Adjuvant Chemotherapy Guidance for pT1-3N0-1 Breast Cancer Patients with HR+, HER2- subtype: a study based on SEER database

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Abstract

Background

Although the results of gene testing can guide early breast cancer patients with HR+, HER2- to decide whether they need chemotherapy, there are still many patients worldwide whose problems cannot be solved well by genetic testing.

Methods

144 735 patients with HR+, HER2-, pT1-3N0-1 breast cancer from the Surveillance, Epidemiology, and End Results database were included from 2010 to 2015. They were divided into chemotherapy (n = 38 392) and no chemotherapy (n = 106 343) group, and after propensity score matching, 23 297 pairs of patients were left. Overall survival (OS) and breast cancer-specific survival (BCSS) were tested by Kaplan–Meier plot and log-rank test and Cox proportional hazards regression model was used to identify independent prognostic factors. A nomogram was constructed and validated by C-index and calibrate curves. Patients were divided into high- or low-risk group according to their nomogram score using X-tile.

Results

Patients receiving chemotherapy had better OS before and after matching (p < 0.05) but BCSS was not significantly different between patients with and without chemotherapy after matching: hazard ratio (HR) 1.005 (95%CI 0.897, 1.126). Independent prognostic factors were included to construct the nomogram to predict BCSS of patients without chemotherapy. Patients in the high-risk group (score > 238) can get better OS HR 0.583 (0.507, 0.671) and BCSS HR 0.791 (0.663, 0.944) from chemotherapy but the low-risk group (score ≤ 238) cannot.

Conclusion

The well-validated nomogram and a risk stratification model was built. Patients in the high-risk group should receive chemotherapy while patients in low-risk group may be exempt from chemotherapy.

Introduction

Breast cancer is the second leading cause of death among women in the world,(1) and the prognosis of patients with different molecular subtypes is quite different.(2–4) Chemotherapy (CHT) is an important and effective treatment for breast cancer. For high-risk breast cancer with poor prognosis, such as triple negative, HER2 overexpression, larger tumor and more positive lymph nodes, CHT can significantly improve survival and reduce recurrence and metastasis. However, for patients with hormone receptor
(HR)+, HER2- early breast cancer, the effect of CHT is still controversial. Although CHT can reduce the likelihood of cancer recurrence and death,\(^{(5–7)}\) it may have considerable adverse effects.

At present, most guidelines recommend that patients with early breast cancer with HR+, HER2- should be tested for Oncotype DX or MammaPrint to determine whether CHT is necessary.\(^{(8, 9)}\) However, gene testing has its disadvantages: first of all, the high price makes the degree of popularization limited even in developed countries, let alone in developing countries.\(^{(10)}\) There are also copyright problems; Secondly, neither Oncotype DX nor MammaPrint can solve the problem of all patients receiving the test. The results of Oncotype DX were divided into three groups: high-risk group, intermediate-risk group and low-risk group. For high-risk and low-risk patients, endocrine therapy followed CHT or endocrine therapy alone can be selected according to the guideline, but the systematic treatment for intermediate risk population (26–30 points) is still unclear,\(^{(8)}\) which accounted for about 22–36\%.\(^{(11, 12)}\) and in TAILORx study, due to the redefinition of the criteria for risk grouping (intermediate risk: 11–25 points), intermediate risk patients even accounted for 67.3\%.\(^{(13)}\) For the intermediate risk patients, even after 21 gene testing, it is still unclear whether they could benefit from CHT, although the results of TAILORx study on 21 gene detection in these patients showed that endocrine therapy was not inferior to CHT, while some patients 50 years or below in this population may still benefit from CHT.\(^{(13)}\) The clinical utility of the 70-gene signature (MammaPrint®) to guide CHT use in T1-3N0-1 breast cancer was demonstrated in the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid CHT (MINDACT) study, and its clinical risk stratification was based on the modified adjuvant! Online. The evaluation index did not include factors such as age, tumor thrombus \(^{(14, 15)}\) so that the so-called “low risk” and “high risk” need to be considered individually. Based on the above reasons, it is of great significance to construct a simple clinical prediction model independent of gene testing for patients in developing countries and patients without clear stratification of gene testing.

