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

Ther Adv Med Oncol

2020, Vol. 12: 1–14

DOI: 10.1177/1758835920958358

Wei-Ping Li*, Hong-Fei Gao*, Fei Ji*, Teng Zhu, Min-Yi Cheng, Mei Yang, Ci-Qiu Yang, Liu-Lu Zhang, Jie-Qing Li, Jun-Sheng Zhang and Kun Wang

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

Received: 6 May 2020; revised manuscript accepted: 19 August 2020.

Correspondence to:
Kun Wang
Department of Breast Cancer, Cancer Centre, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, No.123 Huifu West, Yuexiu District, Guangzhou510080, China

The Second School of Clinical Medicine, Southern Medical University, Guangzhou, 510515, China
gzwangkun@126.com

Wei-Ping Li
The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China

Department of Breast Cancer, Cancer Centre, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

Hong-Fei Gao
Fei Ji
Teng Zhu
Min-Yi Cheng
Mei Yang
Ci-Qiu Yang
Liu-Lu Zhang
Jie-Qing Li
Jun-Sheng Zhang
Department of Breast Cancer, Cancer Centre, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

*These authors have contributed equally to this work

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 trial[12,13] 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

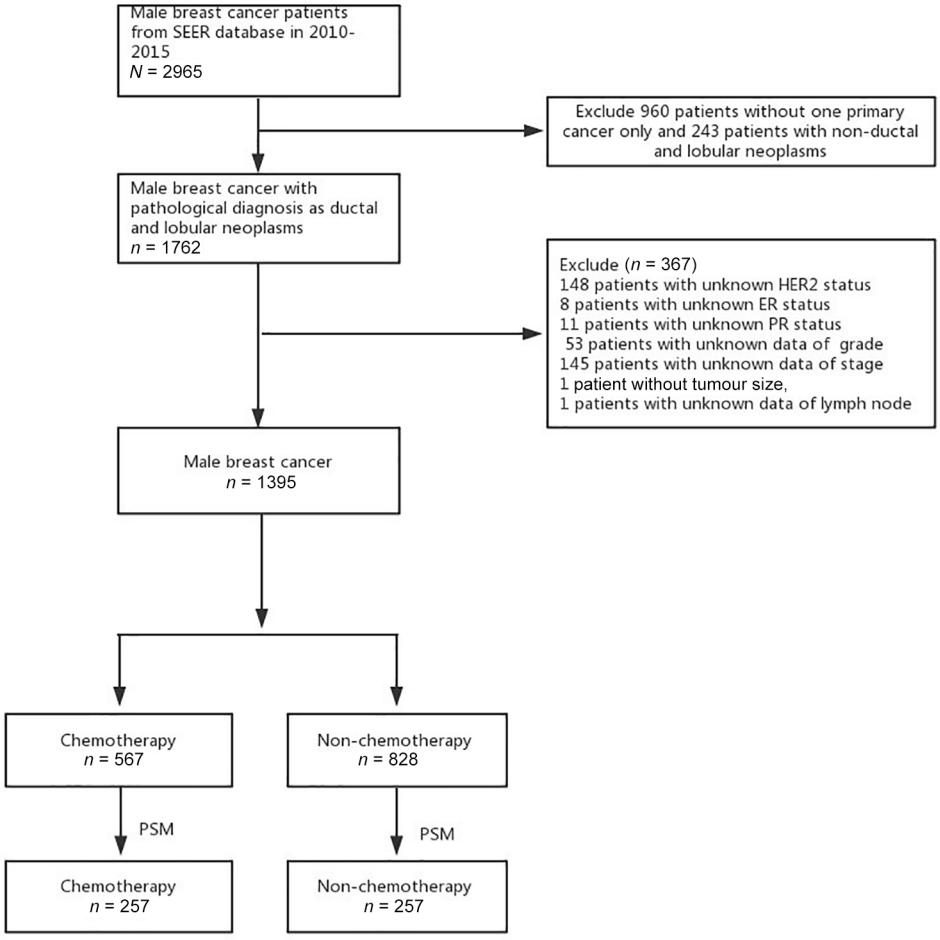

Figure 1. Study flowchart for patients' inclusion and exclusion.
ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; PSM, propensity score matching; SEER, Surveillance, Epidemiology, and End Results.

