Adjuvant chemotherapy could not bring survival benefit to HR-positive, HER2-negative, pT1b-c/N0-1/M0 invasive lobular carcinoma of the breast: a propensity score matching study based on SEER database

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Abstract

Background : The benefit of adjuvant chemotherapy in invasive lobular carcinoma (ILC) is still unclear. The objective of the current study was to elucidate the effectiveness of adjuvant chemotherapy in hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, pT1b-c/N0-1/M0 ILC. Methods: Based on Surveillance, Epidemiology, and End-Results (SEER) database, we identified original 13996 HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC patients, who were then divided into adjuvant chemotherapy group and control group. End-points were overall survival (OS) and breast cancer-specific mortality (BCSM). Aiming to minimize the selection bias of baseline characteristics, Propensity Score Matching (PSM) method was used. Results : In a total of 13996 patients with HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC, 1800 patients (12.9%) were allocated into adjuvant chemotherapy group and 12196 (87.1%) into control group. Used PSM, the 1800 patients in adjuvant chemotherapy group matched to the 1800 patients in control group. By Kaplan-Meier survival analyses, we observed beneficial effect of adjuvant chemotherapy on OS in original samples (P =0.001) but ineffectiveness in matched samples (P =0.400), however, ineffective or even contrary results of adjuvant chemotherapy on BCSM both in original samples (P =0.001) and in matched samples (P= 0.033). In both original and matched multivariate Cox models, we observed ineffectiveness of adjuvant chemotherapy on OS (hazard ratio (HR) for overall mortality = 1.243, 95% confidence interval (CI) [0.954-1.619]; P =0.108 and HR=1.227, 95%CI [0.870-1.731]; P =0.244, respectively), unexpectedly promoting effect of adjuvant chemotherapy on BCSM (HR=2.446, 95%CI [1.598-3.742]; P =0.001 and HR=1.791, 95%CI [1.056-3.037]; P = 0.031, respectively). Lymph node metastasis was detrimental to survival in original samples, but had unobvious effect in matched samples. Radiotherapy and standard surgery were beneficial to the survival of patients. Conclusion: Adjuvant chemotherapy could bring no survival benefit to HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC, even contribute to BCSM.

Background

Invasive lobular carcinoma (ILC) is the most common ‘special’ morphological subtype of breast cancer and presents with a distinctive clinical behavior compared with invasive ductal carcinoma (IDC) (no special type)[1,2]. Classical ILC is characterized by monotonous small, uniform, discohesive cells that infiltrate the stroma in a single-file pattern[2]. The E-cadherin loss on tumor cell membranes may offer the specific metastatic pattern of ILC, such as peritoneum, retroperitoneum and internal genital organs, etc[3,4]. Importantly, multidimensional molecular atlas have identified numerous molecular features discriminating between ILC and IDC, demonstrating different pathways underlying their pathogenesis[5]. Therefore, ILC should be considered to a distinct entity different from IDC[6,7].

Generally, ILC displays features associated with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, being low grade and a good prognosis[8]. It is generally admitted that ILC, especially HR-positive, HER-2-negative ILC, is endocrine responsive, and responds poorly to chemotherapy[9,10]. Thus, if adjuvant chemotherapy is ineffective for relatively early stage patients with HR-positive, HER2-negative ILC? Hereunder this issue is not yet settled in published clinical studies.

In 2011, based on a Dutch regional cohort of 498 ILC patients, Truin et al[11] reported that overall survival (OS) was not statistically different in HR-positive ILC patients treated with adjuvant endocrine therapy and chemotherapy compared to adjuvant endocrine therapy alone (5-year OS 85.2% vs 82.8%, P = 0.68). In 2012, using the data from the Netherlands Cancer Registry (NCR) of 3685 ILC patients, Truin et al[12] also reported that adjuvant chemotherapy seems to confer no additional beneficial effects in postmenopausal patients with pure or mixed type ILC (10-year OS 66% vs 68%, P = 0.45). In 2017, identifying 4638 ILC from California Cancer Registry (CCR), Marmor et al[13] determined a similar result that patients with estrogen receptor (ER)-positive, HER2-negative, stage I/II ILC who received adjuvant endocrine therapy did not benefit from the addition of adjuvant chemotherapy. However, using 2318 ILC data source from 15 academic French cancer centers between 1990 and 2014, Nonneville et al[14] recently reported that the significant disease-free survival (DFS) and OS benefits from adjuvant chemotherapy could be derived in high-risk ILC patients, but not in low-risk ILC patients.

In a dilemma, for HR-positive, HER2-negative pT1a/N0-1/M0 ILC or pT2/N0-1/M0 ILC, we may choose adjuvant endocrine therapy alone or adjuvant endocrine therapy and chemotherapy. However, how should we make a choice for HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC? The Surveillance, Epidemiology, and End-Results (SEER) database is publicly available for studies of

cancer-based epidemiology and TNM staging of breast cancer and other cancers, which covers approximately 28% of the US population[7,15]. Using SEER database, the aims of our study were to confirm whether the adjuvant chemotherapy could bring survival benefit to patients with HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC. To our knowledge, this is the first and the largest, population-based study presenting evidence of effect of adjuvant chemotherapy in patients with ILC used SEER database. Above all, our findings have a direct and meaningful translation to the clinic, allowing us to avoid excessive adjuvant chemotherapy for patients with HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC.