We conducted a retrospective analysis of breast cancer population with HR+, HER2-, T1-3N0-1 in the Surveillance, Epidemiology, and End Results (SEER) database. Patients were matched by propensity score matching (PSM), and then a nomogram was built to predict breast cancer-specific survival (BCSS) among patients without CHT and each patient was scored by the nomogram. Finally, the risk degree was stratified by X-tile, which could help clinicians to classify patients more reasonably, target CHT to those patients who will benefit most, and avoid CHT in patients who were at low risk of recurrence and would therefore obtain limited absolute benefit. We believe that for low-income people who cannot afford genetic testing, this study can provide a practical tool to individually estimate the survival risk of HR+, HER2-, T1-3N0-1 breast cancer patients with or without CHT.

**Materials And Methods**

**Cohort Selection**

Data from the SEER database were required to identify female patients aged between 18 and 85 years old who were diagnosed with HR+, HER2-, T1-3N0-1 (American Joint Committee on Cancer seventh edition,
AJCC T, 7th ed) invasive breast cancer as their only and primary cancer from January 1, 2010, to December 31, 2015. The detailed exclusion criteria were illustrated in Fig. 1. Briefly, patients with < 3 months’ survival or unknown follow-up and with unknown or unspecified variable's information were excluded. After exclusion, 144 735 patients were included in this study.

Variables involved in this study were: demographic characteristics (age at diagnosis, race, marital status), disease characteristics (tumor location, grade, T stage and number of positive nodes), treatment characteristics (breast surgery type, CHT and radiotherapy), survival status (survival time and cause of death) and follow-up months. Based on the code information in SEER, we divided tumor location into three groups (Outer quadrant, Inner quadrant, Others).

Statistical Analysis

Clinicopathologic characteristics between the CHT and no CHT group were compared using Pearson's χ² test or Student t test. To eliminate the obvious differences in baseline of variables and inherent selection bias, we conducted a PSM analysis between the patients who underwent CHT and those who did not (using 1:1 nearest neighbor matching with a caliper of 0.00005). PSM is a tool for narrowing selection bias in nonrandomized studies and achieving balanced variables across treatment groups. We used the Cox regression hazard model to predict the impact of variables on survival outcomes. The primary endpoint of this study was BCSS and the second endpoint was overall survival (OS). BCSS was defined as the time from the date of diagnosis to the date of death attributed to breast cancer and was calculated using cause-specific death classification in SEER database. OS was defined as the time from the date of diagnosis to death due to any causes. Kaplan-Meier plot and log-rank test were utilized to compare OS and BCSS between different groups. Subsequently, a nomogram was developed to predict 3- and 5-year BCSS for no CHT groups by incorporating independent prognostic factors identified by the multivariate COX analysis. Internal validation in the no CHT group and external validation in the CHT group were performed to evaluate the accuracies of the nomogram by bootstrap validation method with 1000 resamples. The concordance index (C-index) was applied to measure the discrimination of the model. The consistency between the actual observed outcome and the nomogram predicted survival probability was estimated by calibration curves. Patients were divided into high- or low-risk group according to their nomogram score using X-tile (version 3.4.7, Yale University).

Analyses were conducted by STATAMP, version 16.0 (StataCorp LP, College Station, TX) and the packages (rms, hmisc, survival etc.) in R software version 3.6.1 (http://www.r-project.org). Statistical significance was determined with a two-tailed p < 0.05.

Results

Characteristics of Eligible Patients

A cohort of 144 735 female patients (38 392 in CHT group and 106 343 in no CHT group) were involved in this analysis. Before PSM, there were statistically significant differences in demographic and disease
characteristics between the CHT and no CHT groups, including age, race, marital status, tumor location, nuclear grade, T stage, tumor size, N stage, number of positive node and breast surgery (all \( p < 0.001 \)). After PSM, no significant difference was found. After PSM, 23 297 pairs of patients were included in the next analysis step. The baseline characteristics of patient before and after PSM (caliper = 0.00005) are shown in Table 1.
Table 1
Demographic and disease characteristics between the CHT cohort and no CHT cohort before and after PSM.

