Observational Study

Medicine®

OPEN

Using a novel T-lymph node ratio model to evaluate the prognosis of nonmetastatic breast cancer patients who received preoperative radiotherapy followed by mastectomy

An observational study

Yang Wang, MD[a], Yuanyuan Zhao, MD[b,c], Song Liu, MD[a], Weifang Tang, MD[a], Hong Gao, MD[a], Xucai Zheng, MD[a], Shikai Hong, MD[a], Shengying Wang, MD[a,*]

Abstract

We aimed to investigate the prognostic value of postpathological characters in nonmetastatic breast cancer (NMBC) patients who received preoperative radiotherapy (PRT) followed by mastectomy (MAST).

We conducted retrospective analyses using the data collected from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. Univariate and multivariate analyses were performed to identify prognostic factors. Disease-specific survival was calculated by the Kaplan–Meier curve and validated by log rank test. The discriminations of independent risk factors and staging systems were compared by the area under receiver operating characteristic curves (AUC) and validated by Harrell concordance index (bootstrapping algorithm). Akaike information criterion (AIC) was applied to compare the difference of model.

One thousand three hundred fifty NMBC patients who had received PRT followed by MAST from 1988 to 2013 were included in the study. We found the metastatic lymph node ratio (mLNR) staging was a superior indicator than pN staging. Thus, we proposed a T-lymph node ratio (T-NR) staging system with simplified-T categories (T0–3 and T4) and the mLNR staging. The novel T-NR staging system provided larger AUC ($P = .024$, .008, respectively) and the smaller AIC ($P < .001$) value than American Joint Committee on Cancer staging system.

The novel T-NR staging system performed more accurate survival prediction and better model fitness for NMBC patients who receive PRT followed by MAST, it may provide a wide applicability in clinical decision-making.

Abbreviations: AIC = Akaike information criterion, AJCC = American Joint Committee on Cancer, AUC = area under receiver operating characteristic curves, BCT = breast-conserving treatment, C-index = Harrell concordance index, DSS = disease-specific survival, ER = estrogen receptor, mLNR = metastatic lymph node ratio, NMBC = nonmetastatic breast cancer, pCR = pathological complete remission, PLN = positive lymph nodes, PR = progesterone receptor, PRT = preoperative radiotherapy, SEER = Surveillance, Epidemiology and End Results, TLN = total lymph nodes examined, T-NR = T-lymph node ratio.

Keywords: breast cancer, mastectomy, preoperative radiotherapy, SEER, survival analysis

Editor: Won Sup Lee.

This research did not receive any funding.

Authors' Contributions: Conception and design: SW, YW.

Development of methodology: SW.

Collection and assembly of data: YW.

Data analysis and interpretation: YW.

Writing, review, and/or revision of the manuscript: All authors.

Administrative, technical, or material support: SW.

Study supervision: SW.

Final approval of manuscript: All authors.

The authors have no conflicts of interest to disclose.

[a] Department of Head—Neck and Breast Surgery, Anhui Provincial Hospital Affiliated to Anhui Medical University, Anhui Provincial Cancer Hospital, Hefei, [b] Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Collaborative Innovation Center of Cancer Medicine, Fudan University Shanghai Cancer Center, [c] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China.

[*] Correspondence: Shengying Wang, Department of Head—Neck and Breast Surgery, Anhui Provincial Hospital Affiliated to Anhui Medical University, Anhui Provincial Cancer Hospital, The 2ed West Ring—Road, Hefei 230000, China (e-mail: Shengywang@163.com).

Medicine (2017) 96:42(e8203)

Received: 9 June 2017 / Received in final form: 22 August 2017 / Accepted: 10 September 2017

http://dx.doi.org/10.1097/MD.0000000000008203

1. Introduction

Recently, as the early detection and systemic treatments are improving, the mortality from breast cancer in the United States has decreased. However, breast cancer, following lung cancer, still ranks as a second common cause of cancer death in the United States.[1,2] The American Cancer Society estimated that about 40,610 American women will die from this disease (14% of female cancer-related death) in 2017.[3]

Currently, in routine clinical practice, preoperative therapies have become widely recommended choices for patients with nonmetastatic breast cancer (NMBC).[4] Some phase II/III studies have demonstrated the survival benefits from preoperative therapies in breast cancer.[5–7] Indeed, preoperative therapies can reduce the size of primary tumors and decrease the incidence of positive nodes,[8] which may achieve a clinical downstaging before surgery and increase the rate of R0 resection and breast-conserving treatment (BCT).[9,10]