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 calliper 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.[17] In the present study, tumour stage, grade and ER status were independent prognostic factors for OS.[18] 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, stage, receptors 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,[19] which may be

Table 1. Patients' demographics and clinicopathological characteristics.

Variables	Data before PSM			Data after PSM		
	Chemotherapy *n* = 567	Non-chemotherapy *n* = 828	*p* value	Chemotherapy *n* = 257	Non-chemotherapy *n* = 257	*p* value
Age (%)			<0.001			0.859
<65 years	344 (60.7)	286 (34.5)		114 (44.4)	112 (43.6)	
⩾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 (%)			0.772			0.736
White	447 (78.8)	665 (80.3)		211 (82.1)	217 (84.4)	
Black	83 (14.6)	115 (13.9)		37 (14.4)	31 (12.1)	
Other	37 (6.5)	48 (5.8)		9 (3.5)	9 (3.5)	
Grade (%)			<0.001			0.707
I	29 (5.1)	118 (14.3)		14 (5.4)	16 (6.2)	
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 (%)			0.208			0.331
Left	320 (56.4)	439 (53.0)		141 (54.9)	130 (50.6)	
Right	247 (43.6)	389 (47.0)		116 (45.1)	127 (49.4)	
Stage (%)			<0.001			0.632
I	90 (15.9)	387 (46.7)		74 (28.8)	69 (26.8)	
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			0.669
T⩽2 cm	194 (34.2)	4445 (53.7)		96 (37.4)	105 (40.9)	
2<T⩽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			0.537
Positive	180 (31.7)	602 (72.7)		124 (48.2)	131 (51.0)	
Negative	387 (48.3)	226 (27.3)		133 (51.8)	126 (49.0)	

(Continued)

Table 1. (Continued)

Variables	Data before PSM			Data after PSM		
	Chemotherapy *n* = 567	Non-chemotherapy *n* = 828	*p* value	Chemotherapy *n* = 257	Non-chemotherapy *n* = 257	*p* value
ER status (%)			0.011			0.801
Positive	548 (96.6)	817 (98.7)		251 (97.7)	253 (98.4)	
Negative	19 (3.4)	11 (1.3)		6 (2.3)	4 (1.6)	
PR status (%)			0.012			0.354
Positive	508 (89.6)	773 (93.4)		239 (93.0)	244 (94.9)	
Negative	59 (10.4)	55 (6.6)		18 (7.0)	13 (5.1)	
HER status (%)			<0.001			0.705
Positive	118 (20.8)	52 (6.3)		38 (14.8)	35 (13.6)	
Negative	449 (79.2)	776 (93.7)		219 (85.2)	222 (86.4)	
Surgery			0.066			0.459
Done	555 (97.9)	796 (96.1)		250 (97.3)	247 (96.1)	
None	12 (2.1)	32 (3.9)		7 (2.7)	10 (3.9)	
Radiation			<0.001			1.000
Done	244 (43.0)	148 (17.9)		65 (25.3)	65 (25.3)	
None	323 (57.0)	680 (82.1)		192 (74.7)	192 (74.7)	

ER, oestrogen receptor; HER, human epidermal growth factor receptor; LN, lymph node; PR, progesterone receptor; PSM, propensity score matching; T, tumour size.