| Variables          | Overall | Before PSM | After PSM |  |
|--------------------|---------|------------|-----------|---|
|                    |         | No CHT     | CHT       | p | No CHT | CHT | p  |
| n                  | 144735  | 106343     | 38392     |   | 23297  | 23297 |   |
| Age (%)            | < 35    | 1888 (1.3) | 519 (0.5) | 1369 (3.6) | 253 (1.1) | 261 (1.1) | < 0.001 | 0.926 |
|                    | 30–59   | 63580 (43.9) | 38954 (36.6) | 24626 (64.1) | 12937 (55.5) | 12950 (55.6) |   |
|                    | > 60    | 79267 (54.8) | 66870 (62.9) | 12397 (32.3) | 10107 (43.4) | 10086 (43.3) |   |
| Race (%)           | < 35    | 118159 (81.6) | 88103 (82.8) | 30056 (78.3) | 19075 (81.9) | 19034 (81.7) | < 0.001 | 0.511 |
|                    | 30–59   | 12622 (8.7) | 8297 (7.8) | 4325 (11.3) | 2106 (9.0) | 2175 (9.3) |   |
|                    | > 60    | 13954 (9.6) | 9943 (9.3) | 4011 (10.4) | 2116 (9.1) | 2088 (9.0) |   |
| Marital (%)        | < 35    | 55884 (38.6) | 42458 (39.9) | 13426 (35.0) | 8401 (36.1) | 8429 (36.2) | < 0.001 | 0.795 |
|                    | 30–59   | 88851 (61.4) | 63885 (60.1) | 24966 (65.0) | 14896 (63.9) | 14868 (63.8) |   |
| Tumor Location (%) | < 35    | 62693 (43.3) | 46010 (43.3) | 16683 (43.5) | 10189 (43.7) | 10205 (43.8) | < 0.001 | 0.958 |

Note: PSM propensity score matching; CHT chemotherapy; AIA American Indian/Alaska Native; API Asian or Pacific Islander

a “Others” includes “Central portion of breast”, “Breast includes Nipple” and “Overlapping lesion of breast such as 3, 6, 9, 12 o’clock” as recorded in the SEER database

b “IV” represents undifferentiated
| Variables        | Overall | Before PSM | | | | | After PSM | | | |
|------------------|---------|------------|------------|------------|------------|------------|---|---|---|
|                  |         | No CHT     | CHT        | p           | No CHT     | CHT        | p  |
| Inner            | 28480 (19.7) | 21610 (20.3) | 6870 (17.9) | < 0.001    | 4159 (17.9) | 4173 (17.9) | 0.823 |
| Others           | 53562 (37.0) | 38723 (36.4) | 14839 (38.7) | < 0.001 | 8949 (38.4) | 8919 (38.3) |
| Grade (%)        |         | < 0.001    | 0.823      | 0.999 |
| I                | 47013 (32.5) | 41814 (39.3) | 5199 (13.5) | 3852 (16.5) | 3897 (16.7) |
| II               | 71743 (49.6) | 53374 (50.2) | 18369 (47.8) | 12442 (53.4) | 12387 (53.2) |
| III/IV           | 25979 (17.9) | 11155 (10.5) | 14824 (38.6) | 7003 (30.1) | 7013 (30.1) |
| T (%)            |         | < 0.001    | 0.972      | 0.999 |
| T1               | 102808 (71.0) | 84932 (79.9) | 17876 (46.6) | 13287 (57.0) | 13287 (57.0) |
| T2               | 37111 (25.6) | 19746 (18.6) | 17365 (45.2) | 9019 (38.7) | 9029 (38.8) |
| T3               | 4816 (3.3) | 1665 (1.6) | 3151 (8.2) | 991 (4.3) | 981 (4.2) |
| Tumor Size (cm) (%) |         | < 0.001    | 0.999      | 0.999 |
| 0–1              | 44665 (30.9) | 40793 (38.4) | 3872 (10.1) | 3168 (13.6) | 3162 (13.6) |
| 1–2              | 58143 (40.2) | 44139 (41.5) | 14004 (36.5) | 10119 (43.4) | 10125 (43.5) |
| 2–3              | 25398 (17.5) | 14424 (13.6) | 10974 (28.6) | 6298 (27.0) | 6327 (27.2) |