The successes of preoperative therapies have significantly increased the interest in BCT which has been established as an intended surgical treatment.[11] However, some studies have indicated that about half the Locally Advanced Breast Cancer patients were not amenable to BCT after preoperative-therapy.[12,13] In addition, according to National Cancer Data Base, nearly 25% of patients in early breast cancer who underwent initial BCT needed a subsequent completion partial mastectomy (MAST) or MAST in the United States.[14] In fact, approximately 30% to 40% of American women were not candidates for BCT or choose MAST.[11,13] Therefore, MAST was still the potential routine surgical approach for NMBC patients.[15]

For patients who received preoperative-therapy, pathological complete remission (pCR) was a validated prediction model.[16] Patients with pCR were expected to have a relatively favorable outcome compared with those without pCR,[4,6,17–19] whereas this model was over-simplified. The outcome may be different for patients with tumor residual after preoperative-therapy (non-pCR). Nowadays, the American Joint Committee on Cancer (AJCC) T-N-M staging system was still effective for prognosis evaluation in these patients,[17] while the pN staging was based on the number of the involved lymph nodes, regardless of the total retrieved lymph nodes. Recently, some researchers have proposed that the metastatic lymph nodes ratio (mLNR) was a better indicator than the number of involved lymph nodes in the field of breast cancer.[20,21] However, it was still controversial for post-therapy patients, especially for NMBC patients who received PRT.[22,23]

In this study, we aimed to investigate the prognostic value of significant risk factors in NMBC patients who received PRT followed by MAST and assessed the role of the mLNR for prognosis evaluation in these patients.

2. Methods

2.1. Data and definition

All the data was obtained from Surveillance, Epidemiology, and End Results (SEER) database, which was a large population-based collaboration program and surveyed by the National Cancer Institute. It covers approximately 30% of total US population and collects information of cancer patients in 18 registries.

The inclusion criteria were as follows: female patients received radiotherapy before surgery; patients received mastectomy; patients without distant metastasis; patients with complete data of lymph node status and 1 or more total lymph nodes examined. Patients' clinic pathological characteristics such as age at diagnosed, sex, race, marital, surgery, tumor location, tumor size, histologic type, grade, T stage, N stage, M stage, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor-2, number of positive lymph nodes (PLN), and total lymph nodes examined (TLN) were collected. A total of 1350 breast cancer patients (ICD-O-3 code within the range of 8000–8576, 8940–8950, 8980–8981, 9020) between 1988 and 2013 from SEER database were eligible for the current study.

2.2. Ethical approval

The current research does not contain any studies with human participants or animals performed by any of the authors.

2.3. Statistical analysis

The primary endpoint was disease-specific survival (DSS), which was defined as the time form surgery to cancer-related death or the last follow-up. The pathological characteristics T stage, N stage were restaged according to the 7th edition AJCC staging system.

The mLNR was defined as the number of PLN divided by the number of TLN. Since patients with no excised PLN had much better prognosis than other patients (HR = 0.465, $P < .001$), we grouped those patients into a separate category (mLNRs0). The patients with ratio higher than 0% were separated into 3 groups by X-tile software and by the minimal P value approach.[24]

T0 to T3 diseases were based on tumor size, while T4 disease was defined as a tumor of any size with direct extension to the chest wall (T4a) and/or to the skin (T4bc) and inflammatory breast (T4d). In our study, T0 to T3 stage had similar better prognosis than T4 stage in our study. Thus, we regrouped T stages into 2 categories: T0–3 and T4 (HR = 2.475, $P < .001$).

According to AJCC 7th edition of breast cancer, we divided the histologic types into 2 groups: Invasive carcinoma and In situ Carcinoma.

DSS was calculated by the Kaplan–Meier estimator and validated by log rank test. The statistical differences were identified by the univariate Cox-Regression analysis. The significant variables were included to identify the possible independent prognostic factors in multivariate analyses. To distinguish the prognostic performance of node classifications, we adopted the 3-step multivariate analyses (3 different Cox Proportional Hazard Models): step-1 model included the N staging but excluded mLNR staging; step-2 model included the mLNR staging but excluded N staging; step-3 model included both the N staging and mLNR staging.