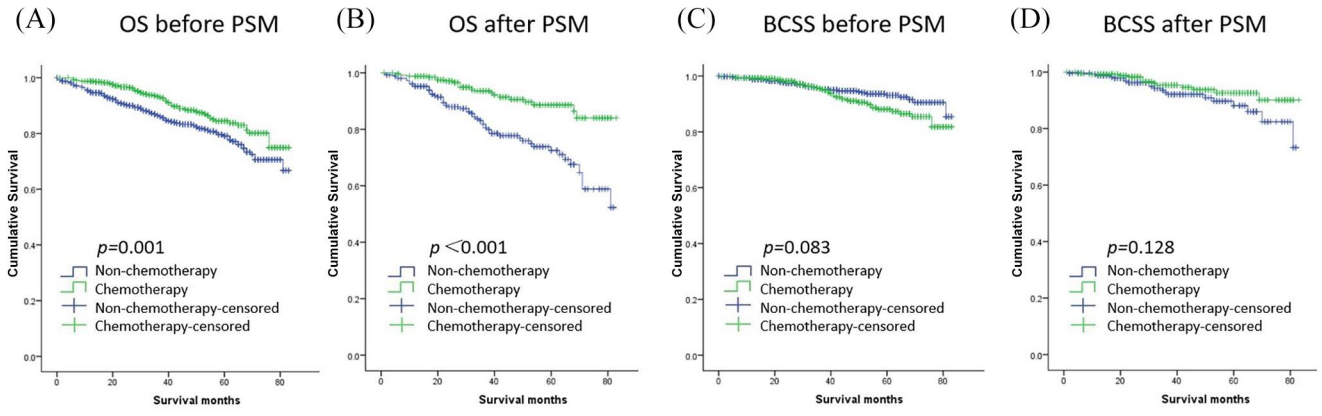

Figure 2. Kaplan–Meier survival curves of the effect of chemotherapy and non-chemotherapy.
BCSS, breast cancer-specific survival; OS, overall survival; PSM, propensity score matching.

explained by men's general lack of awareness of this rare disease and the ignorance of the related risk factors causing male breast cancer.[9] Our study found that most male breast cancers are ER-positive and HER2 negative, which is consistent with that of a previous study.[20] Previous studies have evaluated the effect of adjuvant chemotherapy on survival in male breast cancer.

Table 2. Four-year OS and BCSS of the two groups.

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.

