RESEARCH ARTICLE

Prognostic validation and therapeutic decision-making of the AJCC eighth pathological prognostic staging for T3N0 breast cancer after mastectomy

San-Gang Wu1 | Jun Wang1 | Jian Lei3 | Chen-Lu Lian1 | Li Hua3 | Juan Zhou3 | Zhen-Yu He2

1Department of Radiation Oncology, The First Affiliated Hospital of Xiamen University, Teaching Hospital of Fujian Medical University, Xiamen, People’s Republic of China
2Department of Radiation Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, People’s Republic of China
3Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xiamen University, Teaching Hospital of Fujian Medical University, Xiamen, People’s Republic of China

Correspondence
Juan Zhou, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xiamen University, Teaching Hospital of Fujian Medical University, Xiamen 361003, People’s Republic of China.
Email: zhoujuan@xmu.edu.cn
Zhen-Yu He, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, 651 Dongfeng Road East, Guangzhou 510060, People’s Republic of China.
Email: hezhy@sysucc.org.cn

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 81802600, 81872459; The Commission Young and Middle-aged Talents Training Project of Fujian Health

Abstract
Background: T3N0 breast cancer might be a distinct clinical and biological entity, with higher heterogeneity and presenting diverse responses to locoregional and systemic therapy. The aim of the current study was to validate the prognostic effect and assess the treatment decision-making of the American Joint Committee on Cancer (AJCC) eighth pathological prognostic staging in T3N0 breast cancer after mastectomy.

Methods: We retrospectively included 2465 patients with stage T3N0 breast cancer who had undergone mastectomy between 2010 and 2014 using the data from Surveillance, Epidemiology, and End Results program. The primary endpoint of this study was breast cancer–specific survival (BCSS).

Results: Of the entire cohort, 76.0% of patients in the seventh AJCC staging system were restaged to the eighth AJCC pathological prognostic staging system. A total of 1431 (58.1%) and 1175 (47.7%) of them received chemotherapy and postmastectomy radiotherapy (PMRT), respectively. Pathological staging was an independent prognostic factor for BCSS. Using pathological prognostic stage IA as the reference, BCSS gradually became worse with increased hazard ratios. The 5-years BCSS was 96.9%, 95.5%, 91.1%, 85.6%, and 75.5% in pathological prognostic stage IA, IB, IIA, IIB, and IIC.

Abbreviations: AJCC, American Joint Committee on Cancer; BCSS, breast cancer–specific survival; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; HER2, human epidermal growth factor receptor 2; IDC, infiltrating ductal carcinoma; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Database; OS, overall survival; PMRT, postmastectomy radiotherapy; PR, progesterone receptor; SEER, Surveillance, Epidemiology, and End Results.

San-Gang Wu and Jun Wang contributed equally to this work.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. Clinical and Translational Medicine published by John Wiley & Sons Australia, Ltd on behalf of Shanghai Institute of Clinical Bioinformatics
IIIA breast cancers, respectively ($P < .001$). In pathological prognostic stage IA, IB, and IIA breast cancers, the receipt of PMRT or chemotherapy was not correlated with better BCSS. However, PMRT was correlated with better BCSS in pathological prognostic stage IIB disease ($P = .006$), but not in pathological prognostic IIIA disease. Moreover, chemotherapy was correlated with better BCSS in pathological prognostic stage IIIA disease ($P = .006$), but not in pathological prognostic stage IIB disease.

**Conclusions:** The eighth AJCC pathological prognostic staging system provides more risk stratification of T3N0 breast cancers after mastectomy and might affect individualized decision-making for chemotherapy and PMRT in this patient subset.

**KEYWORDS**
breast neoplasms, drug therapy, mastectomy, neoplasm staging, radiotherapy

## 1 | BACKGROUND

The traditionally anatomical American Joint Committee on Cancer (AJCC) TNM system (T, tumor; N, nodes; M, metastasis) has been widely adopted to predict the outcome and treatment decision-making of breast cancer worldwide.\(^1\) Breast cancer is a highly heterogeneous entity with diverse prognoses. Several biological factors including histological grade, human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR) status have been identified and validated for their prognostic and predictive role in breast cancer.\(^2\) The new eighth AJCC pathological prognostic staging system has integrated these biological factors into the anatomical TNM stages.\(^1\)\(^-\)\(^4\) The effect of new pathological prognostic stages on survival outcomes has been confirmed by several studies, which showed that the new pathological prognostic stages provide accurate prognostic information compared with the anatomical stages.\(^5\)\(^-\)\(^8\) However, currently, no study has assessed the effect of the new pathological prognostic staging on prognosis and treatment decision-making in various anatomical TNM stages.

In the breast cancer treatment guidelines from the National Comprehensive Cancer Network (NCCN), the recommendation for systemic therapy and postmastectomy radiotherapy (PMRT) still refers to the tumor size and nodal status.\(^9\)

Breast cancer with tumor size greater than 5 cm and negative nodal status was defined as stage T3N0, and accounts for approximately 0.5-4% of all breast cancers.\(^10\)\(^-\)\(^15\) A secondary data analysis from randomized clinical trials showed that chemotherapy and endocrine therapy were not correlated with better locoregional control and lower risk of distant metastasis (DM).\(^10\) However, two studies from the National Cancer Database (NCDB) showed better overall survival (OS) with the administration of chemotherapy.\(^16\)\(^,\)\(^17\) There were also conflicting results regarding the role of PMRT in this patient subset.\(^10\)\(^,\)\(^11\)\(^,\)\(^18\)\(^-\)\(^25\) Therefore, T3N0 breast cancer might be a distinct clinical and biological entity, with higher heterogeneity and presenting diverse responses to locoregional and systemic therapy. However, no studies determining the role of the treatment decision-making in T3N0 breast cancer have been published. Our study aimed to validate the prognostic effect and assess the decision-making of treatment using the AJCC eighth pathological prognostic staging in T3N0 breast cancer using the data from the Surveillance, Epidemiology, and End Results (SEER) program.