Methods

Data source and study design

The SEER program is a national database and primary source of cancer statistics that is currently maintained by the National Cancer Institute. We have got permission to acquire the research data file in SEER*Stat Database: Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying) - Linked To County Attributes - Total U.S., 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission. We obtained patients diagnosed with ILC of pT1b-c/N0-1/M0 according to Site Recode classification and AJCC 7^{th} ed stage system. The collected patients were diagnosed from 2010 to 2016, because breast cancer subtype was available in SEER database since 2010. We retrieved 14844 record of HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC (Supplementary Table 1). After omitting censored data, a total of 13996 patients were enrolled in our study (Fig.1).

Statistical analysis

The mean of age between chemotherapy group and control group was compared by t test. The differences of clinic-pathological features between two groups were analyzed by chi-square, t test and Wilcoxon ranksum test. Propensity Score Matching (PSM) method (Match Ratio 1:1; Logit model; the nearest neighbor matching approach) was used to eliminate clinic-pathological mixed bias in two groups. Overall survival (OS) was defined as the time from admission to the date of death from any cause. Breast cancer-specific mortality (BCSM) was defined as the period from the operative date to death of breast cancer. The OS curves and BCSM curves of each group were estimated by Kaplan-Meier survival analyses, and the curves were analyzed by the log-rank test. In the multivariate analysis, a COX's Proportional Hazard Model was employed to estimate whether a factor was a significant independent prognostic factor of survival. All statistical tests were two-sided, *P* values less than 0.05 were considered as statistically significant. The statistical analyses were performed using STATA version 15.1 for windows (StataCorp LLC).

Results

Characteristics of the original patients

After omitting censored data, an original of 13996 patients with HR-positive, Her-2-negative, pT1b-c/N0-1/M0 ILC were enrolled in our study (Supplementary Table 2). In total patients, 1800 patients (12.9%) received the adjuvant chemotherapy (chemotherapy group) and 12196 patients (87.1%) not (control group). Compared with patients of control group, patients of chemotherapy group presented significantly more adverse prognostic features, such as young age (mean 57.2 vs. 66.1 years, $P<0.05$), larger tumor size (mean 1.42 vs. 1.30 cm, $P=0.001$), high grade (75.9 vs. 65.7% grades 2–3, $P<0.05$), more lymph node involvement (49.5 vs. 11.6% pN1, $P<0.05$). Patients of chemotherapy group underwent more mastectomy (50.7 vs. 32.8%, $P<0.05$). The comparisons of characteristics between two groups were shown in Table 1.

PSM method to minimize the selection bias of baseline characteristics

In order to study the effect of chemotherapy on survival by equilibrium, we employed PSM method (Match Ratio 1:1) to minimize the selection bias of demographic and clinic-pathological characteristics between the two groups. The kernel density functions of the chemotherapy group and the control group, based on pre-matching showed that the characteristics of the variables in the two groups had remarkable bias (Fig.2A). After matching, as shown in Fig.2B, the kernel density functions of the chemotherapy group and the control group (1800 patients from original control group) were a lot closer, indicating that the clinic-pathological characteristics in chemotherapy group and the control group are similar (Supplementary Table 3).

Characteristics of the matched patients

The matched results showed that the bias between chemotherapy group and the control group has no statistically significant (bias≤±10, *P*≥0.05). In matched samples, apart from age (mean 57.2 vs 58.1 years, *P*=0.006), almost all of the demographic and clinic-pathological characteristics were similarly distributed between chemotherapy group and control group (*P*≥0.05) (Table 2)

OS and BCSM analysis before or after matching

In the original 13996 patients with HR-positive, Her-2-negative, T1b-c/N0-1/M0 ILC were followed-up for a median of 42 months (range of 1 to 83 months). By the end of follow-up period, 75 of 1800 patients (chemotherapy group) had died, 41 patients died of breast cancer, with the corresponding, 685 of 12196 patients (control group) had died,122 patients due to recurrence and metastasis of breast cancer. Thus before matching, the OS of the chemotherapy group was obviously better than that of the control group (*P* = 0.001, log-rank test) (Fig.3A). However, the BCSM of the chemotherapy group was higher than that of the control group, which reach obvious levels of statistical significance (*P* = 0.001, log-rank test) (Fig.3B).

After matching, 58 of 1800 patients in the control group had dead, 21 of whom owing to the breast cancer. The OS curve of chemotherapy group and control group interwove with each other (*P* = 0.400, log-rank test) (Fig.3C). Unexpectedly, the BCSM of the chemotherapy group was statistical significantly higher than that of the control group (*P* < 0.033, log-rank test) (Fig.3D). Accordingly, adjuvant chemotherapy was likely on the contrary to induced more breast cancer mortality.