Note: PSM propensity score matching; CHT chemotherapy; AIA American Indian/Alaska Native; API Asian or Pacific Islander

a “Others” includes “Central portion of breast”, “Breast includes Nipple” and “Overlapping lesion of breast such as 3, 6, 9, 12 o’clock” as recorded in the SEER database

b “IV” represents undifferentiated
| Variables | Overall | Before PSM |   | After PSM |   |
|-----------|---------|------------|---|-----------|---|
|           |         | No CHT | CHT | p | No CHT | CHT | p |
| 3–4       |         | 8265 (5.7) | 3864 (3.6) | 4401 (11.5) | 2005 (8.6) | 1997 (8.6) |
| 4–5       |         | 3448 (2.4) | 1458 (1.4) | 1990 (5.2) | 716 (3.1) | 705 (3.0) |
| > 5       |         | 4816 (3.3) | 1665 (1.6) | 3151 (8.2) | 991 (4.3) | 981 (4.2) |
| N (%)     |         | < 0.001 |   |   | 0.134 |   |
| N0        |         | 112335 (77.6) | 93734 (88.1) | 18601 (48.5) | 15069 (64.7) | 14913 (64.0) |
| N1        |         | 32400 (22.4) | 12609 (11.9) | 19791 (51.5) | 8228 (35.3) | 8384 (36.0) |
| Node Positive node (%) |   | < 0.001 |   |   | 0.998 |   |
| 0         |         | 112723 (77.9) | 93757 (88.2) | 18966 (49.4) | 15075 (64.7) | 15065 (64.7) |
| 1         |         | 20500 (14.2) | 9377 (8.8) | 11123 (29.0) | 5896 (25.3) | 5910 (25.4) |
| 2         |         | 7745 (5.4) | 2357 (2.2) | 5388 (14.0) | 1725 (7.4) | 1718 (7.4) |
| 3         |         | 3767 (2.6) | 852 (0.8) | 2915 (7.6) | 601 (2.6) | 604 (2.6) |
| Breast Surgery (%) |   | < 0.001 |   |   | 0.903 |   |
| Lumpectomy |         | 94731 (65.5) | 74948 (70.5) | 19783 (51.5) | 13509 (58.0) | 13495 (57.9) |
| Mastectomy |         | 50004 (34.5) | 31395 (29.5) | 18609 (48.5) | 9788 (42.0) | 9802 (42.1) |
| Radiation (%) |   | 0.218 |   |   | 0.717 |   |

Note: PSM propensity score matching; CHT chemotherapy; AIA American Indian/Alaska Native; API Asian or Pacific Islander

a “Others” includes “Central portion of breast”, “Breast includes Nipple” and “Overlapping lesion of breast such as 3, 6, 9, 12 o’clock” as recorded in the SEER database

b “IV” represents undifferentiated
Variables | Overall | Before PSM | After PSM |
|---|---|---|---|
| | No CHT | CHT | p | No CHT | CHT | p |
| No/unknown | 60046 (41.5) | 44016 (41.4) | 16030 (41.8) | 11064 (47.5) | 11024 (47.3) | 0.001 |
| Yes | 84689 (58.5) | 62327 (58.6) | 22362 (58.2) | 12233 (52.5) | 12273 (52.7) | 0.001 |
| Survival months (mean (SD)) | 43.45 (21.17) | 43.00 (21.12) | 44.71 (21.25) | 42.54 (21.05) | 45.07 (21.36) | 0.001 |

Note: PSM propensity score matching; CHT chemotherapy; AIA American Indian/Alaska Native; API Asian or Pacific Islander

a “Others” includes “Central portion of breast”, “Breast includes Nipple” and “Overlapping lesion of breast such as 3, 6, 9, 12 o’clock” as recorded in the SEER database

b “IV” represents undifferentiated

Analysis of Survival Benefits from CHT before and after PSM

As shown in the Kaplan-Meier plot, among the unmatched patients, patients in CHT group had better OS (HR 0.908, 95%CI 0.861 to 0.958, p = 0.00041) but had worse BCSS (HR 2.529, 95%CI 2.342 to 2.731, p < 0.0001); after PSM, the CHT group still had better OS, and the difference was more obvious than before (HR 0.663, 95%CI 0.611 to 0.719, p < 0.0001). However, there was no significant difference in BCSS between CHT group and no CHT group in the matched cohort (HR 1.005, 95%CI 0.897 to 1.126, p = 0.93) (Fig. 2)

