

Better survival in PMRT of female breast cancer patients with >5 negative lymph nodes

A population-based study

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Abstract

Many studies have confirmed the role of postmastectomy radiotherapy (PMRT) for breast cancer patients with at least 4 lymph nodes invasion in the postoperative therapy. Recently, the number of negative lymph nodes (NLNs) has been increasingly paid attention to and recognized as a prognostic indicator in different kinds of cancers. Therefore, it is very necessary to study the association between the number of NLNs and the prognosis of PMRT in breast cancer patients. In our study, we used Surveillance, Epidemiology, and End Results (SEER) population-based data and identified 16,686 breast cancer patients to explore their correlation. The ROC curve and the log-rank χ^2 test were applied to determine the appropriate cutoff point of the number of NLNs and 5 was selected as the cutoff point. Furthermore, the cutoff point 5 was validated as an independent prognostic factor affecting cancer-specific survival (CSS) and overall survival (OS) in breast cancer patients, as confirmed by both univariate and multivariate analysis ($P < 0.001$). In addition, subgroup analysis showed that the number of NLNs >5 can be a prognostic indicator in patients with PMRT according to different clinical variables (all, $P < 0.001$). Importantly, our results showed that PMRT obviously improved CSS and OS in patients regardless of the number of NLNs ($P < 0.001$). In conclusion, our study showed the number of NLNs is an independent prognostic factor for breast cancer patients with PMRT, and those who have higher number of NLNs have an increased CSS and OS.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, DFS = disease-free survival, FBC = female breast cancer, HR = hazard ratio, LRFS = locoregional recurrence-free survival, NLNs = negative lymph nodes, OS = overall survival, PMRT = postmastectomy radiotherapy, SEER = Surveillance, Epidemiology, and End Results.

Keywords: breast cancer, mastectomy, negative lymph nodes, radiotherapy, SEER

1. Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide, with an estimated 1.7 million incidence and 521,900 mortalities in 2012.^[1] Breast cancer alone accounts for 25% of all cancers and 15% of all cancer-related deaths among females.^[1] Lack of effective adjuvant therapies mainly account for the recurrence and metastasis of the disease, which would even result in the

death of the patients. Postmastectomy radiotherapy (PMRT), a commonly used practice, can prevent locoregional recurrence and increase survival in breast cancer patients after definite surgery. PMRT has already become a standard adjuvant postoperative therapy for patients with four or more lymph nodes invasion.^[2–4]

Many factors can affect the PMRT for breast cancer patients, which include lymph node involvement, large tumor size, positive or close surgical margins, et al.^[5] Interestingly, the number of NLNs has recently been paid attention to and recognized as a prognostic indicator in breast cancer.^[6–8] To date, studies, NLNs can be regarded as a prognostic factor for PMRT of breast cancer, are limited and controversial. Given the growing predominance of PMRT in the management of patients with breast cancer, it is vital to explore the optimal cutoff point and to further confirm the specific value of the number of NLNs in breast cancer patients with PMRT. Therefore, we assessed the effect of the number of NLNs on the prognosis of breast cancer patients with PMRT by analyzing the Surveillance, Epidemiology, and End Results (SEER)-registered database.

2. Methods

2.1. Patient selection

The SEER database was used to identify all young female patients diagnosed with breast cancer between 1990 and 2012.^[9] A total of 18 population-based cancer registries in the United States were included in the current SEER database. The SEER*Stat software (SEER*Stat 8.2.1) was used to identify patients. The included patients should meet the following criteria: the diagnosis was

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confirmed microscopically, they should be female with the confirmed age, active follow-up, and only 1 primary tumor. In addition, the patients should be received modified radical mastectomy, with at least 4 positive lymph nodes removed. Patients with benign or borderline tumors, unknown age, unknown cause of death, and unknown survival months were excluded. In addition, to guarantee the accuracy, we excluded the patients diagnosed between 2009 and 2012 to have enough follow-up.