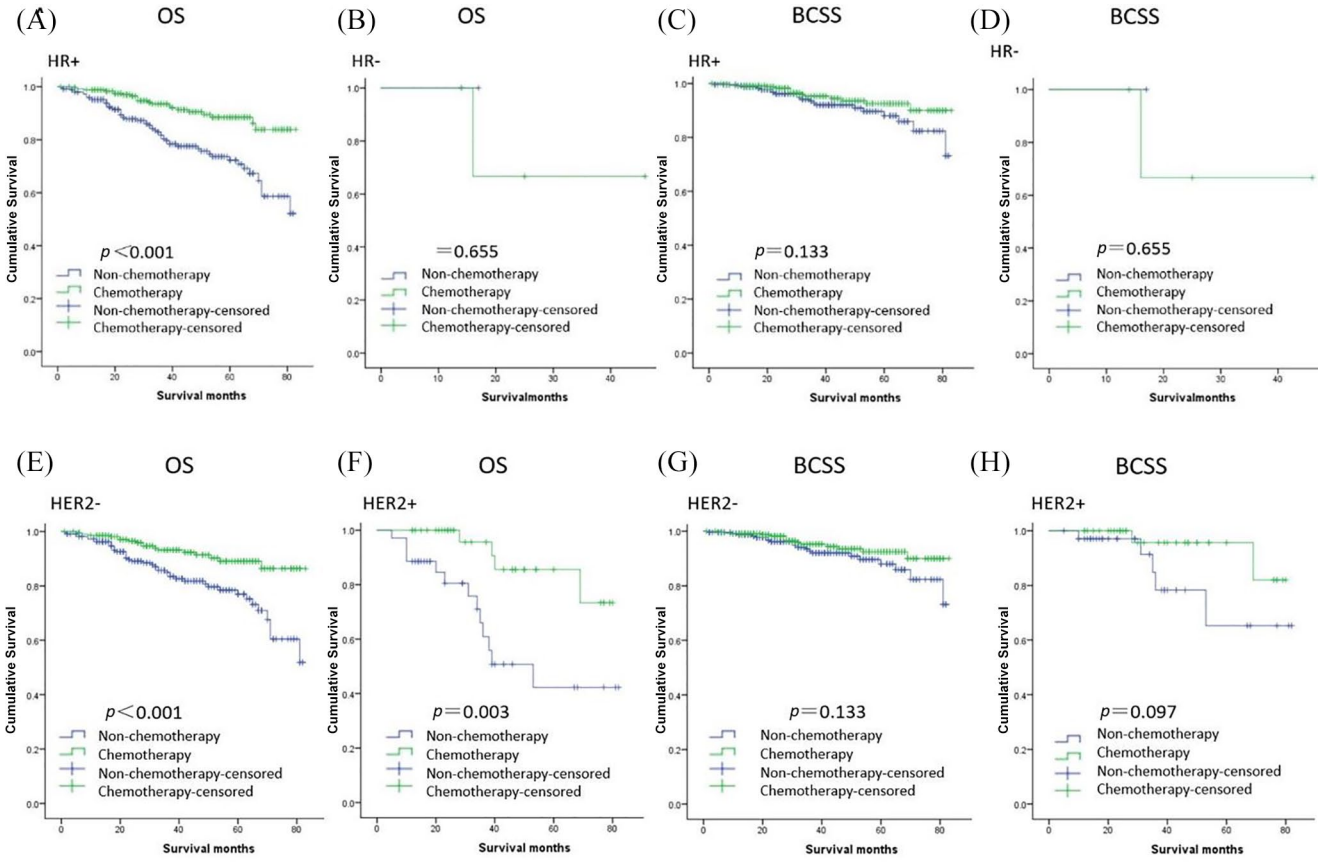

Figure 3. Kaplan–Meier survival curves of the effect of chemotherapy on OS (A, B, E, F) and BCSS (C, D, G, H) by HR+ or HER2 status.
BCSS, breast cancer-specific survival; HR, hormone receptor; HER2, human epidermal growth factor receptor-2; OS, overall survival.

Wang *et al.* stated that whether to apply radiation or chemotherapy or not should be carefully considered for ER+ HER2– male patients.[21] In addition, a retrospective study[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

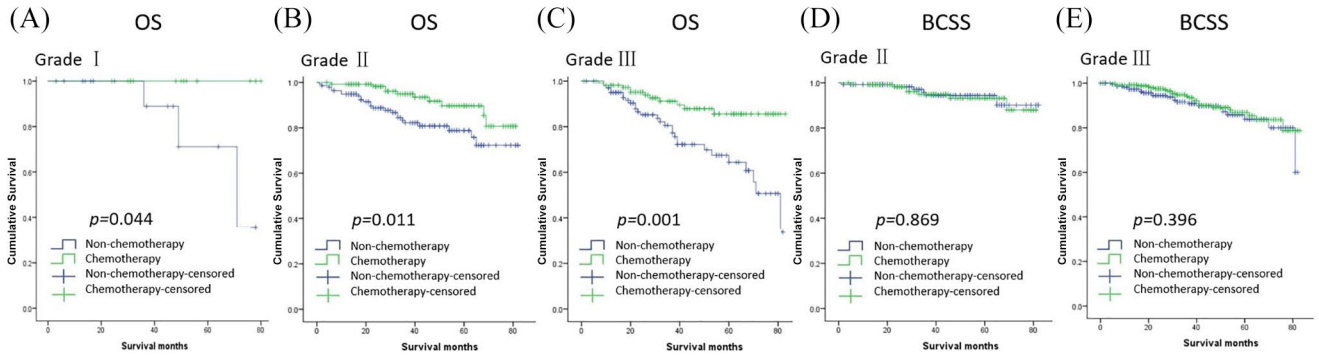

Figure 4. Kaplan–Meier survival curves of the effect of chemotherapy on OS (A–C) and BCSS (D, E) by tumour grade.
BCSS, breast cancer-specific survival; OS, overall survival.