The predictive accuracy of 10-year and overall-time point DSS in different lymph node staging or tumor-node staging systems was compared by the Area Under the receiver operating characteristic Curves (AUC) value. The higher the AUC value, the more accurate the survival prediction. Harrell concordance index (C-index) which is similar to the AUC but more appropriate for censored data was calculated and validated by the bootstrapping method.[25] The value of C-index ranges from 0.5 to 1 and the model with highest value was chosen as the best prognostic prediction model.[26] Akaike information criterion (AIC) was also adopted as criteria for evaluating prognostic performance of prediction models. When the AIC value is lower, the model fitness is better.[27]

All analyses were performed by the software statistical package for social sciences version 19.0 (Chicago, IL), X-tile (http://www.tissuearray.org/rimmlab/), and the R software version 3.4.0

(http://r-project.org/) with statistical packages of *survival*, *boot*, *and Hmisc*. All the statistical tests were 2 sided. And in order not to overlook any potentially important predictors, a P value of $<.1$ was used as the cut-off value for statistical significance in the variable selection of the multivariate analyses. Statistical significance remained conventionally defined as $P<.05$ in all other cases.

3. Result

3.1. Baseline characteristics

There were 1350 eligible NMBC breast cancer patients who underwent MAST following PRT from the SEER cancer registry analyzed in the study. The patients' characteristics were listed in Table 1. Overall, the mean age was 55.4 years old. And 406

Table 1

Demographics and univariate survival analyses results of all patients.

	Patients (n = 1350)		
		Univariate analyses	
Characteristics	No. (%)	HR (95% CI)	P
Age, y		1.006 (1.000–1.013)	.053
Mean	55.4 ± 13.7		
Range	25–93		
Race			.005
White	1075 (79.6)	Ref	
Black	199 (14.7)	1.453 (1.163–1.815)	
API	66 (4.9)	0.868 (0.548–1.375)	
AI	10 (0.7)	1.703 (0.760–3.813)	
Marital status (n = 1303)		1.263 (1.049–1.520)	.014
Yes	921 (68.2)		
No	382 (28.3)		
Tumor size (cm)		1.005 (1.005–1.012)	<.001
Mean (n = 580)	4.3 ± 3.4		
Range	0–23		
Tumor location			.026
Nipple	16 (1.2)	Ref	
Center	99 (7.3)	0.628 (0.312–1.264)	
Upper-inner	92 (6.8)	0.434 (0.210–0.897)	
Lower-inner	63 (4.7)	0.479 (0.223–1.031)	
Upper-outer	416 (30.8)	0.629 (0.322–1.192)	
Lower-outer	65 (4.8)	0.848 (0.149–1.716)	
Overlapping	293 (21.7)	0.668 (0.085–5.224)	
Axillary tail	4 (0.3)	0.739 (0.338–1.410)	
Breast, NOS	302 (22.4)	0.822 (0.433–1.563)	
Grade (n = 1189)			<.001
GI	69 (5.8)	Ref	
GII	433 (36.4)	1.700 (0.981–2.947)	
GIII	656 (55.2)	2.986 (1.747–5.104)	
GIV	31 (2.6)	4.410 (2.210–8.800)	
Histologic type		0.918 (0.530–1.593)	.762
Invasive carcinoma	1249 (92.5)		
In situ carcinoma	101 (7.5)		
T stage			<.001
T0	3 (0.2)	Ref	
T1	280 (20.7)	0.816 (0.114–5.862)	
T2	434 (32.1)	1.097 (0.154–7.842)	
T3	261 (19.3)	1.508 (0.210–10.815)	
T4	372 (27.6)	2.475 (0.347–17.341)	
PLN (mean ± SD)	4.55 ± 5.72	1.054 (1.043–1.066)	<.001
TLN (mean ± SD)	13.48 ± 7.95	0.990 (0.979–1.001)	.070
N stage			<.001
N0	382 (28.3)	Ref	
N1	420 (31.1)	1.647 (1.261–2.152)	
N2	324 (24.0)	2.312 (1.778–3.007)	
N3	224 (16.6)	3.167 (2.413–4.157)	
mLNR (mean ± SD)	0.34 ± 0.34		<.001
0< mLNR≤1	968 (71.7)	Ref	
0 = mLNR	382 (28.3)	0.465 (0.373–0.582)	
Adjuvant radiotherapy		0.938 (0.779–1.130)	.503
Yes	406 (30.1)		
No	944 (69.9)		
ER (n = 1105)		0.473 (0.389–0.574)	<.001
Negative	373 (33.8)		
Positive	732 (66.2)		
PR (n = 1095)		0.600 (0.495–0.728)	<.001
Negative	508 (46.4)		
Positive	587 (53.6)		
HER-2 (n = 211)		0.106 (0.111–1.236)	.106
Negative	160 (75.8)		
Positive	51 (24.2)		
AJCC stage system			<.001
I	98 (7.3)	Ref	
IIA	174 (12.9)	2.018 (1.012–3.695)	
IIB	198 (14.7)	2.574 (1.425–4.652)	
IIIA	340 (25.2)	4.146 (2.390–7.193)	
IIIB	304 (22.5)	6.735 (3.892–11.655)	
IIIC	236 (17.5)	7.007 (4.040–12.153)	