2.2. Ethical statement

This study was mainly based on the SEER database and was conducted in compliance with the Helsinki Declaration. We obtained permission to access the SEER program research data files and the reference number is 11824-Nov2014. The informed consent was not required because personal identifying information was not involved. This study was approved by the ethics committee of the Shandong Cancer Hospital affiliated to Shandong University.

2.3. Statistical analysis

For all patients, the following variables were analyzed: age, race, year of diagnosis, tumor size, grade, estrogen receptor (ER) status, progesterone receptor (PR) status, and number of NLNs. In addition, the overall survival (OS) and cancer-specific survival (CSS) were regarded as the primary endpoint of this study and extracted from the SEER database. χ^2 tests were used to compare

Table 1
Characteristics of breast cancer patients with ≥ 4 positive lymph nodes after PMRT from SEER Database from 1990 to 2009.

Characteristic	Number	%
Age, y		
<40	1778	10.7
≥ 40	14,908	89.3
Race		
White	13,357	80.0
Black	1878	11.3
Others	1451	8.5
Year of diagnosis		
1990–2000	3176	19.0
2001–2005	7801	46.8
2006–2009	5709	34.2
Tumor size		
T1	2662	16.0
T2	7406	44.4
T3	3583	21.5
T4	2626	15.7
Unknown	409	2.5
Grade		
I	994	6.0
II	5820	34.9
III	8509	51.0
Unknown	1017	8.2
ER status		
Positive	11,361	68.1
Negative	4251	25.5
Unknown	1073	6.4
PR status		
Positive	9346	56.0
Negative	6061	36.3
Unknown	1279	7.7

ER=estrogen receptor, PR=progesterone receptor, PMRT=postmastectomy radiotherapy, SEER=Surveillance, Epidemiology, and End Results.

the patient baseline characteristics. The Kaplan–Meier analyses were used to generate the survival curves and the Log Rank test was applied to analyze the differences among the curves. Comparative risks of mortality were evaluated using univariate and multivariate Cox proportional hazards regression models. All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant. The statistical software SPSS 18.0 (SPSS Inc, Chicago, IL) was used for all data analyses.

3. Results

3.1. Patient demographics

There were 16,686 female breast cancer (FBC) patients reported in the SEER database from 1990 to 2009. The clinical characteristics and pathological features of all the patients were summarized in Table 1. Most patients were diagnosed at the age of above 40 years (89.3%). Most patients were white race (80.0%) and were diagnosed after 2000 (81.0%). A total of 44.4% of patients were in AJCC T2 stage (tumor size) and 51.0% of patients were in Grade III. In addition, 68.1% of patients were ER-positive and 56% of patients were PR-positive. The detailed statistical results were showed in Table 1.

3.2. Identification of appropriate cutoff points of NLNs

The ROC curve was applied to determine the appropriate cutoff points of NLNs. The results showed that the Youden index is the largest, when the cutoff point of NLNs is 4.5 to 5.5 (Supplementary Table 1, <http://links.lww.com/MD/B540>). Therefore, 5 was the appropriate cutoff point for NLNs (Area Under roc Curve=0.628, $P < 0.001$) (Fig. 1). To further verify the feasibility of the 5 as appropriate cutoff point for NLNs, we treated NLNs as a continuous variable. The results showed that NLN was validated as a significant prognostic factor using univariate log-rank test ($P < 0.001$) (Table 2). We further analyzed individual NLNs from 5 to 16. The 5-year and 10-year CSS or OS with different numbers of NLNs were calculated,