Risk Factors Related with Survival in patients without CHT

To determine the multiple factors associated with OS and BCSS, the univariate and multivariate Cox proportional hazards regression model was performed in no CHT patients. Initially, the univariate analysis showed that all of the 11 variables were significant risk factors for OS (P < 0.05) and except for tumor location, 10 variables were significant risk factors for BCSS (P < 0.05): age, race, marital, tumor location, T stage, tumor size, N stage, number of positive nodes, nuclear grade, breast surgery type, radiation (Table 2). We included these factors in the next multivariate analysis in order to find the independent risk factors affecting the survival of patients. In multivariate Cox analysis, we found that age, race, marital, tumor size, number of positive nodes, nuclear grade, breast surgery type, radiation were independent risk factors of breast cancer (Table 3).
Table 2
Univariate Cox models for patients without CHT

| Variables          | OS                  |          | BCSS                |          |
|--------------------|---------------------|----------|---------------------|----------|
|                    | HR (95% CI)         | P-value  | HR (95% CI)         | P-value  |
| Age (%)            | < 0.001             |          | < 0.001             |          |
| < 35               | ref                 |          | ref                 |          |
| 35–59              | 3.452(0.860, 13.857)| 0.081    | 2.007(0.498, 8.078) | 0.327    |
| 60–85              | 13.056(3.261, 52.275)| < 0.001 | 4.595(1.145, 18.443)| 0.031    |
| Race (%)           | < 0.001             |          | < 0.001             |          |
| White              | ref                 |          | ref                 |          |
| Black              | 1.284(1.089, 1.515) | 0.003    | 1.402(1.092, 1.800) | 0.008    |
| AIA/ API           | 0.619(0.489, 0.784) | < 0.001 | 0.606(0.417, 0.882) | 0.009    |
| Marital (%)        | < 0.001             |          | < 0.001             |          |
| Unmarried          | ref                 |          | ref                 |          |
| Married            | 0.496(0.446, 0.551) | < 0.001 | 0.590(0.501, 0.695) | < 0.001 |
| Tumor Location (%) | 0.028               |          | 0.115               |          |
| Outer              | ref                 |          | ref                 |          |
| Inner              | 1.072(0.922, 1.245) | 0.367    | 1.068(0.843, 1.352) | 0.585    |
| Others a           | 1.172(1.043, 1.316) | 0.007    | 1.209(1.009, 1.449) | 0.039    |
| T (%)              | < 0.001             |          | < 0.001             |          |
| T1                 | ref                 |          | ref                 |          |
| T2                 | 2.295(2.052, 2.566) | < 0.001 | 3.022(2.516, 3.629) | < 0.001 |
| T3                 | 3.106(2.530, 3.813) | < 0.001 | 5.012(3.737, 6.721) | < 0.001 |
| Tumor Size (cm)    | < 0.001             |          | < 0.001             |          |
| < 1                | Ref                 |          | ref                 |          |
| 1–2                | 1.494(1.193, 1.872) | < 0.001 | 1.763(1.170, 2.658) | 0.007    |
| 2–3                | 2.624(2.096, 3.284) | < 0.001 | 3.889(2.600, 5.816) | < 0.001 |