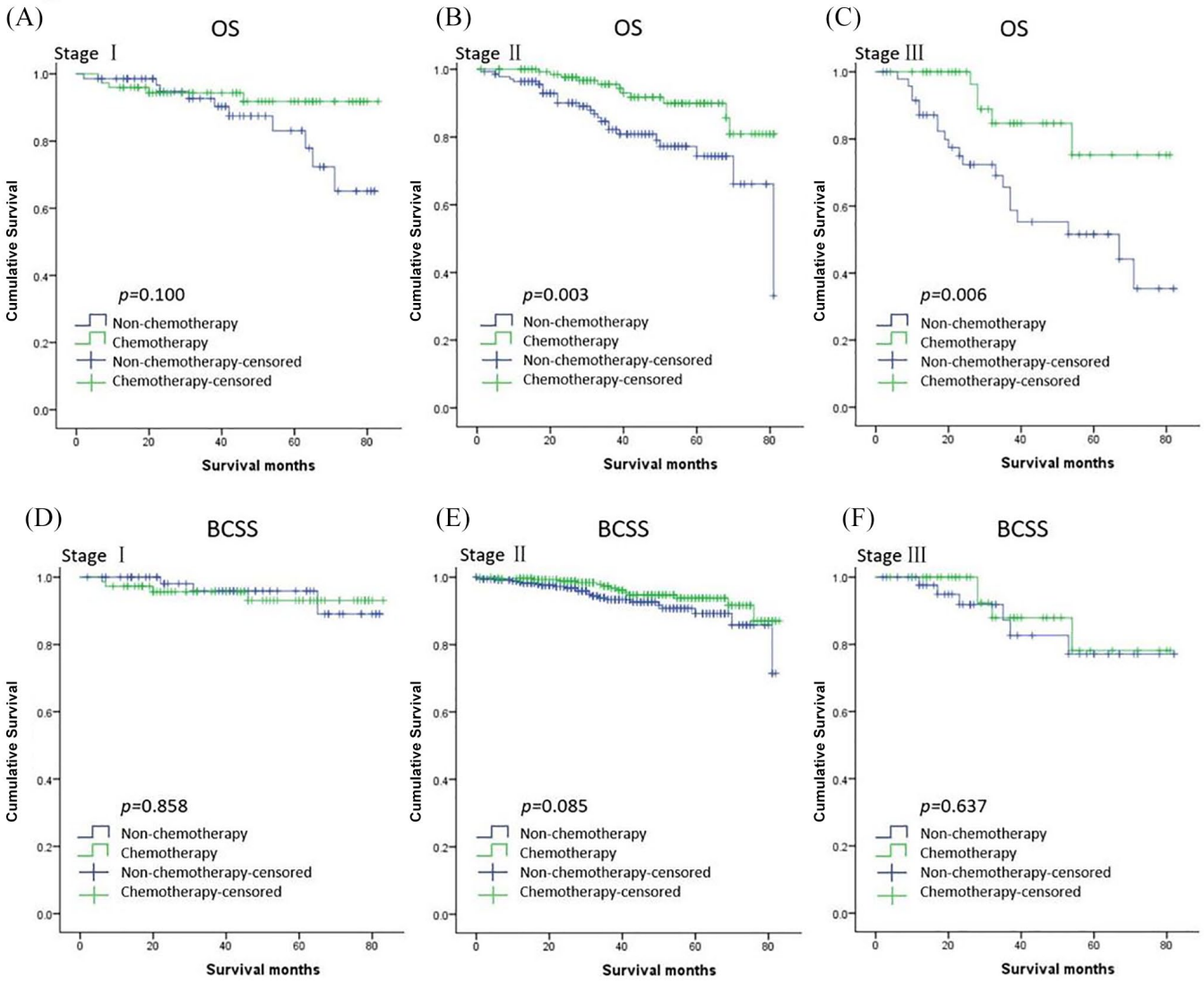

Figure 5. Kaplan–Meier survival curves of the effect of chemotherapy on OS (A–C) and BCSS (D–F) by stage.
BCSS, breast cancer-specific survival; OS, overall survival.