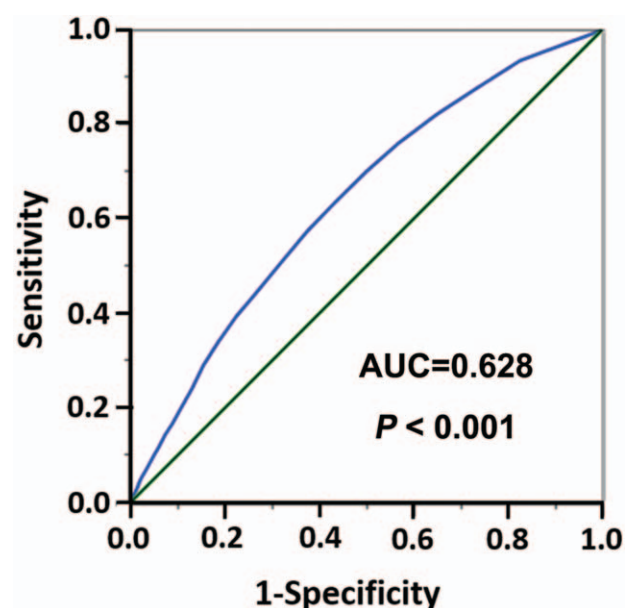


Figure 1. The receiver-operating characteristic curve of the appropriate cutoff point of the number of negative lymph nodes. AUC=area under the curve.

Table 2
Univariate analysis for the influence of different cutoff points of the number of NLNs on CSS or OS in breast cancer patients with PMRT.

Cut-off	Number	CSS (%)				OS (%)			
		5-year	10-year	χ^2	P	5-year	10-year	χ^2	P
>5	8997	81.5	67.7	608.1	<0.001	77.5	59.1	636.6	<0.001
≤5	7689	66.8	48.7			61.8	40.3		
>6	7982	82.2	68.7	556.3	<0.001	78.2	60.0	573.1	<0.001
≤6	8758	68.0	50.1			63.0	41.8		
>7	6876	82.7	69.5	483.3	<0.001	78.8	61.0	507.6	<0.001
≤7	9810	69.1	51.6			64.3	43.1		
>8	5939	82.9	70.3	414.3	<0.001	79.2	61.9	452.3	<0.001
≤8	10747	70.2	52.7			65.3	44.1		
>9	5121	83.8	71.3	393.7	<0.001	80.2	62.9	426.6	<0.001
≤9	11565	70.7	53.5			65.9	45.0		
>10	4344	84.3	72.3	353.7	<0.001	80.7	63.6	375.5	<0.001
≤10	12342	71.3	54.3			66.6	45.8		
>11	3664	84.6	72.6	297.8	<0.001	81.2	64.1	323.2	<0.001
≤11	13022	71.9	55.1			67.2	46.6		
>12	3086	85.1	73.3	262.8	<0.001	81.5	64.7	281.1	<0.001
≤12	13600	72.4	55.7			67.7	47.2		
>13	2576	84.9	73.9	216.0	<0.001	81.4	65.2	230.2	<0.001
≤13	14110	72.9	56.3			68.2	47.7		
>14	2137	84.8	73.8	170.2	<0.001	81.5	65.2	185.8	<0.001
≤14	14549	73.2	56.8			68.6	48.2		
>15	1770	84.7	73.6	134.7	<0.001	81.4	65.9	156.3	<0.001
≤15	14916	73.5	57.2			68.9	48.6		
>16	1459	84.9	73.4	108.9	<0.001	81.4	65.6	124.5	<0.001
≤16	15227	73.8	57.6			69.2	48.9		

CSS=cancer-specific survival, OS=overall survival, NLNs=negative lymph nodes.

respectively. The results showed the number of NLNs from 5 to 16 has the same impact on CSS and OS (all, $P < 0.001$); however, the patients with ≥ 5 NLNs had a maximum log-rank χ^2 value both in CSS ($\chi^2=608.1$, $P < 0.001$) and OS ($\chi^2=636.6$, $P < 0.001$) (Table 2). Therefore, 5 can be selected as the appropriate cutoff point for the number of NLNs for all patients. The 5-year and 10-year survival rate of the patients with the number of > 5 NLNs were 81.5% and 67.7% in CSS and 77.5% and 59.1%, respectively. Therefore, the appropriate cutoff value of 5 was validated as a prognostic factor to analyze the clinical effect of the number of NLNs.