The original and the matchedmultivariate Cox proportional hazards models for overall mortality and BCSM

To adjust potential modifier effects to adjuvant chemotherapy, both the original and the propensity score matched multivariate Cox proportional hazards models were fitted for overall mortality and BCSM. As shown in Fig.4A and Table 3, adjuvant chemotherapy was not detrimental to overall mortality in both original and matched Cox models (HR=1.243, 95%CI [0.954-1.619]; *P*=0.108 and HR=1.227, 95%CI [0.870-1.731]; *P*=0.244, respectively). However, as shown in Fig.4B and Table 3, adjuvant chemotherapy unexpectedly increased the risk of BCSM in both original and matched Cox models (HR=2.446, 95%CI [1.598-3.742]; *P*=0.001 and HR=1.791, 95%CI [1.056-3.037]; *P*=0.031, respectively). Additionally, in both original and matched Cox models, radiotherapy and standard surgery were negatively correlated with both the risk of overall mortality and BCSM (all coefficients < 0, *P*<0.05) shown in Fig.4A, Fig.4B and Table 3, but age was a pernicious factor. Lymph node metastasis was positively related to both the risk of overall mortality and BCSM in original Cox models (all coefficients > 0, *P*<0.05), however, they were no longer significant for the risk of overall mortality and BCSM in matched Cox models shown in Fig.4A, Fig.4B and Table 3. In matched samples, the prognosis of white race is better than that of black race (HR for overall mortality and BCSM < 1, *P*<0.05). High histological grade was only positively associated with the risk of overall mortality in matched samples (HR=1.832, 95%CI [1.022-3.283]; *P*=0.042), but with BCSM in original samples that just fail to reach conventional levels of statistical significance (*P* = 0.076).

Discussion

As well as HR and HER2 status, some studies have indicated that the histological subtype of the breast cancer also plays an important role in predicting the response to adjuvant chemotherapy and/or neoadjuvant chemotherapy (NAC)[16-19]. In 2005, Cristofanilli et al[16,17] reported that ILC is characterized by lower pathologic complete response (pCR) rates to NAC but better long-term outcomes compared to IDC. In 2007, Katz et al[18] reviewed randomized trials of NAC and noted that the pCR rate was 1.7% in ILC and 11.6% in IDC (no special type). In 2010, in the era of tailored therapy for individual patients, Purushotham et al[19] documented that we would no longer routinely recommend NAC in patients with ER-positive, HER2-negative, classical type ILC.

However, though it is generally admitted that ILC, especially HR-positive, HER2-negative ILC, responds poorly to chemotherapy, currently available data do not unanimously support these assumptions. In 2012, Lips et al[9] reported a similar pCR rate in both ER-positive, HER2-negative IDC and ER-positive, HER2-negative ILC patients (4.2% and 4.3%, respectively). In 2014, Guiu et al[20] reported that in multivariate analysis, histology of ILC was not an independent negative predictive factor of pCR in seven[21-27] of nine studies[28,29,21-27].

Thus, we could not draw a conclusion that ILC or even HR-positive, HER2-negativeis ILC is an independent predictor of poor response to adjuvant chemotherapy and/or NAC. In fact, minority of past and current studies take lobular histology into account in pretreatment stratification or subgroup analysis. Consequently, findings of these studies limit our ability to indicate whether patients with IDC or ILC should be managed with similar or different treatments. At present, the National Comprehensive Cancer Network (NCCN) and the St Gallen International Expert Consensus guidelines for systemic therapy decisions are almostly derived from studies based on IDC. Neither of these two guidelines consider histologic subtype as a factor for determining systemic therapy decisions. Making systemic therapy decisions for patients with ILC is thus challenging for the oncology community. It is unlikely that a future randomized clinical trial (RCT) concerning this subject will be accomplished. There is lack of stronger evidence support, this may be why our guidelines still do not distinguish ILC from IDC for treatment allocation or classification therapy.

In this study by using SEER database, we firstly compared the cohort characteristics between the included HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC patients with and without adjuvant chemotherapy, in both original and propensity score matched sample, respectively. Secondly, OS and BCSM analyses between chemotherapy and control groups were made, before or after PSM, respectively. Thirdly, to adjust the potential confounding factors to chemotherapy, the multivariate Cox regression analyses were performed for overall mortality and BCSM, in both original and matched sample, respectively. Our data demonstrate that patients with HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC could not derive survival benefit from the adjuvant chemotherapy shown in Fig.2, Fig.3 and Table 3, neither for OS nor for BCSM. In both original and propensity score matched sample, ILC patients with adjuvant endocrine therapy and chemotherapy had a worse BCSM than ILC patients with adjuvant endocrine therapy alone. This finding is almost certainly secondary to selection bias and not cause and effect of adjuvant chemotherapy.

Histological grading is an important part of breast cancer classification, and is performed using the Nottingham histological grading system. However, it has been controversial as to the relevance of this system for ILC, since tubule formation is rare (except in the tubulo-lobular variant)[30]. With limited nuclear pleomorphism and sparse mitotic count, ILC (including variants) is often characterized by lower histologic grade compared to IDC[31]. In both our original and matched samples, almost or more than ninety percentages of ILC were histologic grade 1-2 (Table 1 and Table 2). Consequently, a therapeutic dilemma can occur in the event of the relative resistance of ILC to conventional chemotherapeutic agents[32,33]. Moreover, lack of E-cadherin protein expression in ILC is distinctive from IDC[34]. It has been hypothesized that the lack of chemosensitivity of ILC is explained by the inactivation of E-cadherin in ILC. Loss of E-cadherin protein is thought to increase of epithelial to mesenchymal transition (EMT), which in turn become more resistant to chemotherapy[35]. Accordingly, lower histologic grade and deficiency of E-cadherin of ILC both supported our results.