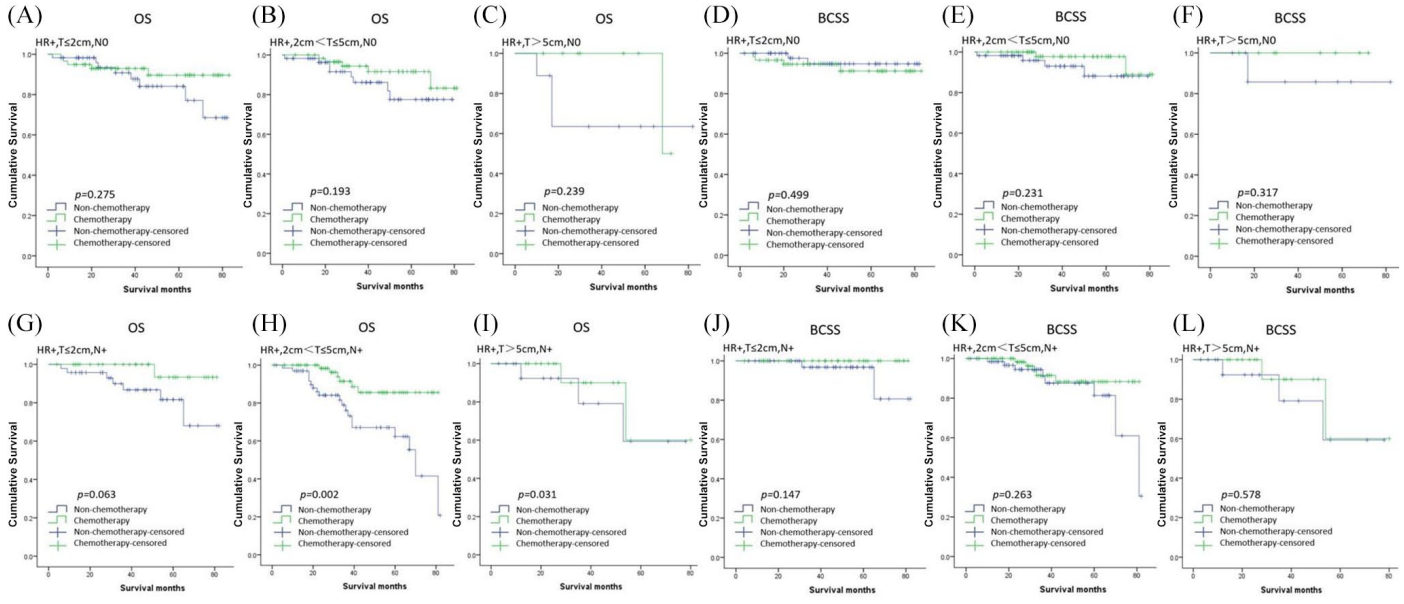

Figure 6. Kaplan–Meier survival curves of the effect of chemotherapy on OS (A–C) and BCSS (D–F) stratified by tumour size with N0 and Kaplan–Meier survival curves of the effect of chemotherapy on OS (G–I) and BCSS (J–L) stratified by tumour size with N+.
BCSS, breast cancer-specific survival; HR+, hormone receptor-positive; N0, lymph node-negative; N+, lymph node-positive; OS, overall survival; T, tumour size.

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.[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 *et al.*[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+, HER2–, T$\leqslant$2 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)
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					
Black	0.936	1.026	0.540–1.950			
Other	0.759	1.199	0.376–3.823			
Grade						
I	Reference					
II	0.639	1.327	0.407–4.324			
III	0.267	1.945	0.601–6.296			
Laterality						
Left	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)

Table 3. (Continued)

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

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

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					
Black	0.312	1.538	0.667–3.547			
Other	0.976	0	0			
Grade						
I	Reference					
II	0.895	6689.655	0–6.218E+60			
III	0.887	13335.763	0–1.239E+61			
Laterality						
Left	Reference					
Right	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)

Table 4. (Continued)

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					
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.

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.

Acknowledgements

The authors acknowledge the efforts of the SEER programme tumour registries in the creation of the SEER database and thank all of the patients analysed in this study. The funding source had no role in this study. All of the authors have final responsibility for the decision to submit this manuscript for publication.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This paper was supported by the National Natural Science Foundation of China (Grant Nos. 81871513), the Science and Technology Planning Project of Guangzhou City under Grant number 202002030236, and the CSCO-Constant Rui Tumor Research Fund, China under Grant number Y-HR2016-067. The funders had only

provided financial support for the conduct of our work.