3.3. Prognostic value of the number of NLNs on CSS and OS

The prognoses of all the patients were further analyzed using univariate analysis. The number of NLNs and other clinicopathological factors, including race, year of diagnosis, tumor size, grade, ER, PR, were significant risk factors for CSS and OS (Table 3). The Kaplan–Meier estimates showed that the CSS and OS for patients with the number of > 5 NLNs were significantly higher than the patients with the number of ≤ 5 NLNs ($\chi^2=608.099$, $P < 0.001$ for CSS; $\chi^2=636.564$, $P < 0.001$ for OS) (Fig. 2). Multivariate analysis with Cox regression was further performed and found that the number of NLNs (with the cutoff of 5) were independent prognostic factors for CSS and OS and the number of > 5 NLNs were found to have a positive effect on CSS (hazard ratio [HR] 0.620; 95% confidence interval [CI] 0.587–0.656; $P < 0.001$) and OS (HR 0.649; 95% CI 0.618–0.682; $P < 0.001$) (Table 4).

3.4. Subgroup analysis to evaluate the prognostic value of the number of NLNs according to different variables

Univariate analyses have showed that race, year of diagnosis, tumor size, grade, ER status, PR status, number of NLNs were

Table 3
Univariate survival analyses to evaluate the influence of the number of NLNs on CSS or OS in breast cancer patients with PMRT.

Variable	CSS		OS	
	Log rank χ^2	P	Log rank χ^2	P
Age, y	13.799	<0.001	0.215	0.643
<40				
≥40				
Race	133.282	<0.001	161.878	<0.001
White				
Black				
Others				
Year of diagnosis	36.159	<0.001	33.290	<0.001
1990–2000				
2001–2005				
2006–2009				
Tumor size	819.059	<0.001	853.148	<0.001
T1				
T2				
T3				
T4				
Unknown				
Grade	<0.001		375.969	<0.001
I				
II				
III				
Unknown				
ER status	790.314	<0.001	673.190	<0.001
Positive				
Negative				
Unknown				
PR status	618.030	<0.001	577.984	<0.001
Positive				
Negative				
Unknown				
Number of NLNs	608.099	<0.001	636.564	<0.001
>5				
≤5				

CSS=cancer-specific survival, ER=estrogen receptor, OS=overall survival, PMRT=postmastectomy radiotherapy, NLNs=negative lymph nodes, PR=progesterone receptor.

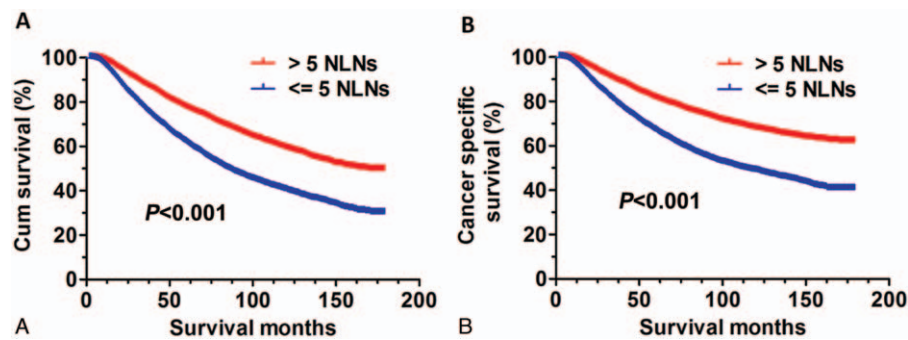


Figure 2. The OS and CSS curves in breast cancer patients after PMRT with the number of NLNs >5 and ≤5 between 1990 and 2009. (A) The OS curves: the number of NLNs >5 vs. the number of NLNs ≤5 ($\chi^2 = 636.564$, $P < 0.001$). (B) The CSS curves: the number of NLNs >5 vs. the number of NLNs ≤5 ($\chi^2 = 608.099$, $P < 0.001$). CSS=cancer-specific survival, OS=overall survival, PMRT=postmastectomy radiotherapy, NLNs=negative lymph nodes.