Note: PSM propensity score matching; CHT chemotherapy; OS overall survival; BCSS breast cancer–specific survival
| Variables          | OS              | BCSS             |
|-------------------|-----------------|------------------|
|                   | HR (95% CI)     | P-value          | HR (95% CI)     | P-value |
| 3–4               | 4.383(3.440, 5.586) | < 0.001          | 6.760(4.423, 10.333) | < 0.001 |
| 4–5               | 4.606(3.426, 6.192) | < 0.001          | 7.307(4.473, 11.937) | < 0.001 |
| > 5               | 4.267(3.236, 5.625) | < 0.001          | 7.902(5.017, 12.446) | < 0.001 |
| N                 | < 0.001         |                  | < 0.001         |         |
| N0                | ref             |                  | ref             |         |
| N1                | 1.578(1.420, 1.754) | < 0.001          | 1.864(1.581, 2.197) | < 0.001 |
| No. of positive Nodes | < 0.001 |                  | < 0.001         |         |
| 0                 | ref             |                  | ref             |         |
| 1                 | 1.317(1.163, 1.491) | < 0.001          | 1.512(1.247, 1.833) | < 0.001 |
| 2                 | 2.022(1.713, 2.386) | < 0.001          | 2.446(1.907, 3.137) | < 0.001 |
| 3                 | 2.801(2.233, 3.513) | < 0.001          | 3.553(2.552, 4.946) | < 0.001 |
| Nuclear Grade (%) | < 0.001         |                  | < 0.001         |         |
| Well              | ref             |                  | ref             |         |
| Moderately        | 1.210(1.013, 1.444) | 0.036            | 1.542(1.093, 2.177) | 0.014 |
| Poorly            | 2.265(1.900, 2.701) | < 0.001          | 4.739(3.402, 6.601) | < 0.001 |
| Breast Surgery (%)| < 0.001         |                  | < 0.001         |         |
| Lumpectomy        | ref             |                  | ref             |         |
| Mastectomy        | 1.330(1.197, 1.478) | < 0.001          | 1.401(1.189, 1.652) | < 0.001 |
| Radiation (%)     | < 0.001         |                  | < 0.001         |         |
| No/unknown        | ref             |                  | ref             |         |
| Yes               | 0.618(0.555, 0.687) | < 0.001          | 0.555(0.469, 0.658) | < 0.001 |

Note: PSM propensity score matching; CHT chemotherapy; OS overall survival; BCSS breast cancer-specific survival
Table 3
Multivariate Cox result of OS and BCSS for breast cancer patients in no CHT cohort

| Variables         | OS                      |                | BCSS                      |                |
|-------------------|-------------------------|----------------|--------------------------|----------------|
|                   | HR (95% CI)             | P-value        | HR (95% CI)              | P-value        |
| Age (%)           |                         |                |                          |                |
| < 35              | ref                     | ref            | ref                      | ref            |
| 35–59             | 3.453(0.860, 13.866)    | 0.081          | 2.007(0.498, 8.078)      | 0.399          |
| 60–85             | 11.188(2.792, 44.841)   | 0.001          | 4.595(1.145, 18.443)     | 0.095          |
| Race (%)          |                         |                |                          |                |
| White             | ref                     | ref            | ref                      | ref            |
| Black             | 1.156(0.977, 1.368)     | 0.092          | 1.402(1.092, 1.800)      | 0.114          |
| AIA/ API          | 0.750(0.591, 0.952)     | 0.018          | 0.606(0.417, 0.882)      | 0.044          |
| Marital (%)       |                         |                |                          |                |
| Unmarried         | ref                     | ref            | ref                      | ref            |
| Married           | 0.608(0.545, 0.677)     | < 0.001        | 0.590(0.501, 0.695)      | 0.001          |
| Tumor Size (cm)   |                         |                |                          |                |
| < 1               | Ref                     | ref            | ref                      | ref            |
| 1–2               | 1.314(1.049, 1.648)     | 0.018          | 1.490(0.988, 2.248)      | 0.057          |
| 2–3               | 1.980(1.581, 2.488)     | < 0.001        | 2.803(1.868, 4.205)      | < 0.001        |
| 3–4               | 3.079(2.408, 3.939)     | < 0.001        | 4.618(3.007, 7.094)      | < 0.001        |
| 4–5               | 3.091(2.289, 4.174)     | < 0.001        | 5.104(3.102, 8.399)      | < 0.001        |
| > 5               | 3.224(2.445, 4.315)     | < 0.001        | 6.714(4.214, 10.696)     | < 0.001        |
| No. of Node       |                         |                |                          |                |
| 0                 | ref                     | ref            | ref                      | ref            |
| 1                 | 1.308(1.152, 1.486)     | < 0.001        | 1.816(1.491, 2.211)      | < 0.001        |
| 2                 | 1.631(1.377, 1.931)     | < 0.001        | 2.318(1.799, 2.987)      | < 0.001        |
| 3                 | 1.939(1.540, 2.441)     | < 0.001        | 2.743(1.967, 3.845)      | < 0.001        |
| Grade (%)         |                         |                |                          |                |
|                   | < 0.001                 |                |                          |                |

CHT chemotherapy; OS overall survival; BCSS breast cancer–specific survival
### Construction and Validation of the Nomogram