## 2 | MATERIALS AND METHODS

### 2.1 | SEER database and study population

We conducted a retrospective analysis including female T3N0 breast cancer patients who underwent mastectomy from 2010 to 2014 using the data from the SEER program, a population-based national cancer registry including tumor incidence, demographic and tumor characteristics, treatment, and survival for approximately 28% of the U.S. population.\(^26\) Patients with male breast cancer, de novo stage IV disease, nonpositive pathological diagnosis, those treated with nonbeam external irradiation, and insufficient data were excluded. We analyzed the de-identified information for patients contained in the SEER database; therefore, the present study was exempted from approval by Institutional Review Board.

We identified the patients’ demographic and clinicopathological data, including age, race/ethnicity, tumor grade, histology, HER2, ER, and PR status. In addition, whether chemotherapy or PMRT was administered was also included in the analysis. The classification of pathological prognostic stages was based on the AJCC eighth edition pathological prognostic staging manual.\(^1\)\(^,\)\(^2\)
2.2 | Statistical analysis

A chi-squared test was performed to compare the patient demographic and clinicopathological characteristics among treatment arms. Kaplan-Meier analysis was used to calculate breast cancer–specific survival (BCSS), and the difference in BCSS rates was compared using the log-rank test. The BCSS was defined as the interval from the diagnosis of breast cancer to the date of death from breast cancer or the follow-up cutoff. Concordance index (c-statistic) was then used to investigate the discriminatory ability of pathological prognostic staging system in predicting BCSS. Cox proportional hazards regression models were constructed to assess the indicators that were independently related to BCSS. In addition, a competing risks model was also used to investigate the combined effects of the pathological prognostic staging system on breast cancer–specific mortality. Other causes of death were considered as competing events. P values < .05 were indicated statistically significant. All data analyses were performed using Stata/SE version 14 (StataCorp, TX) and IBM SPSS 22.0 (IBM Corp., Armonk, NY).

3 | RESULTS

3.1 | Patient characteristics

A total of 2465 patients who underwent a mastectomy and had the required information to determine the prognostic stages were included in this study. Table 1 summarizes the patient characteristics. The study cohort included 383 patients (15.5%) with well-differentiated disease, 1035 (42.0%) with moderately differentiated disease, and 1047 (42.5%) with poorly and/or undifferentiated breast cancer. With regard to hormone receptor status, 72.5%, 60.0%, and 16.0% of the tumors were ER positive, PR positive, and HER2 overexpressed, respectively.

In the entire cohort, 1431 (58.1%) patients received chemotherapy. Patients with age <50 years, black race, poorly and/or undifferentiated disease, infiltrating ductal carcinoma (IDC), hormone receptor negative disease, and HER2 positive disease were more likely to receive chemotherapy (all P < .001). In addition, patients with pathological prognostic stage IIB and IIIA breast cancers were also associated with receipt of chemotherapy (Table 1).

A total of 1175 patients (47.7%) had undergone PMRT. Patients with age <50 years, higher tumor grade, non-IDC histology, and those receiving chemotherapy were more likely to receive PMRT (all P < .05). Patients with pathological prognostic stage IIA-IIIA disease had a comparable probability of receiving PMRT (P = .798) (Table 1).

Among the patients with available information on the number of removed lymph nodes (n = 2446), the median number of removed lymph nodes was four (range 1-42), and 47.8% of them had three or fewer lymph nodes removed.

3.2 | Restaging

Of the 2465 patients, 76.0% of patients in the seventh AJCC staging system were restaged to the eighth AJCC pathological prognostic staging system, with 17.6% being upstaged and 58.4% downstaged. A total of 322 (13.1%), 890 (36.1%), and 228 (9.2%) patients with seventh edition stage IIB disease were downstaged to pathological prognostic stage IA, IB, and IIA according to the eighth edition criteria. In addition, 434 (17.6%) patients were upstaged to pathological prognostic stage IIIA disease in the eighth edition criteria.

3.3 | Survival and multivariate prognostic analysis

With a median follow-up of 45 months (range 0-83 months), the overall 5-year BCSS was 89.5%, and was 96.9%, 95.5%, 91.1%, 85.6%, and 75.5% in pathological prognostic stage IA, IB, IIA, IIB, and IIIA breast cancers, respectively (P < .001) (Figure 1). However, BCSS was comparable between pathological prognostic stage IA and IB breast cancers (P = .272). BCSS was also comparable between pathological prognostic stage IIA and IIB breast cancers (P = .063).

The results of multivariate prognostic analysis indicated that pathological prognostic staging was an independent prognostic indicator associated with BCSS. Using pathological prognostic stage IA as the reference, worse BCSS was observed with gradually increasing hazard ratios (HRs). The HR for pathological prognostic stage IIA, IIB, and IIIA disease was 3.082 times (95% confidence interval [CI] 1.307-7.269, P = .010), 5.053 times (95% CI 2.410-10.596, P < .001), and 10.447 times (95% CI 4.981-21.913, P < .001) than that of pathological prognostic stage IA disease, while no significant difference was found between pathological prognostic stage IB and IA disease (HR = 1.668, 95% CI 0.767-3.630, P = .197). In addition, age, histology, and PMRT were also independent prognostic factors affecting BCSS. However, chemotherapy had no effect on BCSS in the entire cohort (Table 2). C-statistic was assessed using BCSS as the dependent variable, and the pathological prognostic staging demonstrated moderate discriminative ability (c = 0.740, SE = 0.016, 95% CI 0.709-0.771).