AI = American Indian or Alaska Native, AJCC = American Joint Committee on Cancer, API = Asian or Pacific Islander, Breast, NOS = breast, not other special, ER = estrogen receptor, HER-2 = human epidermal growth factor receptor-2, mLNR = metastatic lymph node ratio, PLN = positive lymph node, PR = progesterone receptor, TLN = total lymph node.

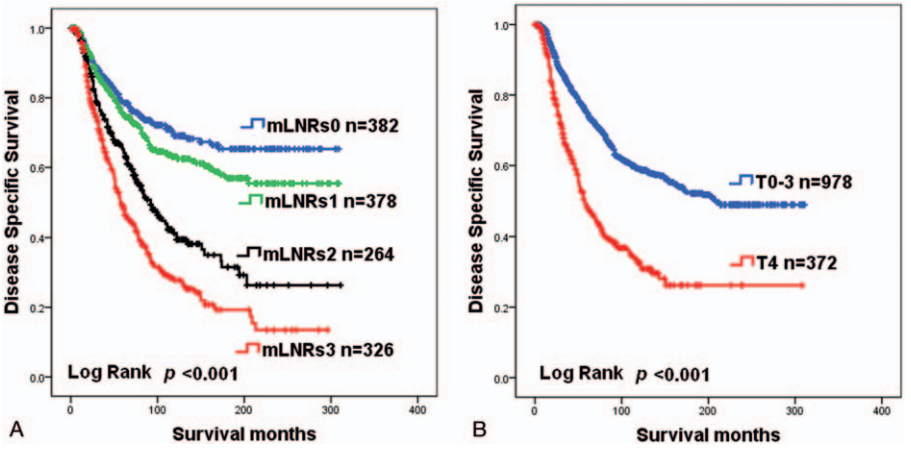

Figure 1. (A) mLNR staging and (B) simplified-T categories validated by Kaplan–Meier curves and log rank test. mLNRs = metastatic lymph node ratio staging.

(30.1%) patients had received adjuvant radiotherapy after MAST. The mean number of positive lymph nodes and total retrieved lymph nodes was 4.55 and 13.48, respectively. Until the last follow-up time, 51.3% (n = 692) of all patients had died, and 78.0% (n = 540) of them had died of breast cancer-related death.

3.2. Survival and lymph node ratio categories and simplified-T categories

The median follow-up time was 61 months. The median DSS for all the patients was 141.7 months. The 5-year DSS, 10-year DSS were 68% and 52%. The mLNR was calculated as the number of positive lymph nodes divided by the total retrieved lymph nodes (PLN/TLN retrieved). The continuous mLNR were classified into 4 groups by using X-tile analysis, as the following intervals, mLNRs0: 0; mLNRs1: 0 to 0.31; mLNRs2: 0.31 to 0.63; mLNRs3: 0.63 to 1. Ten-year DSS for the 4-level mLNR were 69.0%, 63.1%, 41.3%, and 27.8%, respectively (Fig. 1A, $P < .001$). By comparison, 10-year DSS for the simplified-T categories (T0–3 and T4) were 58.9% and 32.7%, respectively (Fig. 1B, $P < .001$).