prognostic factors affecting CSS or OS (all, $P < 0.001$) (Table 3). Further multivariate analysis showed that the number of NLNs was an independent prognostic factor of CSS or OS. In addition, race, year of diagnosis, tumor size, grade, ER status, PR status were also independent risk factors affecting CSS or OS (all, $P < 0.01$) (Table 4). Then we conducted subgroup analysis of the impact of the number of NLNs on CSS or OS by different variables. As our expected, the results showed that patients with the number of more than five NLNs had better CSS in all subgroups (all, $P < 0.001$) (Fig. 3). Interestingly, the

maximum hazard ratio (HR) could be found in Stage T4 subgroup (HR, 0.65; 95% CI, 0.58–0.73; $P < 0.001$), and the minimal HR could be found in Grade I subgroup (HR, 0.34; 95% CI, 0.25–0.46; $P < 0.001$) (Fig. 3). In addition, the results also showed that patients with the number of >5 NLNs had better OS in all subgroups (all, $P < 0.001$) (Fig. 4). The maximum HR could be found in Stage T4 subgroup (HR, 0.67; 95% CI, 0.61–0.74; $P < 0.001$), and the minimal HR could be found in Grade I subgroup (HR, 0.45; 95% CI, 0.35–0.57; $P < 0.001$) (Fig. 4).

Table 4

Multivariate survival analyses to evaluate the influence of the number of NLNs on CSS or OS in breast cancer patients with PMRT.

Variable	CSS			OS		
	HR	95% CI	P	HR	95% CI	P
Race						
White	Reference			Reference		
Black	1.378	1.274–1.489	<0.001	1.363	1.271–1.461	<0.001
Others	0.964	0.874–1.063	0.459	0.944	0.864–1.031	0.198
Year of diagnosis						
1990–2000	Reference			Reference		
2001–2005	0.915	0.857–0.977	0.008	0.919	0.868–0.974	0.004
2006–2009	0.813	0.749–0.882	<0.001	0.831	0.772–0.894	<0.001
AJCC T						
T1	Reference			Reference		
T2	1.450	1.323–1.589	<0.001	1.380	1.275–1.492	<0.001
T3	1.829	1.656–2.019	<0.001	1.681	1.543–1.831	<0.001
T4	2.587	2.341–2.858	<0.001	2.361	2.165–2.575	<0.001
Unknown	1.480	1.223–1.792	<0.001	1.397	1.181–1.652	<0.001
Grade						
I	Reference			Reference		
II	1.285	1.104–1.496	0.001	1.249	1.100–1.417	0.001
III	1.729	1.489–2.008	<0.001	1.527	1.347–1.731	<0.001
Unknown	1.472	1.231–1.759	<0.001	1.409	1.213–1.638	<0.001
ER status						
Positive	Reference			Reference		
Negative	1.575	1.455–1.705	<0.001	1.446	1.347–1.552	<0.001
Unknown	0.959	0.782–1.176	0.687	0.962	0.802–1.153	0.674
PR status						
Positive	Reference			Reference		
Negative	1.275	1.182–1.376	<0.001	1.259	1.178–1.346	<0.001
Unknown	1.482	1.225–1.792	<0.001	1.425	1.203–1.687	<0.001
Number of NLNs						
>5	Reference			Reference		
≤5	0.620	0.587–0.656	<0.001	0.649	0.618–0.682	<0.001

CI=confidence interval, CSS=cancer-specific survival, ER=estrogen receptor, HR=hazard ratio, OS=overall survival, PMRT=postmastectomy radiotherapy, NLNs=negative lymph nodes, PR=progesterone receptor.