Subdistribution hazard ratio (sdHR) adjusted for age at diagnosis, race/ethnicity, histology, chemotherapy, and PMRT was evaluated (Table 2). The results showed an
**Patient characteristics in the study cohort**

| Variables                | n  | Radiotherapy | Chemotherapy |
|--------------------------|----|--------------|--------------|
|                          |    | No (%)       | Yes (%)      | No (%)       | Yes (%)      |
| **Age (years)**          |    |              |              |              |              |
| <50                      | 652| 288 (22.3)   | 364 (31.0)   | 114 (11.0)   | 538 (37.6)   |
| ≥50                      | 1813| 1002 (77.7)  | 811 (69.0)   | 920 (89.0)   | 893 (62.4)   |
| **Race/ethnicity**       |    |              |              |              |              |
| White                    | 1889| 999 (77.4)   | 890 (75.7)   | 831 (80.4)   | 1058 (73.9)  |
| Black                    | 350 | 175 (13.6)   | 175 (14.9)   | 117 (11.3)   | 233 (16.3)   |
| Other                    | 226 | 116 (9.0)    | 110 (9.4)    | 86 (8.3)     | 140 (9.8)    |
| **Grade**                |    |              |              |              |              |
| Well differentiated      | 383 | 223 (17.3)   | 160 (13.6)   | 239 (23.1)   | 144 (10.1)   |
| Moderately differentiated | 1035| 521 (40.4)   | 514 (43.7)   | 506 (48.9)   | 529 (37.0)   |
| Poorly/undifferentiated  | 1047| 546 (42.3)   | 501 (42.6)   | 289 (27.9)   | 758 (53.0)   |
| **Histological subtypes**|    |              |              |              |              |
| Infiltrating ductal carcinoma | 1503| 823 (63.8)  | 680 (57.9)   | 509 (49.2)   | 994 (69.5)   |
| Infiltrating lobular carcinoma | 704 | 315 (24.4)  | 389 (33.1)   | 389 (37.6)   | 315 (22.0)   |
| Other                    | 258 | 152 (11.8)   | 106 (9.0)    | 136 (13.2)   | 122 (8.5)    |
| **ER status**            |    |              |              |              |              |
| Negative                 | 677 | 356 (27.6)   | 321 (27.3)   | 167 (16.2)   | 510 (35.6)   |
| Positive                 | 1788| 934 (72.4)   | 854 (72.7)   | 867 (83.8)   | 921 (64.4)   |
| **PR status**            |    |              |              |              |              |
| Negative                 | 986 | 509 (39.5)   | 477 (40.6)   | 292 (28.2)   | 694 (48.5)   |
| Positive                 | 1479| 781 (60.5)   | 698 (59.4)   | 742 (71.8)   | 737 (51.5)   |
| **HER2 status**          |    |              |              |              |              |
| Negative                 | 2071| 1075 (83.3)  | 996 (84.8)   | 955 (92.4)   | 1116 (78.0)  |
| Positive                 | 394 | 215 (16.7)   | 179 (15.2)   | 79 (7.6)     | 315 (22.0)   |
| **Pathological prognostic stages** | | | | | |
| IA                       | 322 | 194 (15.0)   | 128 (10.9)   | 207 (20.0)   | 115 (8.0)    |
| IB                       | 890 | 445 (34.5)   | 445 (37.9)   | 431 (41.7)   | 459 (32.1)   |
| IIA                      | 228 | 121 (9.4)    | 107 (9.1)    | 96 (9.3)     | 132 (9.2)    |
| IIB                      | 591 | 310 (24.0)   | 281 (23.9)   | 187 (18.1)   | 404 (28.8)   |
| IIIA                     | 434 | 220 (17.1)   | 214 (18.2)   | 113 (10.9)   | 321 (22.4)   |
| **Chemotherapy**         |    |              |              |              |              |
| No                       | 1034| 599 (54.2)   | 335 (28.5)   | –            | –            |
| Yes                      | 1431| 591 (54.8)   | 840 (71.5)   | –            | –            |
| **PMRT**                 |    |              |              |              |              |
| No                       | 1290| –            | –            | 699 (67.6)   | 591 (41.3)   |
| Yes                      | 1175| –            | –            | 335 (32.4)   | 840 (58.7)   |

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; PMRT, postmastectomy radiotherapy; PR, progesterone receptor.

Increasing risk of breast cancer–specific mortality with increasing staging. Using pathological prognostic stage IA as the reference, the sdHR for pathological prognostic stage IIA, IIB, and IIIA disease was 3.000 times (95% CI 1.290-6.978, \( P = .011 \)), 4.817 times (95% CI 2.313-10.030, \( P < .001 \)), and 8.984 times (95% CI 4.280-18.859, \( P < .001 \)) compared to pathological prognostic stage IA, while no significant difference was found between pathological prognostic stage IB and IA disease (sdHR = 1.631, 95% CI 0.750-3.546, \( P = .217 \)). The cumulative incidence function of the pathological prognostic stages is displayed in Figure 2. The 5-year breast cancer–specific mortality was 3.0%, 4.3%, 8.6%, 13.8%, and 23.3% in pathological prognostic stage IA, IB, IIA, IIB, and IIIA breast cancers, respectively (\( P < .001 \)).