In the previous survival analysis, we found patients with CHT had better OS in the matched patient cohort, but there was no significant difference in BCSS. Obviously, compared with OS, BCSS can more objectively reflect the CHT benefits of patients. The reason why BCSS had no difference between CHT and no CHT patients may be explained by that CHT cannot improve survival for some patients but even increase CHT-related complications. On contrary, there are some people who can benefit from CHT but do not receive CHT. Therefore, in order to identify the population who can benefit from CHT and those who cannot, we constructed a nomogram to predict 3- and 5- BCSS for patients without CHT using independent risk factors found in multivariate Cox analysis (age, race, marital, grade, tumor size, number of positive nodes, breast surgery type, radiation) (Fig. 3). According to the point scale in the nomogram, a total point can be calculated by adding all points based on patient’s individual clinicopathological characteristics. A lower score was considered to have better prognosis. By comparing the survival outcomes predicted by the nomograms, clinicians and patients can weigh the risk-benefit gained from CHT and make a tailored decision.

The baseline between patients with and without CHT was well-balanced after PSM so the two cohorts conformed to the random cohorts. Therefore, the nomogram was validated internally and externally using the no CHT cohort (training set) and the CHT cohort (validation set). The C-index was 0.794 (95%CI 0.774 to 0.814) in the internal validation and 0.736 (95%CI 0.716 to 0.756) in the external validation. Calibration curves showed high consistency between observed outcomes and nomogram-predicted outcomes (Fig. 4). Both the internal validation and the external validation demonstrated a sufficient accuracy of the model.

| Variables       | OS          | BCSS        |
|-----------------|-------------|-------------|
|                 | HR (95% CI) | P-value     | HR (95% CI) | P-value     |
| Well            | ref         | ref         |
| Moderately      | 1.056(0.884, 1.263) | 0.548 | 1.354(0.958, 1.914) | 0.086 |
| Poorly          | 1.929(1.611, 2.310) | < 0.001    | 4.466(3.188, 6.256) | < 0.001 |
| Breast Surgery (%) | 0.003       | 0.008       |
| Lumpectomy      | ref         | ref         |
| Mastectomy      | 0.821(0.719, 0.937) | 0.003 | 0.761(0.622, 0.932) | 0.008 |
| Radiation (%)   | < 0.001     | < 0.001     |
| No/unknown      | ref         | ref         |
| Yes             | 0.558(0.489, 0.635) | < 0.001    | 0.549(0.448, 0.671) | < 0.001 |

CHT chemotherapy; OS overall survival; BCSS breast cancer-specific survival
Risk Group Stratification Based on Nomogram Score

The nomogram could calculate the risk score for each patient and then all patients were divided into two groups using X-tile: risk score ≤ 238 belonged to the low-risk group and > 238 belonged to the high-risk group (Fig. 5).

Interestingly, Kaplan-Meier plots showed that in the low-risk group, patients received CHT had better OS (HR 0.718, 95%CI 0.649 to 0.794, p < 0.0001) while they had worse BCSS (HR 1.216, 95%CI 1.046 to 1.414, p = 0.011). However, in the high-risk group, patients with CHT had better OS (HR 0.583, 95%CI 0.507 to 0.671, p < 0.0001) and BCSS (HR 0.791, 95%CI 0.663 to 0.944, p = 0.0091) (Fig. 6). These results indicated that patients in the high-risk group could benefit from CHT while those in the low-risk group should avoid CHT to avoid unnecessary side effects.

Discussion

After screening and analyzing the data from SEER database, eight independent prognostic factors (age, race, marital, grade, tumor size, number of positive nodes, breast surgery type, radiation) were included to build the nomogram to predict patients’ BCSS. Then, X-tile was used to find a binary critical point of risk model which could help T1-3N0-1 breast cancer patients with HR+, HER2- judge whether CHT is necessary. We were surprised to find that CHT should be recommended for the high-risk patients but patients in the low-risk group may receive endocrine monotherapy because no benefit was gained from CHT, which is of great significance for clinical practice. It means that we can divide people into two groups: those who need CHT or do not, without intermediate risk group. For low-risk patients, CHT may not improve survival but increase the burden of patients and is more likely to bring CHT-related complications and side effects; for high-risk patients, CHT can bring survival benefits.