3.3. Analysis of post-therapy risk factors

The univariate and multivariate analyses were employed to investigate the significant risk factors and identify the more significant lymph node classification correlated with prognosis. In the univariate analysis (Table 1), age, race, marital status, grade, T stage, N stage, mLNR stage, location, ER and PR were significant risk factors for NMBC patients after PRT followed by MAST. Moreover, T0 to T3 disease had similarly better survival than T4 disease (HR = 2.475). For the 3-step multivariate analysis, all the significant factors in the univariate analysis were included (Table 2). In the step 1 and step 2 multivariate survival analyses, pN staging and mLNR staging were identified as independent prognostic factors respectively. (All P value $< .001$) In the step 3 multivariate survival analysis, pN staging ($P = .290$) lost the significance while mLNR staging ($P < .001$) remained statistically significant in the same model. Other independent prognostic factors included age (only in step-1 model), Grade, and ER, simplified-T categories.

3.4. The novel T-metastatic lymph node ratio (T-NR) staging system

According to the multivariate Cox-regression analyses, we subdivided all the patients into 8 groups (Group 1: mLNRs0 and T0–3; Group 2: mLNRs1 and T0–3; Group 3: mLNRs0 and T4; Group 4: mLNRs1 and T4; Group 5: mLNRs2 and T0–3; Group 6: mLNRs3 and T0–3; Group 7: mLNRs2 and T4; Group 8: mLNRs3 and T4) based on mLNR stage and simplified-T stage

Table 2

3-step multivariate analyses (cox proportional hazard models) of prognostic factors.

	Step-1 model		Step-2 model		Step-3 model	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Marital status	1.228 (0.970–1.554)	.087	1.201 (0.949–1.521)	.128	1.207 (0.953–1.529)	.118
Race*	0.592 (0.324–1.084)	.090	0.579 (0.317–1.059)	.076	0.581 (0.318–1.063)	.078
Histologic type	1.201 (0.924–1.561)	.170	1.235 (0.951–1.604)	.113	1.226 (0.942–1.594)	.129
Location	1.014 (0.969–1.061)	.540	1.010 (0.965–1.057)	.669	1.009 (0.965–1.056)	.685
PR	0.867 (0.657–1.145)	.315	0.839 (0.636–1.105)	.212	0.842 (0.639–1.110)	.223
Age	1.008 (1.000–1.017)	.047	1.006 (0.998–1.015)	.119	1.007 (0.999–1.015)	.108
ER	0.607 (0.453–0.813)	.001	0.628 (0.471–0.838)	.002	0.620 (0.464–0.828)	.001
Grade	1.414 (1.173–1.706)	<.001	1.446 (1.197–1.747)	<.001	1.433 (1.185–1.732)	<.001
T stage†	1.898 (1.488–2.422)\	<.001	1.797 (1.410–2.291)	<.001	1.823 (1.427–2.328)	<.001
N stage	1.504 (1.358–1.664)	<.001	–	–	1.095 (0.926–1.295)	.290
mLNR stage	–	–	1.539 (1.399–1.692)	<.001	1.443 (1.237–1.682)	<.001

ER = estrogen receptor, mLNR = metastatic lymph node ratio, PR = progesterone receptor.
* API versus non-API.
† T0–3 versus T4.

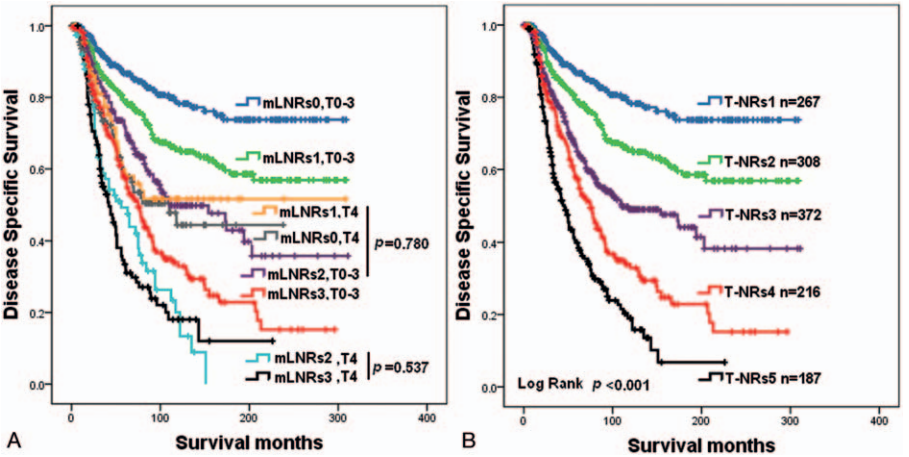

Figure 2. A, The patients were subdivided into 8 groups and validated by Kaplan–Meier curves. B, The patients were redistributed into 5 groups and validated by Kaplan–Meier curves. mLNRs = metastatic lymph node ratio staging, T-NRs = T-metastatic lymph node ratio staging.