We then used three multivariate prognostic models to assess the effect of pathological prognostic staging on...
FIGURE 1 Kaplan-Meier curves of breast cancer-specific survival stratified using the eighth AJCC pathological prognostic stages BCSS by different treatment approaches (Table 3). The results showed similar results regarding the differences in BCSS among the five pathological substages comprising nonchemotherapy, non-PMRT, and neither of chemotherapy nor PMRT. In the nonchemotherapy cohort, the 5-year BCSS was 96.8%, 94.8%, 82.0%, 83.0%, and 64.8% in pathological prognostic stage IA, IB, IIA, IIB, and IIIA breast cancers, respectively (P < .001) (Figure 3A); in the non-PMRT cohort, the 5-year BCSS was 96.5%, 94.8%, 89.7%, 79.9%, and 71.6%, respectively (P < .001) (Figure 3B); and was 95.2%, 93.5%, 82.3%, 79.1%, and 67.9%, respectively, in the nonchemotherapy and non-PMRT cohort (P < .001) (Figure 3C). However, BCSS was comparable between pathological prognostic stage IA and IB disease in the nonchemotherapy cohort (P = .205) and in the nonchemotherapy and non-PMRT cohort (P = .395). In addition, BCSS was also comparable between pathological prognostic stage IIA and IIB disease in the non-chemotherapy cohort (P = .865) and in the non-chemotherapy and non-PMRT cohort (P = .621). Similar trends were found using cumulative incidence function. The cumulative incidence function of the pathological prognostic stages by different treatment approaches is displayed in Figure 4.

TABLE 2 Multivariate prognostic analysis in the entire cohort using Cox proportional hazards model and competing risks model

| Variables                  | Cox proportional hazards model | Competing risks model |
|----------------------------|--------------------------------|-----------------------|
|                            | HR    | 95%CI      | P       | sdHR   | 95%CI      | P       |
| Age (continuous variable)  | 1.022 | 1.013-1.032| <.001   | 1.019  | 1.007-1.031| .002    |
| Race/ethnicity             |       |            |         |        |            |         |
| White                      | 1     | 1          |         | 1.319  | 0.938-1.854| .111    |
| Black                      | 1.328 | 0.954-1.849| .093    | 1.319  | 0.938-1.854| .111    |
| Other                      | 0.734 | 0.407-1.324| .304    | 0.728  | 0.407-1.303| .285    |
| Histological subtypes      |       |            |         |        |            |         |
| IDC                        | 1     | 1          |         | 1.46   | 0.998-2.138| .051    |
| ILC                        | 0.658 | 0.422-1.026| .065    | 0.691  | 0.449-1.062| .092    |
| Other                      | 1.440 | 1.00-2.055 | .045    | 1.46   | 0.998-2.138| .051    |
| Pathological prognostic stages |       |            |         |        |            |         |
| IA                         | 1     | 1          |         | 1.631  | 0.750-3.546| .217    |
| IB                         | 1.668 | 0.767-3.630| .197    | 1.631  | 0.750-3.546| .217    |
| IIA                        | 3.082 | 1.307-7.269| .010    | 3.000  | 1.290-6.978| .011    |
| IIB                        | 5.053 | 2.410-10.596| <.001   | 4.817  | 2.313-10.030| <.001   |
| IIIA                       | 10.447| 4.981-21.913| <.001   | 8.984  | 4.280-18.859| <.001   |
| Chemotherapy               |       |            |         |        |            |         |
| No                         | 1     | 1          |         | 1.012  | 0.701-1.461| .949    |
| Yes                        | 0.976 | 0.688-1.386| .894    | 1.012  | 0.701-1.461| .949    |
| PMRT                       |       |            |         |        |            |         |
| No                         | 1     | 1          |         | 1.012  | 0.701-1.461| .949    |
| Yes                        | 0.640 | 0.481-0.852| .002    | 0.656  | 0.489-0.881| .005    |

Abbreviations: CI, confidence interval; HR, hazard ratio; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; PMRT, postmastectomy radiotherapy; sdHR, subdistribution hazard ratio.
FIGURE 2 The cumulative incidence function according to the eighth AJCC pathological prognostic stages

3.4 The effect of chemotherapy and PMRT on BCSS in various pathological stages

Five multivariate prognostic models were performed to assess the prognostic effect of chemotherapy and PMRT on BCSS in various pathological prognostic stages after adjustment for age at diagnosis, race/ethnicity, and histology (Table 4). The results showed that the use of chemotherapy or PMRT was not correlated with better BCSS in pathological prognostic stage IA, IB, and IIA breast cancers. However, the use of chemotherapy was related to better BCSS in pathological prognostic stage IIIA disease (HR 0.539, 95% CI 0.347-0.837, P = .006). The 5-year BCSS was 78.7% and 64.8% in patients with and without chemotherapy (P = .001) (Figure 5A), while comparable BCSS was observed between the chemotherapy and nonchemotherapy cohorts in pathological prognostic stage IIB disease. Moreover, the use of PMRT was correlated with better BCSS in pathological prognostic stage IIB disease (HR 0.476, 95% CI 0.279-0.812, P = .006). The 5-year BCSS was 91.5% and 79.9% in patients with and without PMRT (P = .001) (Figure 5B), while comparable BCSS was observed between PMRT and non-PMRT cohorts in pathological prognostic stage IIIA disease. Similar trends were found using cumulative incidence function. The cumulative incidence function to assess the use of chemotherapy on breast cancer–specific mortality in pathological prognostic stage IIIA breast cancers and PMRT on breast cancer–specific mortality in pathological prognostic stage IIB breast cancers is displayed in Figure 6.