It has been demonstrated that ILC and IDC have distinct genomic, transcriptomic and expression profiles[36]. Recent major advances in genome-wide transcription analyses, comparative genomic hybridization (CGH) and genomic tests further acknowledged the natural history and also the heterogeneity of ILC[37]. It has been suggested that the genomic signatures could be used to assist systemic therapy decisions for patients with ILC, and especially the decision of adding chemotherapy to hormonal therapy[38]. For instance, mutations in exon 9 of the PIK3CA gene have previously been reported more frequent in ILC than in IDC[39-41]. These mutations increase kinase activity, confer increased resistance to paclitaxel and are associated with metastatic capability[42,43]. Intriguingly, loss of E-cadherin of ILC has been also associated with many genetic and molecular alterations including the inactivation of the CDH1 gene at 16q22 by mutation, loss of heterozygosity, or CDH1 promoter methylation, which finally lead to the poor response to cytotoxic chemotherapy[4,3,44].

Oncotype Dx Breast Cancer Assay is a 21-gene assay used in estrogen receptor (ER)-positive breast cancer to predict benefit from chemotherapy[45,46]. In 2015, Conlon et al[47] reported that Oncotype Dx recurrence score (RS) currently plays a clinically useful role in the management of ILC, which may prevent the over-treatment of adjuvant chemotherapy. In 2017, Kizy et al[48] reported that patients with ER-positive ILC, 8% were in the high-risk and 72% were in the intermediate-risk groups as per the trial assigning individualized options for treatment (TAILORx) RS cutoffs. Adjuvant chemotherapy did not seem to confer a survival benefit for either the intermediate- or the high-risk cohorts[48].

Some limitations of our study have to be considered, thus we ought to be caution about our results. Our SEER database does not include information regarding the ILC and its variants, the loss of E-cadherin, the exact ER and PR and Ki67 expression, the 21-

gene assay, the administration of chemotherapy and endocrine therapy, ect. Additionally, we should exclude all cases where breast cancer has only been reported by death certificate or autopsy. All these confounding factors may have affected our results. For example, the most recent 2012 WHO classification of breast cancer distinguishes the ILC and its variants: classic, solid, alveolar, pleomorphic, tubulo-lobular, and mixed variant [1]. Lack of E-cadherin is observed in all histological ILC variants, except for tubulo-lobular variant (tubulo-lobular carcinoma, TLC). Pleomorphic variant (pleomorphic invasive lobular carcinoma, PILC) shares many additional genomic changes with classic ILC such as TP53 stabilization, amplifications of MYC, MDM2, HER2/TOP2A and 20q13[49].

Our study is subject to some methodologic limitations too, which will lead to inevitable bias. The present study is a retrospective cohort study, however, not a RCT. The patient demographics and tumor characteristics are not totally consistent between the included ILC patients with and without adjuvant chemotherapy, even though after PSM analysis. Furthermore, the PSM analysis is also limited by the lack of adjustment for the cointervention of surgery therapy or radiation therapy, which demotivates our study due to reduce the sample sizes or event rates.

Nevertheless, until now, it is not clear whether there is a difference ineffectiveness between chemotherapy regimens administered to patients with ILC. Therefore, we suggest that further research on the type of chemotherapy administered to patients with ILC should be carried out. Moreover, evaluation of the response of ILC patients to endocrine therapy is an emerging direction of clinical breast cancer research[50]. It was reported that the magnitude of benefit of adjuvant letrozole is greater for patients diagnosed with ILC compared to those with IDC[51]. In fact, it may be time for the oncologists to consider a prospective RCT to evaluate the role of NAC versus neoadjuvant endocrine therapy in ILC patients [18]. Additionally, whether CDK4/6 inhibitor is more effective for HR-positive, HER2-negative ILC than for HR-positive, HER2-negative IDC is worth to study. Finally, we advise to the oncologists that ILC and its variants should be studied, with further efforts made to develop more individualized treatment for them and to identify potential mechanisms of their biological inferiority and superiority, respectively[52,53].

Conclusions

Adjuvant chemotherapy could bring no survival benefit to HR-positive, HER2-negative, pT1b-c/N0-1/M0 ILC, even contribute to BCSM.

Abbreviations

BCSM Breast cancer-specific mortality

CGH Comparative genomic hybridization

CI Confidence interval

DFS Disease-free survival

EMT Epithelial to mesenchymal transition

ER Estrogen receptor

HER2 Human epidermal growth factor receptor 2

HR Hormone receptor

HR Hazard ratio

IDC Invasive duct carcinoma of no special type

ILC Invasive lobular carcinoma

NAC neoadjuvant chemotherapy

NCCN National Comprehensive Cancer Network

OS Overall survival

pCR Pathologic complete response

PSM Propensity score matching

RCT randomized clinical trial

RS Recurrence score

SEER Surveillance, Epidemiology, and End-Results database

Declarations

Ethics approval and consent to participate

The study was approved by medical ethics committee of the Central Hospital of Huangpu District and conforming to the principles outlined in the Declaration of Helsinki for the use of human data.

Consent for publication

Not applicable

Availability of data and material

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

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Author contributions

Literature search GFH, GXH and NRJ. *Study design* GFH, HY, XYL, MS, YMY, YWL, CW and CX. *Methodology* GFH and CX. *Writing* GFH, GXH, CX, and CW. *Review and editing* CX, XYL and CW. All authors have critically reviewed the final version of the manuscript and approved its content. The corresponding author had final responsibility for the decision to submit for publication.