(Fig. 2A). However, as is shown in Fig. 2A, there was no significant difference between Groups 3, 4, and 5 ($P = .780$), and also had insignificant difference in Groups 7 and 8 ($P = .537$). As a result, we propose a novel T-lymph Node Ratio staging (T-NRs) system, which was redistributed from the above 8 groups and respectively as follows, T-NRs1: T0–3 and mLNRs0; T-NRs2: T0–3 and mLNRs1; T-NRs3: T0–3 and mLNRs2 or T4 and mLNRs0–1; T-NRs4: T0–3 and mLNRs3; T-NRs5: T4 and mLNRs2–3. The survival curves for overall time DSS based on novel T-NR staging were shown in Fig. 2B.

3.5. Comparisons of prognostic performance and bootstrap validation for different lymph node staging, T-NR staging system, and AJCC staging system

The AUC values were applied to compare the discrimination between different models at 10-year and overall-time point. Harrell C indices were calculated and internal validated by 1000 times bootstrapping resamples. The differences between prediction models were reflected by the AIC values with bootstrapping algorithm and tested by Welch 2 sample *t* test. As shown in Fig. 3 and Table 3, the novel T-NR staging system with larger AUC value was more accurate in 10-year and overall-time DSS prediction than the AJCC staging system ($P = 0.024$, 0.008, respectively). And it was validated by C-index value ($\text{C-index}_{\text{T-NR}}$ vs $\text{C-index}_{\text{AJCC}}$, all $P < .001$). The T-NR staging system with lower AIC value manifested better model fitness than the AJCC staging system (all $P < .001$).

Additionally, the results also demonstrate that the mLNR staging revealed superior discrimination ($P = .012$, .015, respectively) and better model fitness (all $P < .001$) over pN staging (Table 3).

4. Discussion

The prognostics of breast cancer patients after preoperative therapy had been discussed in several studies.[17,19,23,28] However, factors that independently and optimally reflect breast cancer patients' survival who received PRT followed by MAST were still scarcely discussed. In the current study, we evaluated 1350 NMBC patients who received MAST after PRT and first developed a novel T-NR staging system. We demonstrated that

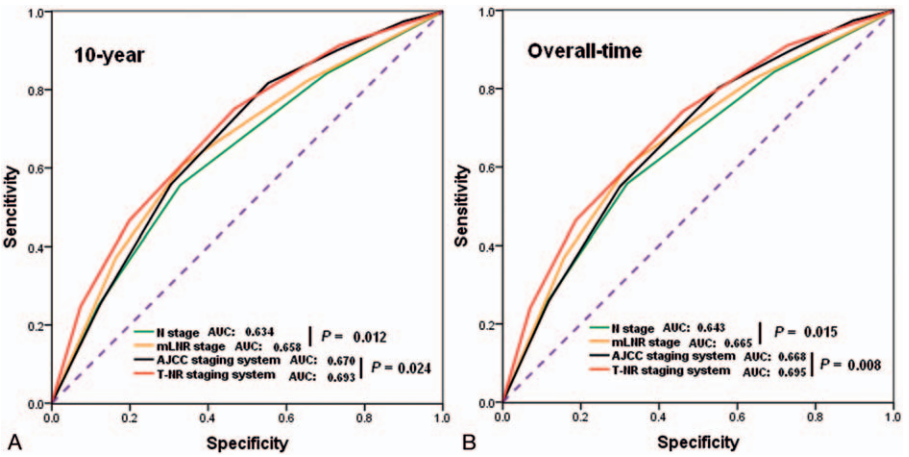

Figure 3. Comparison of the AUC for pN staging, mLNR staging, AJCC staging system and T-NR staging system to predict DSS at 10-year (A) and overall-time (B). AUC = areas under the receiver operating characteristic curves, DSS = disease-specific survival, AJCC = American Joint Committee on Cancer, mLNRs = metastatic lymph node ratio stage, T-NR = T-metastatic lymph node ratio.

Table 3

The prognostic performance of 10-year, overall time point DSS and model fitness between different lymph node staging or tumor-node staging system.