4 DISCUSSION

The present study was the first to validate the prognostic effect of the AJCC eighth edition pathological prognostic staging in T3N0 breast cancer, and to further analyze the impact of treatment decision-making in different stages. Our results showed

| Variables | Cox proportional hazards model | Competing risks model |
|-----------|-------------------------------|-----------------------|
|           | HR 95%CI | P | sdHR 95% CI | P |
| No chemotherapy cohort |          |    |            |    |
| IA        | 1       |   | 1          |   |
| IB        | 1.859   | 0.689-5.014 | .221 | 1.755 | 0.658-4.683 | .261 |
| IIA       | 4.934   | 1.712-14.216 | .003 | 4.240 | 1.491-12.061 | .007 |
| IIB       | 4.838   | 1.827-12.810 | .002 | 4.547 | 1.735-11.919 | .002 |
| IIIA      | 15.107  | 5.791-39.407 | <.001 | 10.876 | 3.968-29.810 | <.001 |
| No PMRT cohort |          |    |            |    |
| IA        | 1       |   | 1          |   |
| IB        | 1.763   | 0.65-4.737 | .261 | 1.748 | 0.654-4.667 | .265 |
| IIA       | 3.099   | 1.049-9.158 | .041 | 3.084 | 1.070-8.886 | .037 |
| IIB       | 6.139   | 2.424-15.550 | <.001 | 5.957 | 2.391-14.840 | <.001 |
| IIIA      | 10.802  | 4.257-27.407 | <.001 | 9.463 | 3.707-24.158 | <.001 |
| Nonchemotherapy and non-PMRT cohort |          |    |            |    |
| IA        | 1       |   | 1          |   |
| IB        | 1.481   | 0.528-4.157 | .456 | 1.396 | 0.501-3.891 | .524 |
| IIA       | 3.810   | 1.276-11.374 | .017 | 3.275 | 1.133-9.473 | .029 |
| IIB       | 4.186   | 1.567-11.181 | .004 | 3.922 | 1.492-10.310 | .006 |
| IIIA      | 10.678  | 4.007-28.454 | <.001 | 7.789 | 2.808-21.606 | <.001 |

Abbreviations: CI, confidence interval; HR, hazard ratio; PMRT, postmastectomy radiotherapy; sdHR, subdistribution hazard ratio.
that the AJCC eighth edition pathological prognostic staging could better express the risk stratification of patients with T3N0 disease, and that chemotherapy only improved BCSS in pathological prognostic stage IIIA disease, while PMRT was only associated with better BCSS in pathological prognostic stage IIB disease.

After the publication of the eighth AJCC staging system in 2017,2 several studies validated the prognostic effect of the new staging compared to the seventh AJCC staging.5–8 However, stage T3N0 breast cancer is a distinct clinical and biological disease,20 and there were no studies assessing the newly pathological prognostic stages for this population. Among the 2465 stage T3N0 patients in our study, patients exhibited a worse prognosis with gradually increasing pathological prognostic staging. The 5-year BCSS was 96.9%, 95.5%, 91.1%, 85.6%, and 75.5% in pathological prognostic stage IA, IB, IIA, IIB, and IIIA breast cancers (P < .001). The results indicated that the new pathological prognostic staging system would be the most accurate predictor for risk stratification in stage T3N0 patients. While the anatomical staging system is more straightforward for the classification of T3N0 breast cancer, the newly developed pathological prognostic stages emphasized the equality of tumor burden and biological factors in the era of personalized care.27 However, there were comparable BCSS between pathological prognostic stages IA and IB disease, and the results were not influenced by the receipt of systemic therapy and PMRT. In addition, in patients who did not receive chemotherapy, there were also comparable BCSS between pathological prognostic stage IIA and IIB disease. Therefore, further validation studies that included an extended series are required to determine the discriminatory power in predicting survival outcome by pathological prognostic stages.

The new pathological prognostic staging system better reflects the tumor heterogeneity of T3N0 breast cancer and helps to provide more detailed individualized management and prognosis assessment in clinical practice, which suggests that systemic and locoregional management might be escalated or de-escalated in several anatomical stage groups. However, according to the new NCCN breast cancer treatment guidelines, postoperative chemotherapy is considered for T3N0 breast cancer.9 By contrast, neither the European Society for Medical Oncology nor the new St. Gallen International Expert Consensus has a detailed description regarding chemotherapy in T3N0 breast cancer.28,29

There is still a lack of recommendations for chemotherapy according to the pathological prognostic staging system. A report from Floyd et al showed that chemotherapy was
### TABLE 4 Multivariate prognostic analysis assessing the prognostic indicators associated with breast cancer–specific survival by different pathological prognostic stages