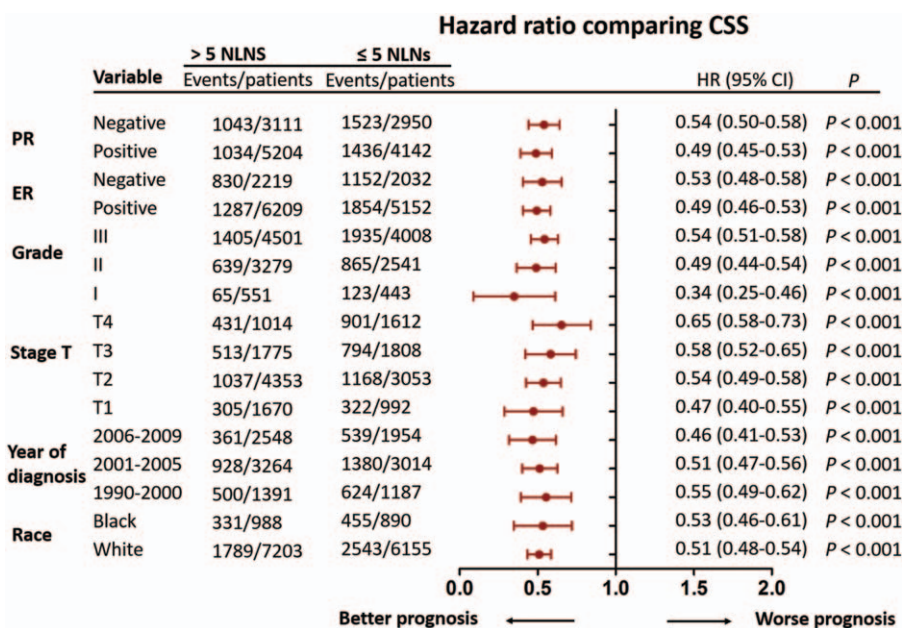


Figure 3. Hazard ratio comparing CSS between patients with >5 NLNs and patients with ≤5 NLNs according to clinical variables (all, P < 0.001). CSS=cancer-specific survival, NLNs=negative lymph nodes.

3.5. Survival rate for patients with PMRT and no-PMRT according to different cutoff point of NLNs

PMRT has been a postoperative standard therapy for patients with ≥4 lymph nodes invasion. In our study, we chose the patients with ≥4 positive lymph nodes after they underwent PMRT. The result showed that the number of NLNs were prognostic factors for CSS and OS in the part of the patients. Interestingly, we found that the patients with the number of >5 NLNs who underwent PMRT had an improved OS and CSS

compared with the patients' non-PMRT ($\chi^2=255.00, P < 0.001$ for OS; $\chi^2=87.04, P < 0.001$ for CSS) (Fig. 5A). Importantly, we then chose 10 or 16 as the cutoff point of the number of NLNs. The results also showed that the patients who underwent PMRT all had an improved OS and CSS compared with the no-PMRT patients regardless of the cutoff point of the number of NLNs (NLNs counts >10: $\chi^2=106.00, P < 0.001$ for OS; $\chi^2=39.56, P < 0.001$ for CSS; NLNs counts >16: $\chi^2=38.09, P < 0.001$ for OS; $\chi^2=14.25, P < 0.001$ for CSS) (Fig. 5 B–C). The clinical characteristics and pathological features of all the patients with

