on some biologic characteristics such as $BRCA1$ and $BRCA2$ mutations and androgen receptor status are not registered in SEER. What is more, regimens of chemotherapy were not available to obtain, which may influence the effect of chemotherapy on the OS and BCSS. However, overall, this study has great reliability. First, we analysed the benefit of adjuvant chemotherapy for male breast cancer patients by further stratifying by clinical characteristics. Second, our study has the advantages of focusing on the latest available data in the SEER database, which strictly excludes the missing data and makes sure that our study is reliable. What is more, this study will help clinicians to realize that men with stage I or stage IIA breast cancer may not necessarily need to receive adjuvant chemotherapy, which would spare these patients the risks associated with overtreatment from adjuvant chemotherapy.

**Conclusion**

In our study, adjuvant chemotherapy improved OS in patients with stage IIB and

| Characteristics | Univariate analysis | Multivariate analysis |
|----------------|--------------------|----------------------|
|                | $p$ value | Hazard ratio | 95.0% CI for $\text{Exp}(B)$ | $p$ value | Hazard ratio | 95.0% CI for $\text{Exp}(B)$ |
| **ER status**  |          |              |                        |          |              |                        |
| Positive       | Reference |              |                        | Reference |              |                        |
| Negative       | 0.513 | 20.591 | 0.002–176,993.654 | 0.969 | 34,863.481 | 0–6.766E+230 |
| **PR status**  |          |              |                        |          |              |                        |
| Positive       | Reference |              |                        | Reference |              |                        |
| Negative       | 0.189 | 2.564 | 0.629–10.450 | 0.415 | 1.812 | 0.434–7.565 |
| **HER status** |          |              |                        |          |              |                        |
| Positive       | Reference |              |                        | Reference |              |                        |
| Negative       | **0.017** | 1.927 | 1.123–3.309 | **0.012** | 2.037 | 1.166–3.559 |
| **Surgery**    |          |              |                        |          |              |                        |
| Done           | Reference |              |                        | Reference |              |                        |
| None           | <**0.001** | 0.189 | 0.086–0.414 | **0.005** | 0.286 | 0.121–0.679 |
| **Chemotherapy** |          |              |                        |          |              |                        |
| Done           | Reference |              |                        | Reference |              |                        |
| None           | <**0.001** | 0.341 | 0.206–0.564 | <**0.001** | 0.365 | 0.218–0.610 |
| **Radiation**  |          |              |                        |          |              |                        |
| Done           | Reference |              |                        |          |              |                        |
| None           | 0.534 | 0.839 | 0.483–1.458 |

CI, confidence interval; ER, oestrogen receptor; $\text{Exp}(B)$, the exponent of $B$; HER, human epidermal growth factor receptor; LN, lymph node; PR, progesterone receptor; T, tumour size.
### Table 4. Univariate and multivariate Cox regression model analysis of BCSS between the chemotherapy group and the non-chemotherapy group.