| Variables | HR | 95%CI     | P   |
|-----------|----|-----------|-----|
| **IA**    |     |           |     |
| Age       | Continuous variable | 1.065 | 1.005-1.128 | .032 |
| Race/ethnicity | White | 1 | | |
|           | Black | 7.239 | 1.151-45.527 | .035 |
|           | Other | | | |
| Histology | IDC | 1 | | |
|           | ILC | 1.660 | 0.270-10.196 | .584 |
|           | Other | 0.673 | 0.052-8.726 | .762 |
| Chemotherapy | Yes vs No | 3.936 | 0.594-26.077 | .156 |
| PMRT      | Yes vs No | 0.710 | 0.148-3.410 | .668 |
| **IB**    |     |           |     |
| Age       | Continuous variable | 1.044 | 1.018-1.071 | .001 |
| Race/ethnicity | White | 1 | | |
|           | Black | 2.063 | 0.774-5.503 | .148 |
|           | Other | 0.740 | 0.173-3.160 | .684 |
| Histology | IDC | 1 | | |
|           | ILC | 1.033 | 0.481-2.218 | .934 |
|           | Other | 1.763 | 0.566-5.491 | .328 |
| Chemotherapy | Yes vs No | 1.427 | 0.617-3.296 | .406 |
| Radiotherapy | Yes vs No | 0.751 | 0.359-1.570 | .447 |
| **IIB**   |     |           |     |
| Age       | Continuous variable | 1.054 | 1.018-1.093 | .003 |
| Race/ethnicity | White | 1 | | |
|           | Black | 2.528 | 0.644-9.925 | .184 |
|           | Other | 2.292 | 0.455-11.553 | .315 |
| Histology | IDC | 1 | | |
|           | ILC | 0.197 | 0.025-1.540 | .122 |
|           | Other | 2.695 | 0.328-22.150 | .356 |
| Chemotherapy | Yes vs No | 0.436 | 0.118-1.607 | .212 |
| Radiotherapy | Yes vs No | 1.438 | 0.464-4.453 | .529 |
| **IIIA**  |     |           |     |
| Age       | Continuous variable | 1.023 | 1.005-1.042 | .014 |
| Race/ethnicity | White | 1 | | |
|           | Black | 0.981 | 0.507-1.901 | .956 |
|           | Other | 0.428 | 0.133-1.384 | .157 |
| Histology | IDC | 1 | | |
|           | ILC | 0.321 | 0.142-0.725 | .006 |
|           | Other | 0.482 | 0.174-1.336 | .160 |
| Chemotherapy | Yes vs No | 1.242 | 0.664-2.325 | .498 |
| Radiotherapy | Yes vs No | 0.476 | 0.279-0.812 | .006 |

(Continues)
TABLE 4 (Continued)

| Variables  | HR     | 95% CI          | P     |
|------------|--------|-----------------|-------|
| Histology  | IDC    | 1               |       |
|            | ILC    | 2.064           | 0.283-15.070 | .475 |
|            | Other  | 2.005           | 1.289-3.120 | .002 |
| Chemotherapy | Yes vs No | 0.539         | 0.347-0.837 | .006 |
| Radiotherapy | Yes vs No | 0.699       | 0.445-1.097 | .120 |

Abbreviations: CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; PMRT, postmastectomy radiotherapy; PR, progesterone receptor.

FIGURE 5 Kaplan-Meier curves to assess the effect of chemotherapy on breast cancer-specific survival in patients with pathological prognostic stage IIIA disease (A) and postoperative radiotherapy on breast cancer-specific survival in patients with pathological prognostic stage IIB disease (B)

FIGURE 6 The cumulative incidence function to assess the effect of chemotherapy on breast cancer-specific mortality in patients with pathological prognostic stage IIIA disease (A) and postoperative radiotherapy on breast cancer-specific mortality in patients with pathological prognostic stage IIB disease (B)

not correlated with a lower risk of locoregional recurrence (LRR) and DM.11 Another secondary data analysis from randomized clinical trials, including 313 patients with T3N0 diseases, found no association of LRR and DM with additional chemotherapy or endocrine therapy.10 Although a study from the NCDB showed an OS benefit in the chemotherapy cohort, the use of chemotherapy decreased from 65% in 2004 to 52% in 2012.16 Our results also showed that the probability of receiving chemotherapy was higher in pathological prognostic stage IIB and IIIA disease compared to the other three stages, which indicated that biological characteristics were important factors affecting chemotherapy decision-making in
T3N0 breast cancer. We also found that receipt of chemotherapy only improved BCSS in pathological prognostic stage IIIA breast cancer. In the current AJCC staging, pathological prognostic stage IIIA was defined as poorly/undifferentiated and triple-negative disease with a 5-year BCSS of only 75.5%. At the recent St. Gallen International Breast Cancer Conference, most of the experts (65.3%) recommended chemotherapy for triple-negative breast cancer, even in patients with small tumors.29 In addition, our results showed that breast cancer-related mortality in pathological prognostic stage IA and IB breast cancers was extremely low; thus, the survival benefit of systemic chemotherapy was relatively small. However, pathological prognostic stage IIIA cancer was the most high-risk subgroup, requiring more aggressive adjuvant chemotherapy to improve survival. Moreover, BCSS for pathological prognostic stage IIA and IIB was comparable (5-year: 82% vs 83%) in nonchemotherapy cohort, suggesting that they may be moderate risk groups, and the best treatment strategy still requires further exploration in pathological prognostic stage IIA-IB breast cancers.

The clinical value of PMRT for stage T3N0 breast cancer remains controversial.20 Currently, the probability of receiving PMRT varies significantly, and a study from the SEER program showed that 22% of patients were treated with PMRT between 1988 and 1997, and the probability of receiving PMRT increased to 41% from 1998 to 2002.21 Another study showed that 42% of patients had received PMRT between 2000 and 2010.19 However, a study from the MD Anderson Cancer Center showed that 73.5% of patients received PMRT.30 Although the NCCN recommend PMRT in T3N0 breast cancer,9 only 47.7% of patients were treated with PMRT in our study. The risk of LRR might have contributed to the decision to recommend PMRT. The results from the Danish Breast Cancer Cooperative Group (DBCG) showed LRR in 17-23% for this population; however, the median number of removed lymph nodes was only seven, which might affect the accurate assessment of axillary lymph nodes.24,25 Two studies with larger cohorts showed lower risks of LRR (7.1-7.6%) with a higher median removed lymph nodes count was 16.10,11 Our previous study showed a median number of removed lymph nodes of 12 and the 5-years LRR was 6.4%.31 In this study, the median number of removed lymph nodes was four, and 47.8% of patients had three or fewer lymph nodes removed. We believe that most of the patients received sentinel lymph node biopsy because the study was carried out in the era of sentinel lymph node biopsy. In the era of modern locoregional and systemic treatment, the risk of LRR in T3N0 breast cancer was lower than previously determined; therefore, PMRT might not be required.32

There have been no prospective studies to address the administration of PMRT in T3N0 breast cancer, and to date, most retrospective studies show a questionable benefit of PMRT.10,18,20 Two previous study published 20 years ago (DBCG 82b and 82c trials) included T3N0 breast cancers; however, the limited number of enrolled patients make it difficult to draw definitive conclusions regarding the survival benefit of PMRT in this setting.24,25 A study from the NCDB included patients diagnosed between 2004 and 2012, among whom PMRT was administered in 45-50% of patients, and PMRT was related to better OS for this population.16 However, several recent retrospective and population-based studies showed conflicting results.10,11,18–25 The study population, clinical pathological features, and differences in treatment patterns might contribute to the significant differences in the above results.