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Tables

Table 1. Comparisons of characteristics between chemotherapy group and control group in original 13996 HR-positive, Her-2-negative, pT1b-c/N0-1/M0 ILC patients

	Control (n= 12196)	Chemotherapy (n=1800)	Statistical value	*P*	bias	t-test for bias	*P*
Age (years)							
(Mean±SD)	66.146±11.676	57.227±9.916	t= 30.811	0.001	-82.3	-30.81	0.001
Race							
Black	972 (7.97%)	176 (9.78 %)	χ2= 6.890	0.032	-4.5	-1.83	0.068
White	10444 (85.63%)	1508 (83.78%)					
Other	780 (6.4%))	116 (6.44%))					
Tumor Size(cm)							
(Mean±SD)	1.301±0.409	1.415±0.400	t= -11.056	0.001	28.2	11.06	0.001
LN metastasis							
No	10784 (88.42%))	909 (50.50%))	χ2= 1.6e+03	0.001	90.3	43.11	0.001
Yes	1412 (11.58%))	891 (49.50%))					
Radiotherapy							
No	5892 (48.31%)	894 (49.67%)	χ2=1.154	0.283	-2.7	-1.07	0.283
Yes	6304 (51.69%)	906 (50.33%)					
Surgery							
No surgery	353 (2.89%)	39 (2.17%)	χ2=220.782	0.001	35.2	14.18	0.001
BCS	7841 (64.29%)	848 (47.11%)					
Mastectomy	4002 (32.81%)	913 (50.72%)					
Grade							
I	4184 (34.31%)	433 (24.06%)	z =-10.468	0.001	27.3	10.92	0.001
II	7465 (61.21%)	1198 (66.56%)					
III	541 (4.44%)	168 (9.33%)					
IV	6(0.05%)	1(0.06%)					

Table 2. Comparisons of characteristics between chemotherapy group and control group 2 in matched 3600 HR-positive, Her-2-negative, pT1b-c/N0-1/M0 ILC patients

	Control (n= 1800)	Chemotherapy (n=1800)	Statistical value	*P*	bias	t-test for bias	*P*
Age (years)							
(Mean±SD)	58.152±10.344	57.227±9.916	t= 2.740	0.006	-8.5	-2.74	0.006
Race							
Black	170 (9.44%)	176 (9.78 %)	χ2=2.004	0.367	1.9	0.55	0.581
White	1533 (85.17%)	1508 (83.78%)					
Other	97 (5.39%)	116 (6.44%))					
Tumor Size(cm)							
(Mean±SD)	1.408±0.396	1.415±0.400	t=-0.520	0.603	1.7	0.52	0.603
LN metastasis							
No	952 (52.89%)	909 (50.50%))	χ2=2.057	0.152	5.7	1.43	0.152
Yes	848 (47.11%)	891 (49.50%))					
Radiotherapy							
No	945 (52.50%)	894 (49.67%)	χ2=2.891	0.089	5.7	1.70	0.089
Yes	855 (47.50%)	906 (50.33%)					
Surgery							
No surgery	43 (2.39%)	39 (2.17%)	χ2=1.436	0.488	4.1	1.20	0.231
BCS	879 (48.83%)	848 (47.11%)					
Mastectomy	878 (48.78%)	913 (50.72%)					
Grade							
I	446 (24.78%)	433 (24.06%)	z =-0.543	0.587	1.9	0.56	0.572
II	1190 (66.11%)	1198 (66.56%)					
III	164 (9.11%)	168 (9.33%)					
IV	0 (0.00%)	1 (0.06%)					

Table 3. Multivariate Analyses of overall mortality and BCSM in original samples and matched samples

Variable	original samples						matched samples					
	HR for mortality	95%CI	P	HR for BCSM	95%CI	P	HR for mortality	95%CI	P	HR for BCSM	95%CI	P
Age	1.076	1.068-1.084	0.001	1.040	1.026-1.054	0.001	1.055	1.038-1.072	0.001	1.019	0.996-1.043	0.106
Race												
Black	Reference			Reference			Reference			Reference		
White	0.784	0.614-1.002	0.051	0.801	0.483-1.329	0.391	0.511	0.319-0.818	0.005	0.467	0.242-0.906	0.024
Others	0.692	0.449-1.067	0.096	0.704	0.291-1.703	0.437	0.415	0.155-1.107	0.079	0.422	0.117-1.525	0.188
Tumor size												
(Ic vs Ib)	1.181	0.999-1.396	0.052	1.341	0.918-1.959	0.129	0.849	0.563-1.279	0.434	1.184	0.613-2.285	0.615
LN metastasis												
(Yes vs No)	1.478	1.217-1.795	0.001	1.922	1.319-2.802	0.001	1.459	1.030-2.067	0.034	1.358	0.819-2.251	0.236
Histologic grade												
I	Reference			Reference			Reference			Reference		
II	0.982	0.843-1.145	0.821	1.098	0.780-1.546	0.591	1.272	0.833-1.942	0.266	1.384	0.739-2.592	0.310
III+IV	1.244	0.921-1.683	0.155	1.695	0.945-3.038	0.076	1.832	1.022-3.283	0.042	1.688	0.695-4.096	0.247
Surgery												
No surgery	Reference			Reference			Reference			Reference		
BCS	0.229	0.180-0.291	0.001	0.104	0.065-0.167	0.001	0.074	0.037-0.151	0.001	0.074	0.030-0.185	0.001
Mastectomy	0.227	0.179-0.288	0.001	0.083	0.053-0.130	0.001	0.123	0.069-0.218	0.001	0.074	0.036-0.154	0.001
Chemotherapy												
(Yes vs No)	1.243	0.954-1.619	0.108	2.446	1.598-3.742	0.001	1.227	0.870-1.731	0.244	1.791	1.056-3.037	0.031
Radiotherapy												
(Yes vs No)	0.520	0.426-0.636	0.001	0.371	0.237-0.580	0.001	0.748	0.463-1.209	0.236	0.431	0.209-0.890	0.023