| Characteristics | Univariate analysis |  | Multivariate analysis |  |
|----------------|--------------------|---|----------------------|---|
|                | p value | Hazard ratio | 95.0% CI for Exp(B) | p value | Hazard ratio | 95.0% CI for Exp(B) |
| **Age**        |         |                |                      |         |                |                      |
| <65 years      | Reference |                |                      | Reference |                |                      |
| ≥65 years      | 0.155 | 1.694 | 0.820–3.498 | 0.231 | 1.600 | 0.742–3.448 |
| **Marital status** |         |                |                      |         |                |                      |
| Married        | Reference |                |                      | Reference |                |                      |
| Unmarried      | **0.004** | 2.814 | 1.386–5.713 | **0.013** | 2.559 | 1.223–5.351 |
| Unknown        | 0.136 | 3.092 | 0.701–13.641 | 0.045 | 4.774 | 1.036–21.989 |
| **Race**       |         |                |                      |         |                |                      |
| White          | Reference |                |                      | Reference |                |                      |
| Black          | 0.312 | 1.538 | 0.667–3.547 | 0.976 | 0 | 0 |
| Other          | 0.976 | 0 | 0 |
| **Grade**      |         |                |                      |         |                |                      |
| I              | Reference |                |                      | Reference |                |                      |
| II             | 0.895 | 6689.655 | 0–6.218E+60 | 0.887 | 13335.763 | 0–1.239E+61 |
| III            | 0.094 | 2.029 | 0.8864.643–5.036 | 0.117 | 5.150 | 0.663–40.001 |
| **Laterality** |         |                |                      |         |                |                      |
| Left           | Reference |                |                      | Reference |                |                      |
| Right          | 0.774 | 0.903 | 0.452–1.807 | 0.774 | 0.903 | 0.452–1.807 |
| **Stage**      |         |                |                      |         |                |                      |
| I              | Reference |                |                      | Reference |                |                      |
| II             | 0.565 | 1.299 | 00.533–3.618 | 0.203 | 0.240 | 0.027–2.165 |
| III            | 0.032 | 2.880 | 1.094–7.580 | 0.349 | 0.303 | 0.025–3.682 |
| **Tumour size** |         |                |                      |         |                |                      |
| T ≤2 cm        | Reference |                |                      | Reference |                |                      |
| 2 cm < T ≤5 cm | 0.094 | 2.029 | 0.8864.643–5.036 | 0.117 | 5.150 | 0.663–40.001 |
| T >5 cm        | 0.014 | 3.762 | 0.892–10.421 | 0.122 | 6.303 | 0.610–65.091 |
| **LN status**  |         |                |                      |         |                |                      |
| Positive       | Reference |                |                      | Reference |                |                      |
| Negative       | 0.141 | 1.692 | 0.841–3.406 | 0.268 | 1.624 | 0.689–3.828 |

(Continued)
stage III breast cancer. However, adjuvant chemotherapy might be safely skipped by male patients with stage I and stage IIA breast cancer. Nevertheless, prospective studies focused on male breast cancer need to be conducted to confirm our results.

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Conflict of interest statement
The authors declare that there is no conflict of interest.

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| Characteristics | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|-----------------------|
|                 | p value  | Hazard ratio | 95.0% CI for Exp(B) | p value  | Hazard ratio | 95.0% CI for Exp(B) |
| ER status       |         |             |                     |         |             |                     |
| Positive        | Reference |             |                     | Reference |             |                     |
| Negative        | 0.675    | 20.580      | 0.285,140,23.70     | 0.981    | 58,412.810  | 0                   |
| PR status       |         |             |                     |         |             |                     |
| Positive        | Reference |             |                     | Reference |             |                     |
| Negative        | 0.554    | 1.692       | 0.841–2.735         | 0.621    | 1.667       | 0.220–12.626        |
| HER status (%)  |         |             |                     |         |             |                     |
| Positive        | Reference |             |                     | Reference |             |                     |
| Negative        | 0.425    | 0.557       | 0.132–2.350         | 0.167    | 1.836       | 0.775–4.350         |
| Surgery         |         |             |                     |         |             |                     |
| Done            | Reference |             |                     | Reference |             |                     |
| None            | 0.005    | 0.179       | 0.054–0.593         | 0.061    | 0.262       | 0.065–1.063         |
| Chemotherapy    |         |             |                     |         |             |                     |
| Done            | Reference |             |                     | Reference |             |                     |
| None            | 0.133    | 0.585       | 0.364–1.612         | 0.181    | 0.611       | 0.297–1.257         |
| Radiation       |         |             |                     |         |             |                     |
| Done            | Reference |             |                     | Reference |             |                     |
| None            | 0.714    | 0.855       | 0.290–1.177         |          |             |                     |

CI, confidence interval; ER, oestrogen receptor; Exp(B), the exponent of B; HER, human epidermal growth factor receptor; LN, lymph node; PR, progesterone receptor; T, tumour size.
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