In the present study, the risk of 5-year BCSS was 96.5%, 94.8%, 89.7%, 79.9%, and 71.6% in the non-PMRT cohort with pathological prognostic stage IA, IB, IIA, IIB, and IIIA breast cancers, respectively. Although we could not obtain the LRR data from SEER program, in our study, PMRT only improved BCSS in stage IIB breast cancers. Theoretically, there is a positive correlation between the risk of LRR and breast cancer–related death. Patients with low risk of LRR were thought to derive less benefit from PMRT. PMRT had no survival benefit in the high-risk group, which was similar to the view of Goodman et al.33 They showed that a higher risk of LRR might not be converted to survival benefit with additional PMRT.33 Moreover, patients in the moderate-risk cohort might have a lower risk of DM than the high-risk cohort, and a positive effect of PMRT might be achieved in this cohort. Our findings were similar to the results from the DBCG 82 b & c trials.34 Currently, the recommendation of PMRT by the St. Gallen panelists remains controversial (yes vs no, 56.2% vs 43.8%), and 54.3% of the panelists voted for a case-by-case decision.30 The German expert group applied PMRT only to T3N0 patients with additional risk factors.35 However, they did not explain the relevant risk factors. According to our study, the pathological prognostic staging system might be used as a decisive tool to predict the outcome of PMRT in T3N0 breast cancer.

Our study does have limitations. The main limitations are the retrospective nature of this study and selection biases in the nonrandomized dataset. Second, the patterns of LRR and DM are not recorded in the SEER program. Third, treatment information regarding the systemic therapy regimen, endocrine therapy, and anti-HER2 directed therapy; the sequential use of chemotherapy; and surgery were not captured in the SEER dataset. In addition, the details regarding the target volume, radiation dose, and radiation technology of PMRT are also not included in the SEER program. Finally, the utilization of chemotherapy and radiotherapy in the SEER program was underreported. However, the primary strength of this study is that it represents a large cohort of patients who received the modern era of systemic and locoregional management, and the utilization of a large cohort of T3N0 breast cancer patients provided real world insight that allowed
for risk-stratified analysis of the new pathological prognostic staging system.

5 | CONCLUSIONS

In conclusion, this study suggests that the newly developed AJCC pathological prognostic stages could provide more risk stratification of T3N0 breast cancer after mastectomy and might affect individualized decision-making for chemotherapy and PMRT for this population. Further prospective studies are needed to incorporate the newly developed pathological prognostic staging system into the multidisciplinary treatment decision-making for T3N0 breast cancer.

ACKNOWLEDGMENTS

This work was partly supported by the National Natural Science Foundation of China (No. 81802600, 81872459), the Commission Young and Middle-aged Talents Training Project of Fujian Health Commission (No. 2019-ZQNB-25), the Science and Technology Planning Projects of Xiamen Science & Technology Bureau (No. 3502Z20174070), and the Natural Science Foundation of Guangdong Province (No. 2018A030313666 and 2017A030310422).

AUTHORS’ CONTRIBUTIONS

SGW, JZ, and ZYH are senior authors who contributed in study design. SGW selected patients for the study and collected clinical data. SGW, CLL, JL, and LH performed data analysis, SGW and JW wrote the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute at http://seer.cancer.gov/.

ETHICAL APPROVAL

We analyzed the de-identified information for patients contained in the SEER database; therefore, the present study was exempted from approval by the Institutional Review Board.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ORCID

San-Gang Wu https://orcid.org/0000-0001-6125-2680
Zhen-Yu He https://orcid.org/0000-0003-1402-8963

REFERENCES

1. Cserni G, Chmielik E, Cserni B, Tot T. The new TNM-based staging of breast cancer. Virchows Arch. 2018;472(5):697-703.

2. Mahul B Amin, Stephen B Edge, American Joint Committee on Cancer. AJCC Cancer Staging Manual. Switzerland: Springer; 2017.

3. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-99.

4. Giuliano AE, Connolly JL, Edge SB, et al. Breast cancer-major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(4):290-303.

5. Lee SB, Sohn G, Kim J, et al. A retrospective prognostic evaluation analysis using the 8th edition of the American Joint Committee on Cancer staging system for breast cancer. Breast Cancer Res Treat. 2018;169(2):257-266.

6. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al. Validation study of the American Joint Committee on Cancer eighth edition prognostic stage compared with the anatomic stage in breast cancer. JAMA Oncol. 2018;4(2):203-209.

7. Plichta JK, Ren Y, Thomas SM, et al. Implications for breast cancer restaging based on the 8th edition AJCC Staging Manual. Ann Surg. 2020;271(1):169-176.

8. Kim I, Choi HJ, Ryu JM, et al. Prognostic validation of the American Joint Committee on Cancer 8th staging system in 24,014 Korean patients with breast cancer. J Breast Cancer. 2018;21(2):173-181.

9. NCCN clinical Practice guidelines in oncology V.2.2019. Breast Cancer. (2019) https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 21, 2019.