Figures

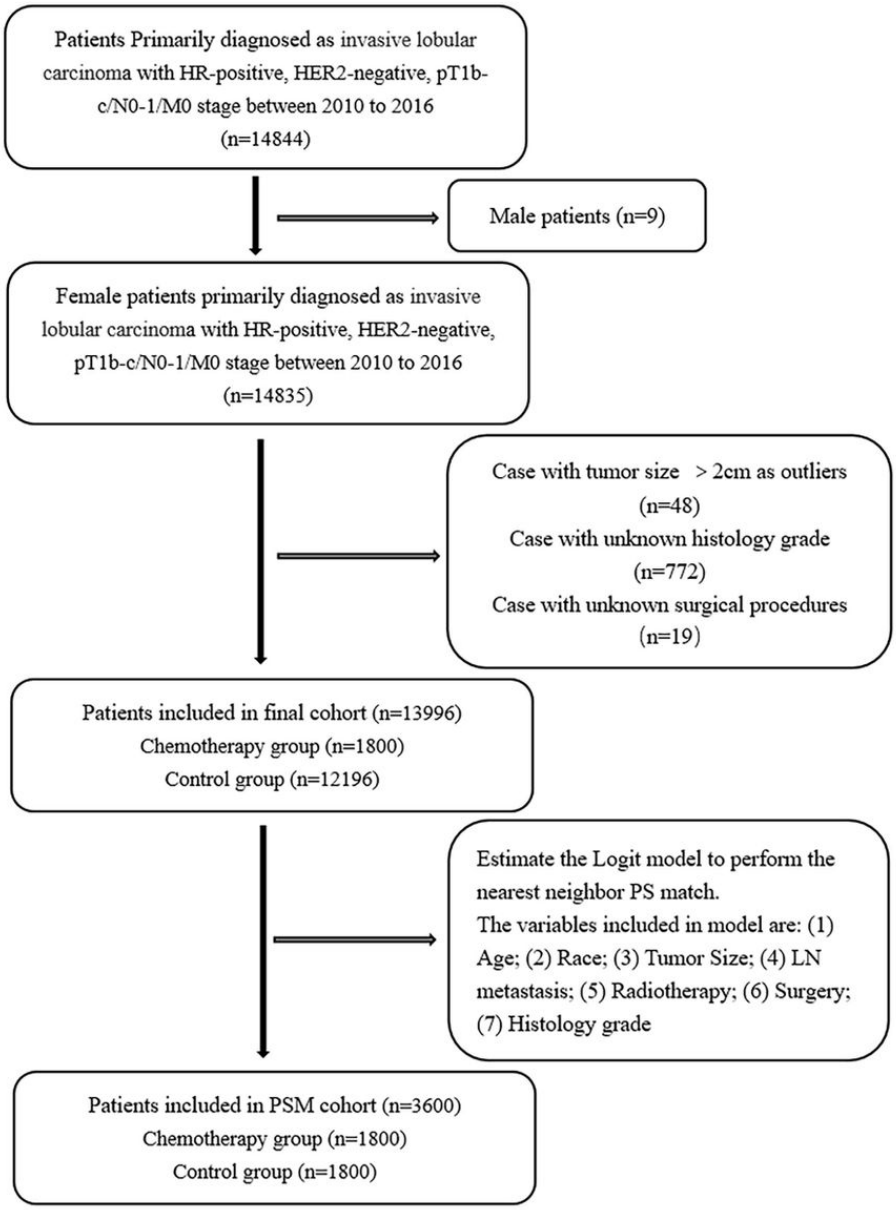

Figure 1

Flow diagram of patient selection and study development.