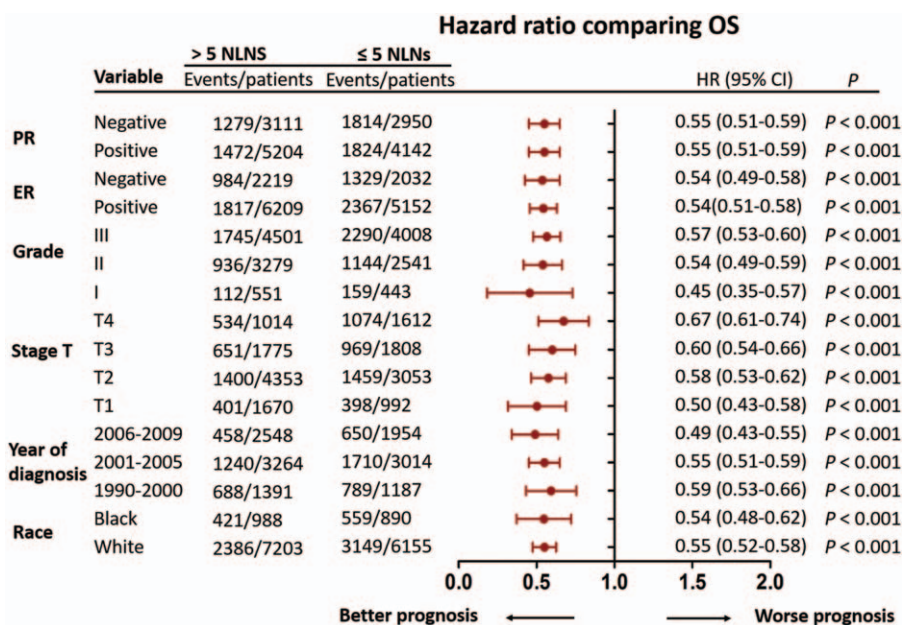


Figure 4. Hazard ratio comparing OS between patients with >5 NLNs and patients with ≤5 NLNs according to clinical variables (all, P < 0.001). OS=overall survival, NLNs=negative lymph nodes.