Time Point	Staging (system)	AUC (95% CI)	C-index*	AIC*	P_{AUC}	$P_{C\text{-index}}$	P_{AIC}
10-year	pN	0.634 (0.608 to 0.660)	0.595	6745.15	.012	<.001	<.001
	mLNR	0.658 (0.632 to 0.683)	0.623	6701.80			
	AJCC	0.670 (0.668 to 0.718)	0.641	6685.07	.024	<.001	<.001
	T-NR	0.693 (0.644 to 0.695)	0.662	6636.91			
Overall-time	pN	0.643 (0.616 to 0.668)	0.596	7073.81	.015	<.001	<.001
	mLNR	0.665 (0.639 to 0.690)	0.625	7025.04			
	AJCC	0.668 (0.642 to 0.693)	0.641	7015.25	.008	<.001	<.001
	T-NR	0.695 (0.670 to 0.720)	0.663	6954.85			

AIC = Akaike information criterion, AJCC = American Joint Committee on Cancer, AUC = area under the receiver operating characteristic (ROC) curve, C-index = Harrell concordance index, DSS = disease-specific survival, mLNR = metastatic lymph node ratio, T-NR = T-metastatic lymph node ratio.

* The C-index and AIC value were internally validated by bootstrapping variable selection algorithm and Welch 2 sample *t* test.

the novel T-NR staging system was more accurate in the 10-year and overall-time survival prediction and had better model fitness than the AJCC staging system.

At present, the AJCC staging system is widely applied in the area of breast cancer,[29] while the pN staging that depends on the number of lymph nodes removed and examined was extensively influenced by the surgical and pathologic procedure. And the potential role of total retrieved lymph nodes should not be overlooked.[20] Indeed, some studies suggested that the mLNR should be an alternative to pN staging in node-positive breast cancer.[21,22] However, whether the mLNR was a better indicator than pN staging for breast cancer patients after preoperative therapy was still controversial. In 2016, Kim et al[23] conducted a multicenter retrospective study, and eventually they demonstrated that mLNR was not superior to pN staging in predicting clinical outcome of breast cancer after preoperative therapy.

Based on a large data from national cancer registry, we identified that the T staging and lymph node status were associated with patient's survival in univariate and multivariate analyses. Interestingly, in step-3 multivariate analyses, the pN staging lost the significance ($P = .290$). Additionally, the mLNR staging showed better discrimination at 10-year and overall-time and better model fitness (all $P < .001$) than pN staging. We concluded that mLNR staging was a superior indicator than pN staging for NMBC patients after PRT followed by MAST. So the conventional AJCC staging system based on the pN staging may not be the optimum classification for these patients. Thus, we devised a novel T-NR staging system that was a combination of simplified-T categories and mLNR staging. And the novel staging system manifested more accurate DSS prediction and better model fitness than AJCC staging system for these patients. As the simplified-T categories (T0–3 and T4) were divided by extent of tumor invasion rather than by both tumor size and extent of invasion in traditional T staging, it may potentially be more convenient for the novel staging system in clinical practice.

The SEER program provided access to a large cohort of patients, making the study results more reliable. However, several limitations remained in our study. First, since the current study was a retrospective study, the patients with incomplete information were excluded from the current study. There may be a selection bias in the present study. Second, several factors that potentially associated with the survival were not analyzed in the present study, such as lymph-vascular invasion, margin status, and molecular biomarkers like Ki-67, P53.[16,30] Third, the enrolled patients may have received endocrine-therapy or/and chemo-therapy, yet the data of (endocrine) chemo-therapy was unavailable from the SEER program, resulting in potential confounders in this study.

In conclusion, the current large population-based study identified that T staging and lymph node status were strongly associated with the survival of NMBC patients after PRT followed by MAST. And the mLNR staging was a superior indicator than pN staging for these patients. Based on these findings, we devised the novel T-NR staging system that performed better survival prediction and model fitness for breast cancer patients after PRT followed by MAST. And it also may potentially be more convenient in clinical practice. With the prevalence of preoperative therapies[4–8,10,16,18,19] and high rate of mastectomy,[11,13] the novel T-NR staging system may be widely applicable.