The risk model provides an objective and clear method for clinicians and patients and it is the largest retrospective analysis of early breast cancer population with T1-3N0-1, HR+, HER2-. In recent years, there have been a number of single-center and multi-center retrospective analyses to discuss whether patients with HR+, HER2- early breast cancer need adjuvant CHT according to the clinicopathological factors. (14, 19, 20) In a population-based study from British Columbia, most of the 1 187 T1–2N0 early breast cancer patients without adjuvant systemic therapies (> 70%) did not recur locoregionally or distantly within 10 years after diagnosis, (20) which meant that a considerable proportion of patients with HR+, HER2- early breast cancer can avoid CHT without sacrificing the curative effect. Another study combined clinicopathological factors with gene test results to determine whether CHT is necessary, (21) which showed that the two methods had their own advantages and perfected each other. There are also some studies hoping to replace Oncotype DX by constructing imaging or clinical indicators model equations. (10, 22) However, most of them are single-center studies and limited by the sample size and follow-up time so the results were somewhat inconsistent and unreliable.
In this study, before PSM, the OS of CHT group is better than that of no CHT group. The possible reasons are as follows: first of all, the underlying diseases and baseline of the two groups are inconsistent (the no CHT group had more patients > 60 years old); secondly, compared with patients without CHT, CHT group patients may have fewer underlying diseases, so the better OS of CHT group may not be completely attributed to the effect of CHT. The BCSS of CHT group is worse than that of no CHT group and the reason may be that patients in the CHT group had larger tumors and a higher stage. After PSM, the CHT group had better OS benefit when the baseline (demographic and clinical characteristics) of the two group was well-balanced but BCSS had no difference between the two groups. However, the underlying diseases of patients in this study could not be obtained from the database.

CHT cannot improve the BCSS of this population, does it mean that these people do not need CHT? The answer is clearly No. Many clinical trials and retrospective analyses have confirmed that some of the patients with HR+, HER2- early breast cancer can benefit from CHT. For instance, the ongoing Southwest Oncology Group (SWOG) S1007 RxPONDER trial assigned women with 1–3 lymph node-positive nodes, HR+, HER2- breast cancer and a RS ≤ 25 to standard endocrine therapy with or without adjuvant CHT. This trial expects to determine the benefit (if any) of CHT for patients in this cohort. Based on the results of our study that there is no difference in BCSS between CHT and no CHT groups, we speculate that CHT can make some high-risk patients get better BCSS, but not benefit the low-risk groups.

In order to identify precisely who can benefit from CHT, we have teamed up with nomogram and X-tile to identify low- /high-risk groups in this study. The results showed that CHT did not improve survival of low-risk patients, and BCSS was slightly damaged. We speculated that breast cancer-related death may be caused by CHT-related injuries (such as CHT-related pneumonia, CHT-related myelosuppression), so such patients should give up CHT. For high-risk patients, CHT can bring obvious BCSS benefit and OS benefit is further increased (HR decreased from 0.663 to 0.583) so from another point of view, CHT is necessary for these people.

This study also had some limitations. For example, we could not get the information of endocrine therapy and CHT regimen from SEER database. Although the baseline of the two groups was balanced by PSM, the retrospective study could not replace the RCT study. It is worth noting that the nomogram and risk model constructed in this study have been verified by survival analysis, which played an effective role in deciding whether to undergo CHT or not for HR+, HER2- early breast cancer patients, and we expect it could be useful for the design of future RCT experiments.

Conclusion

In conclusion, breast cancer patients with HR+, HER2- subtypes and stage pT1-3N0-1 may benefit from CHT if they are in the high-risk group estimated by the risk stratification model (risk score > 238) but patients in the low-risk group (risk score ≤ 238) may be exempt from CHT.

Abbreviations
Declarations

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All authors have no conflicts of interested to declare.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets presented in this study can be found in online repositories. The name of the repository and reference number can be found below: http://seer.cancer.gov/.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JQ and LX contributed to the conception and design of the work; JQ was a major contributor in writing the manuscript. YW and JZ were major contributor in acquiring, analyzing the data; JY, QL and ZD interpreted the data; ZD revised the manuscript. All authors read and approved the final manuscript.

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Our study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

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