References

1. Siegel RL, Miller KD and Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30.
2. Korde LA, Zujewski JA, Kamin L, *et al.* Multidisciplinary meeting on male breast cancer: summary and research recommendations. *J Clin Oncol* 2010; 28: 2114–2122.
3. Cardoso F, Bartlett JMS, Slaets L, *et al.* Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG international male breast cancer program. *Ann Oncol* 2018; 29: 405–417.
4. Pritzlaff M, Summerour P, McFarland R, *et al.* Male breast cancer in a multi-gene panel testing cohort: insights and unexpected results. *Breast Cancer Res Treat* 2017; 161: 575–586.
5. Chen W, Zheng R, Baade PD, *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66: 115–132.
6. Zhang L, Huang Y, Yang C, *et al.* Application of a carbon nanoparticle suspension for sentinel lymph node mapping in patients with early breast cancer: a retrospective cohort study. *World J Surg Oncol* 2018; 16: 112.
7. Hodgson NCF, Button JH, Franceschi D, *et al.* Male breast cancer: is the incidence increasing? *Ann Surg Oncol* 2004; 11: 751–755.
8. Stang A and Thomssen C. Decline in breast cancer incidence in the United States: what about male breast cancer? *Breast Cancer Res Treat* 2008; 112: 595–596.
9. Abdelwahab Yousef AJ. Male breast cancer: epidemiology and risk factors. *Semin Oncol* 2017; 44: 267–272.
10. Gómez-Raposo C, Zambrana Tévar F, Sereno Moyano M, *et al.* Male breast cancer. *Cancer Treat Rev* 2010; 36: 451–457.
11. Crocetti E, Ravaioli A, Amadori D, *et al.* Female breast cancers (T1-2, N0, M0, HR+, HER2–) with an intermediate genetic-based recurrence risk: a real-world estimate in Italy. *Tumori* 2019; 105: 483–487.
12. Sparano JA, Gray RJ, Makower DF, *et al.* Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med* 2018; 379: 111–121.
13. Sparano JA, Gray RJ, Ravdin PM, *et al.* Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. *N Engl J Med* 2019; 380: 2395–2405.
14. Welch HG, Prorok PC, O'Malley AJ, *et al.* Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. *N Engl J Med* 2016; 375: 1438–1447.
15. Merrill RM and Dearden KA. How representative are the surveillance, epidemiology, and end results (SEER) program cancer data of the United States? *Cancer Causes Control* 2004; 15: 1027–1034.
16. Ji F, Xiao W-K, Yang C-Q, *et al.* Tumor location of the central and nipple portion is associated with impaired survival for women with breast cancer. *Cancer Manag Res* 2019; 11: 2915–2925.
17. Tyagi NK and Dhesy-Thind S. Clinical practice guidelines in breast cancer. *Curr Oncol* 2018; 25: S151–S160.
18. Sas-Korczynska B, Niemiec J, Harazin-Lechowska A, *et al.* The biological markers and results of treatment in male breast cancer patients. The Cracow experience. *Neoplasma* 2014; 61: 331–339.
19. Giordano SH, Cohen DS, Buzdar AU, *et al.* Breast carcinoma in men: a population-based study. *Cancer* 2004; 101: 51–57.
20. Ruddy KJ and Winer EP. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. *Ann Oncol* 2013; 24: 1434–1443.
21. Wang J, Sun Y, Qu J, *et al.* Survival analysis for male ductal and lobular breast cancer patients with different stages. *Future Oncol* 2019; 15: 167–180.
22. Yu X-F, Wang C, Chen B, *et al.* The effect of adjuvant chemotherapy in male breast cancer: 134 cases from a retrospective study. *ESMO Open* 2017; 2: e000134.
23. Wei J-L, Zhang J-X and Fu D-Y. Characterization and prognosis of estrogen receptor-positive/progesterone receptor-negative male breast cancer: a population-based study. *World J Surg Oncol* 2018; 16: 236.