Acknowledgments

The authors gratefully thank their colleagues from the Department of Head—Neck and Breast Surgery for their kind help.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
[2] Harbeck N, Gnant M. Breast cancer. Lancet 2017;389:1134–50.
[3] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
[4] Amoroso V, Generali D, Buchholz T, et al. International expert consensus on primary systemic therapy in the management of early breast cancer: highlights of the fifth symposium on primary systemic therapy in the management of operable breast cancer, Cremona, Italy (2013). JNCI Monographs 2015;2015:90–6.
[5] Bollet MA, Belin L, Reyal F, et al. Preoperative radio-chemotherapy in early breast cancer patients: long-term results of a phase II trial. Radiother Oncol 2012;102:82–8.
[6] Bollet MA, Sigal-Zafrani B, Gambotti L, et al. Pathological response to preoperative concurrent chemo-radiotherapy for breast cancer: results of a phase II study. Eur J Cancer 2006;42:2286–95.
[7] Gianni L, Baselga J, Eiermann W, et al. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. J Clin Oncol 2009;27:2474–81.
[8] Erbes T, Orlowska-Volk M, zur Hausen A, et al. Neoadjuvant chemotherapy in breast cancer significantly reduces number of yielded lymph nodes by axillary dissection. BMC Cancer 2014;14:4–14.
[9] Merrill RM, Hunter BD. Conditional survival among cancer patients in the United States. Oncologist 2010;15:873–82.
[10] Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997;15:2483–93.

[11] McLaughlin SA. Surgical management of the breast. Surg Clin North Am 2013;93:411–28.
[12] Tryfonidis K, Senkus E, Cardoso MJ, et al. Management of locally advanced breast cancer—perspectives and future directions. Nat Rev Clin Oncol 2015;12:147–62.
[13] Morrow M. Surgeon recommendations and receipt of mastectomy for treatment of breast cancer. JAMA 2009;302:1551.
[14] Wilke LG, Czechura T, Wang C, et al. Repeat surgery after breast conservation for the treatment of Stage 0 to II breast carcinoma. JAMA Surg 2014;149:1296.
[15] Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 2014;25:1871–88.
[16] Penault-Llorca F, Radosevic-Robin N. Biomarkers of residual disease after neoadjuvant therapy for breast cancer. Nat Rev Clin Oncol 2016;13:487–503.
[17] Carey LA, Metzger R, Dees EC, et al. American Joint Committee on Cancer tumor-node-metastasis stage after neoadjuvant chemotherapy and breast cancer outcome. JNCI J Natl Cancer Instit 2005;97:1137–42.
[18] Guiu S, Arnould L, Bonnetain F, et al. Pathological response and survival after neoadjuvant therapy for breast cancer: a 30-year study. Breast 2013;22:301–8.
[19] Matuschek C, Bölke E, Roth SL, et al. Long-term outcome after neoadjuvant radiochemotherapy in locally advanced noninflammatory breast cancer and predictive factors for a pathologic complete remission. Strahlentherapie Onkol 2012;188:777–81.
[20] Vinh-Hung V, Verschraegen C, Promish DI, et al. Ratios of involved nodes in early breast cancer. Breast Cancer Res 2004;6:R680–8.
[21] Vinh-Hung V, Verkooijen HM, Fioretta G, et al. Lymph node ratio as an alternative to pN staging in node-positive breast cancer. J Clin Oncol 2009;27:1062–8.
[22] Chen S, Liu Y, Huang L, et al. Lymph node counts and ratio in axillary dissections following neoadjuvant chemotherapy for breast cancer: a better alternative to traditional pN staging. Ann Surg Oncol 2013;21:42–50.
[23] Kim SH, Jung KH, Kim T-Y, et al. Prognostic value of axillary nodal ratio after neoadjuvant chemotherapy of doxorubicin/cyclophosphamide followed by docetaxel in breast cancer: a multicenter retrospective cohort study. Cancer Res Treat 2016;48:1373–81.
[24] Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 2004;10:7252–9.
[25] Austin PC, Tu JV. Bootstrap methods for developing predictive models. Am Statist 2004;58:131–7.
[26] Harrell FEJr. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. Springer, New York, NY:2001.
[27] Chaurasia A, Harel O. Using AIC in multiple linear regression framework with multiply imputed data. Health Serv Outcomes Res Methodol 2012;12:219–33.
[28] Ellis P, Smith I, Ashley S, et al. Clinical prognostic and predictive factors for primary chemotherapy in operable breast cancer. J Clin Oncol 1998;16:107–14.
[29] Edge SBBDCCFA. AJCC Cancer Staging Manual 7th. Springer, New York:2010.
[30] Yerushalmi R, Woods R, Ravdin PM, et al. Ki67 in breast cancer: prognostic and predictive potential. *Lancet Oncol*. 2010;11:174–183.