10. Taghian AG, Jeong JH, Mamounas EP, et al. Low locoregional recurrence rate among node-negative breast cancer patients with tumors 5 cm or larger treated by mastectomy, with or without adjuvant systemic therapy and without radiotherapy: results from five national surgical adjuvant breast and bowel project randomized clinical trials. J Clin Oncol. 2006;24(24):3927-3932.

11. Floyd SR, Buchholz TA, Haffty BG, Goldberg S, Niemierko A, Raad RA. Low local recurrence rate without postmastectomy radiation in node-negative breast cancer patients with tumors 5 cm and larger. Int J Radiat Oncol Biol Phys. 2006;66(2):358-364.

12. Helintosh M, Blomqvist C, Heikila P, Joensuu H. Post-mastectomy radiotherapy in pT3N0M0 breast cancer: is it needed. Radiother Oncol. 1999;52(3):213-217.

13. Katz A, Strom EA, Buchholz TA, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. J Clin Oncol. 2000;18(15):2817-2827.

14. Wallgren A, Bonetti M, Gelber RD, et al. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol. 2003;21(7):1205-1213.

15. Trudeau ME, Pritchard KI, Chapman JA, et al. Prognostic factors affecting the natural history of node-negative breast cancer. Breast Cancer Res Treat. 2005;89(1):35-45.

16. Francis SR, Frandsen J, Kokeny KE, Gaffney DK, Poppe MM. Outcomes and utilization of postmastectomy radiotherapy for T3N0 breast cancers. Breast. 2017;32:156-161.

17. Cassidy RJ, Liu Y, Kahn ST, et al. The role of postmastectomy radiotherapy in women with pathologic T3N0M0 breast cancer. Cancer. 2017;123(15):2829-2839.
18. Elmore L, Deshpande A, Daly M, Margenthaler JA. Postmastectomy radiation therapy in T3 node-negative breast cancer. J Surg Res. 2015;199(1):90-96.
19. Johnson ME, Handorf EA, Martin JM, Hayes SB. Postmastectomy radiation therapy for T3N0: a SEER analysis. Cancer. 2014;120(22):3569-3574.
20. Floyd SR, Taghian AG. Post-mastectomy radiation in large node-negative breast tumors: does size really matter. Radiother Oncol. 2009;91(1):33-37.
21. McCammon R, Finlayson C, Schwer A, Rabinovitch. Impact of postmastectomy radiotherapy in T3N0 invasive carcinoma of the breast: a Surveillance, Epidemiology, and End Results database analysis. Cancer. 2008;113(4):683-689.
22. Yu JB, Wilson LD, Dasgupta T, Castrucci WA, Weidhaas JB. Postmastectomy radiation therapy for lymph node-negative, locally advanced breast cancer after modified radical mastectomy: analysis of the NCI Surveillance, Epidemiology, and End Results database. Cancer. 2008;113(1):38-47.
23. Goulart J, Truong P, Woods R, Speers CH, Kennecke H, Nichol A. Outcomes of node-negative breast cancer 5 centimeters and larger treated with and without postmastectomy radiotherapy. Int J Radiat Oncol Biol Phys. 2011;80(3):758-764.
24. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997;337(14):949-955.
25. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet. 1999;353(9165):1641-1648.
26. Surveillance, Epidemiology, and End Results (SEER) Program. 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. www.seer.cancer.gov. Accessed December 15, 2019
27. Jackisch C, Lammers P, Jacobs I. Evolving landscape of human epidermal growth factor receptor 2-positive breast cancer treatment and the future of biosimilars. Breast. 2017;32:199-216.
28. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: eSMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(8):1194-1220.
29. Untch M, Thomssen C, Bauerfeind I, et al. Primary therapy of early breast cancer: evidence, controversies, Consensus: spectrum of opinion of German specialists on the 16th St. Gallen International Breast Cancer Conference (Vienna 2019). Geburtshilfe Frauenheilkd. 2019;79(6):591-604.
30. Nagar H, Mittendorf EA, Strom EA, et al. Local-regional recurrence with and without radiation therapy after neoadjuvant chemotheraphy and mastectomy for clinically staged T3N0 breast cancer. Int J Radiat Oncol Biol Phys. 2011;81(3):782-787.
31. Sun JY, Wu SG, Li S, et al. Locoregional recurrence of pT3N0M0 breast cancer after mastectomy is not higher than that of pT1-2N0M0: an analysis for radiotherapy. Cancer Sci. 2013;104(5):599-603.
32. Mignano JE, Gage I, Piantadosi S, Ye X, Henderson G, Dooley WC. Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treated without postoperative radiation therapy. Am J Clin Oncol. 2007;30(5):466-472.
33. Goodman CR, Seagle BL, Kocherginsky M, Donnelly ED, Shahabi S, Strauss JB. 21-gene recurrence score assay predicts benefit of post-mastectomy radiotherapy in T1-2 N1 breast cancer. Clin Cancer Res. 2018;24(16):3878-3887.
34. Kyndi M, Overgaard M, Nielsen HM, Sørensen FB, Knudsen H, Overgaard J. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol. 2009;90(1):74-79.
35. Wenz F, Budach W. Personalized radiotherapy for invasive breast cancer in 2017: national S3 guidelines and DEGRO and AGO recommendations. Strahlenther Onkol. 2017;193(8):601-603.

How to cite this article: Wu S-G, Wang J, Lei J, et al. Prognostic validation and therapeutic decision-making of the AJCC eighth pathological prognostic staging for T3N0 breast cancer after mastectomy. Clin Transl Med. 2020;10:125–136. https://doi.org/10.1002/ctm2.3