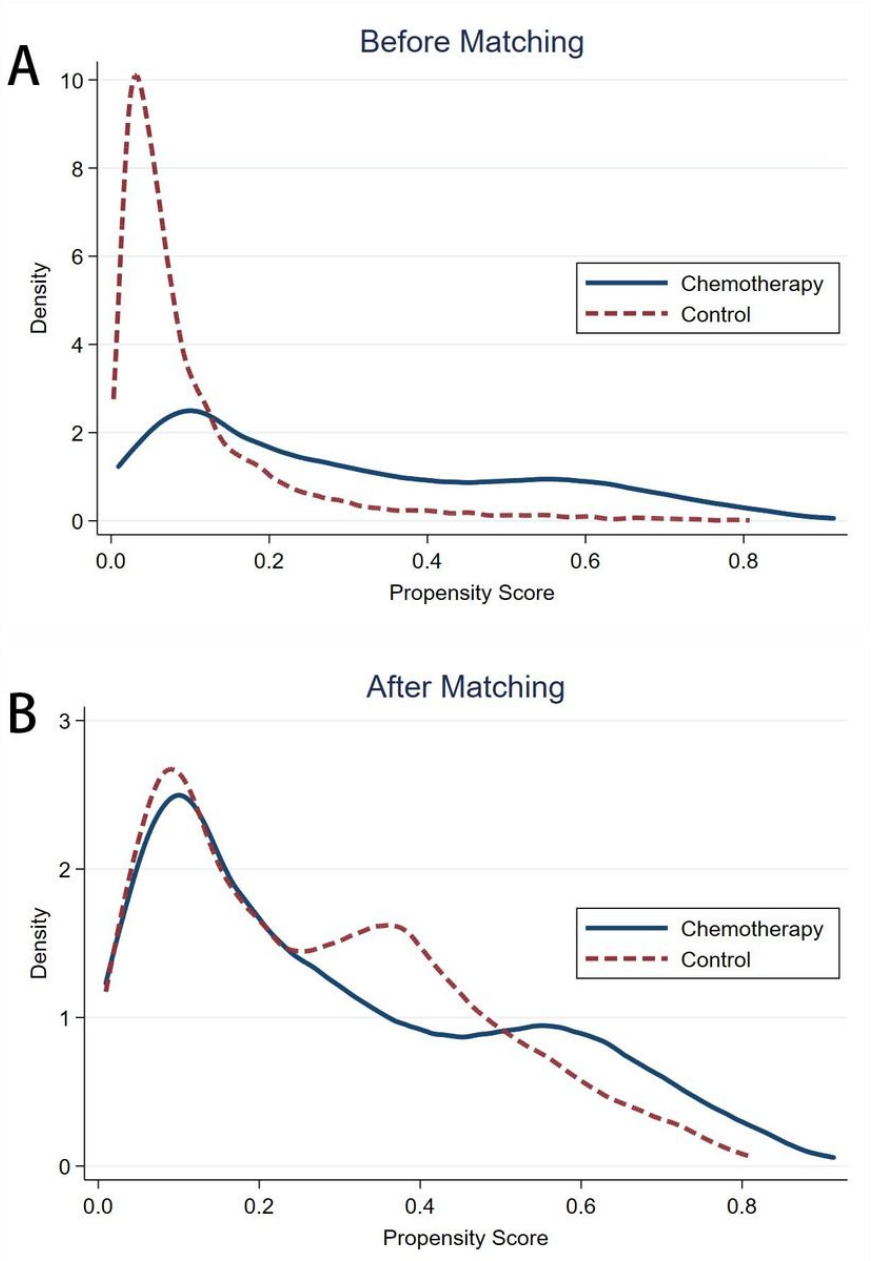

Figure 2

A. Kernel Density of the chemotherapy and control groups before PS matching; B. Kernel Density of the chemotherapy and control groups after PS matching.

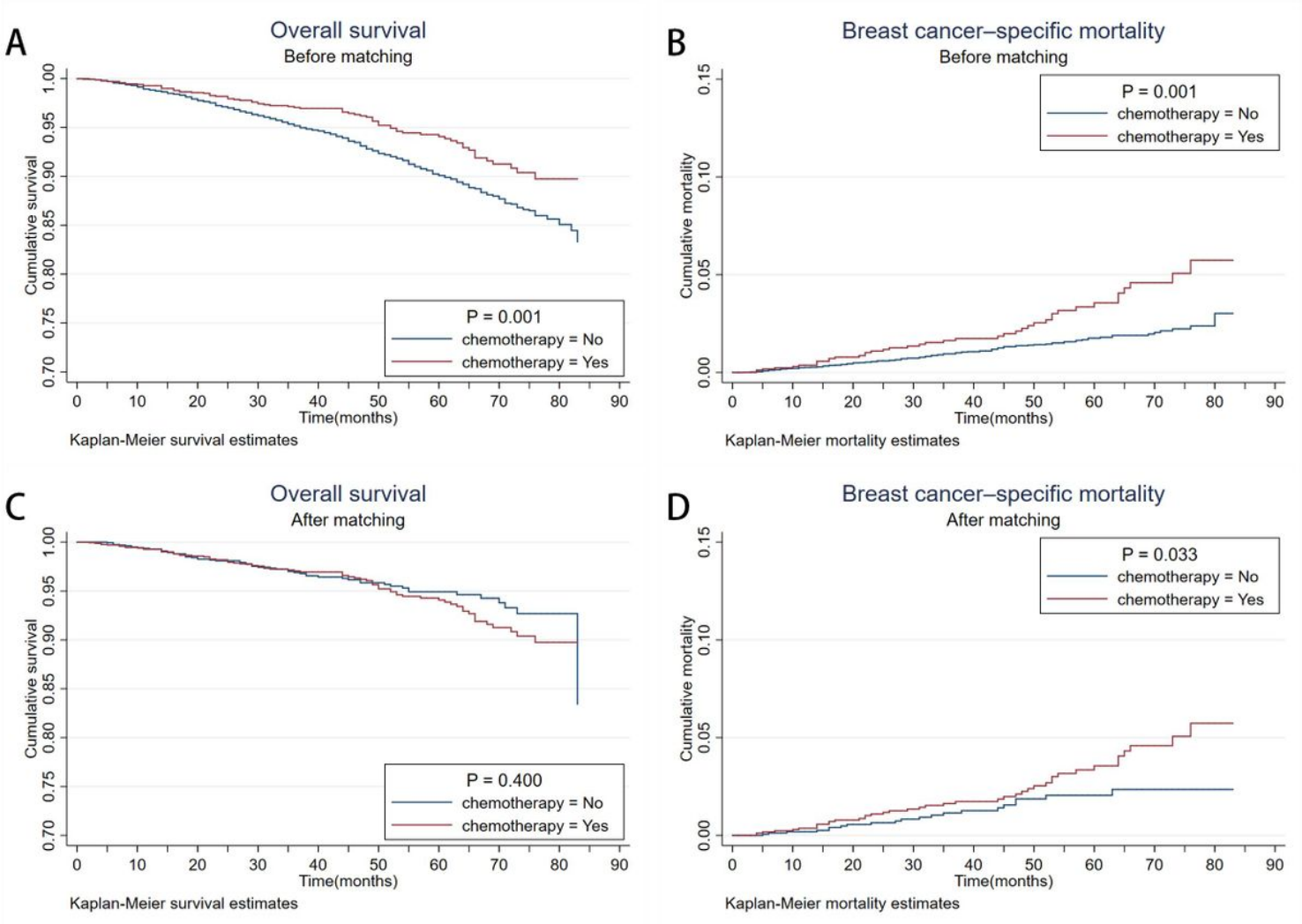

Figure 3

A. Kaplan–Meier analyses of the effect chemotherapy on OS in original samples (P =0.001, log-rank test); B. Kaplan–Meier analyses of the effect chemotherapy on BCSM in original samples (P =0.001, log-rank test); C. Kaplan–Meier analyses of the effect chemotherapy on OS in matched samples (P =0.400, log-rank test); D. Kaplan–Meier analyses of the effect chemotherapy on BCSM in matched samples (P =0.033, log-rank test).

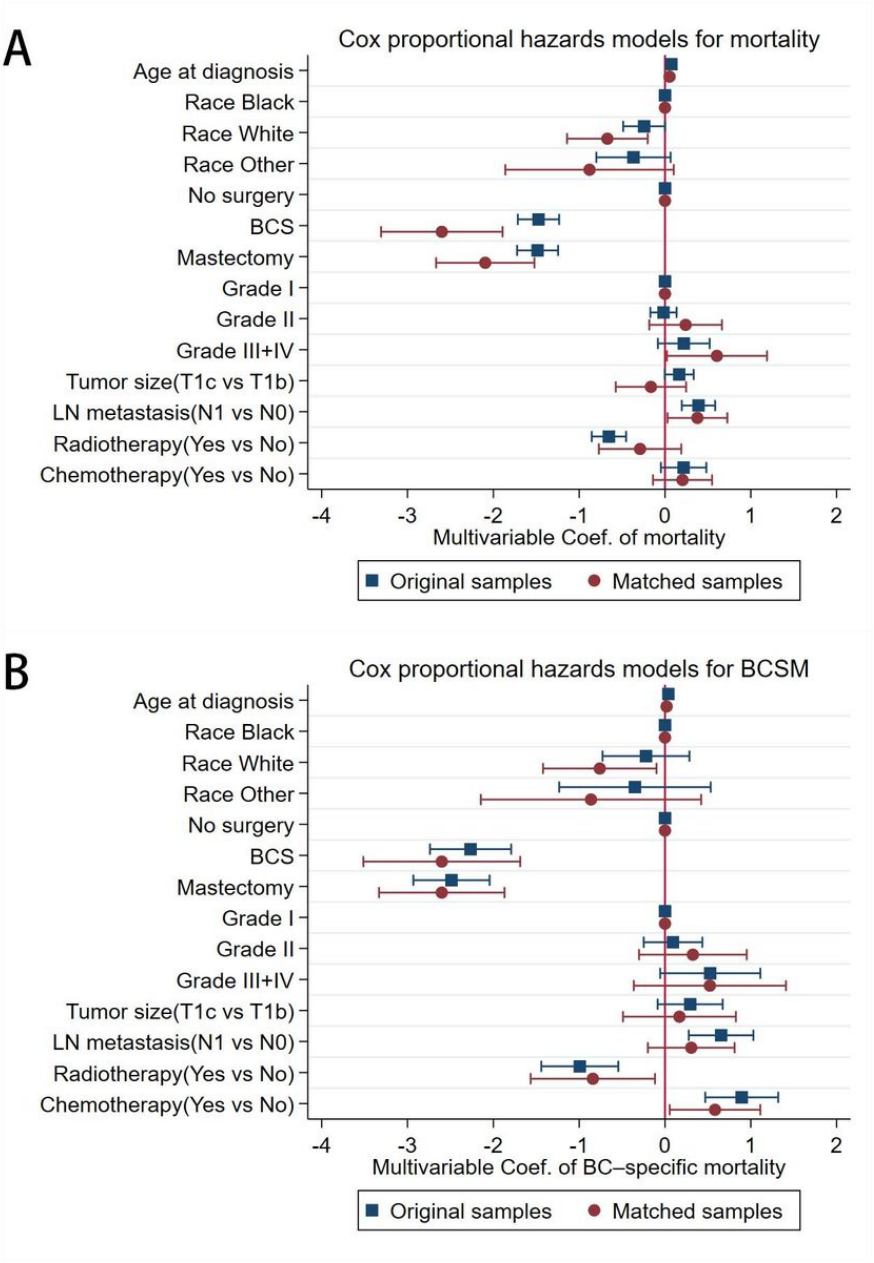

Figure 4

A. Cox proportional hazards models for overall mortality before and after matching; B. Cox proportional hazards models for BCSM before and after matching

Supplementary Files

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

- 13996originalsamples.xlsx
- 14844initialsamples.xlsx
- 3600matchedsamples.xlsx