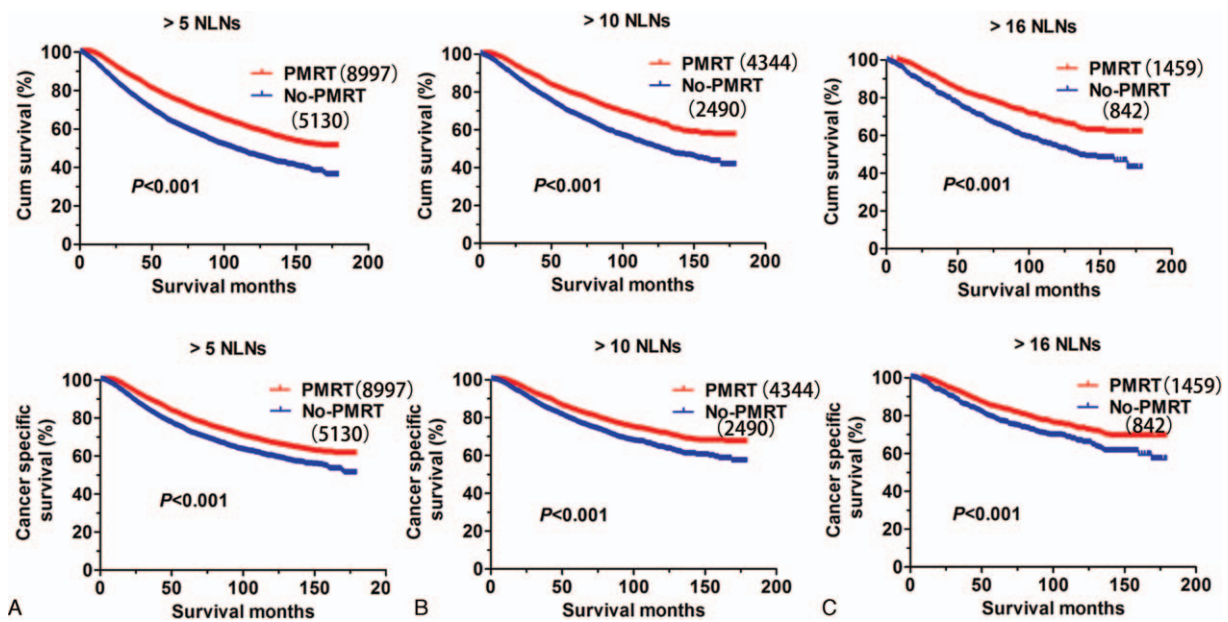


Figure 5. The OS and CSS curves in breast cancer patients with PMRT and no-PMRT according to different cutoff point of NLNs. (A) The OS and CSS curves of the patients with the number of NLNs >5. Patients with PMRT vs. patients with no-PMRT ($\chi^2=255.00$, $P<0.001$ for OS; $\chi^2=87.04$, $P<0.001$ for CSS). (B) The OS and CSS curves of the patients with the number of NLNs >10. Patients with PMRT vs. patients with no-PMRT ($\chi^2=106.00$, $P<0.001$ for OS; $\chi^2=39.56$, $P<0.001$ for CSS). (C) The OS and CSS curves of the patients with the number of NLNs >16. Patients with PMRT vs. patients with no-PMRT ($\chi^2=38.09$, $P<0.001$ for OS; $\chi^2=14.25$, $P<0.001$ for CSS). CSS=cancer-specific survival, OS=overall survival, PMRT=postmastectomy radiotherapy, NLNs=negative lymph nodes.

non-PMRT were summarized in supply Table 2, <http://links.lww.com/MD/B540>.

4. Discussion

In our study, we investigated the prognostic value of the number of NLNs in female breast cancer patients with ≥ 4 positive lymph nodes after PMRT, with CSS and OS as the primary study endpoints. Our results showed that the number of NLNs can be used as an important prognostic factor in breast cancer patients who underwent PMRT.

The number of NLNs is defined as the number derived from the total number of removed lymph nodes by axillary dissection minus the number of positive lymph nodes. The number of NLNs has been confirmed as an independent prognosis factor in colon, esophageal, cervical, and gastric cancer.^[10–13] A recent study also showed that the number of NLNs is an independent prognostic factor of disease-free survival (DFS) in breast cancer patients after mastectomy, and patients with a higher number of NLNs have a better DFS.^[6–8] To analyze the correlation between NLNs and prognosis of cancer, we assumed that identification of more NLNs may reduce the overall risk of occult lesions and help determine accurate postoperative TNM stage, and then serve as an indicator of improve survival.

PMRT has become a standard adjuvant postoperative therapy for patients with positive lymph nodes.^[2–4] Recent studies from China have showed that the number of NLNs can significantly predict the prognosis of patients with PMRT.^[14,15] However, these studies are limited and controversial. Xin et al^[16] found that less number of NLNs would benefit from PMRT in patients of ypN1 stage. Inconsistent with the study, Wu et al^[7] found that patients with an elevated number of NLNs had better survival after PMRT. In our study, we showed that the number of NLNs was a prognostic indicator in patients with PMRT and an

elevated number of NLNs indicated a better prognosis for patients after PMRT, using the American SEER database.

The number of NLNs has been recently paid attention to and recognized as a prognostic indicator in breast cancer patients after PMRT. However, these studies were basically from China with relatively smaller samples. In addition, some limitations can still be found from these studies.

The first limitation was the inconsistency of cutoff point and the number of NLNs. Karlsson et al^[17] found that the patients with the number of NLNs <10 have an increased risk of locoregional failure and the patients with the number of NLNs ≥ 10 had a significantly better prognosis. In a study conducted by Wu et al, it was found that the number of NLNs was an independent prognostic factor of locoregional recurrence-free survival (LRFS), DFS, and OS, whereas it was revealed that patients with a number of NLNs >8 had better survival in patients with PMRT.^[15] Another study coming from China showed that the number of NLNs was an independent prognostic factor affecting the LRFS. Patients with a number of NLNs >12 had better survival in patients with PMRT.^[14] The different cutoff point of the number of NLNs may mainly be attributed to the different clinical and pathological characteristics. And the application of different methods in determining cutoff may also lead to the various cutoff values. In our study, ROC curve was applied to define specific cutoff point, using the same method as Wu et al's. The cut-off of NLN was selected as 5, as confirmed in our study, which was relatively lower as compared with the value in other studies. To further determine the feasibility of the cutoff point, we then treated the number of NLNs as a continuous variable. Univariate log-rank test was used, demonstrating NLNs as a significant prognostic factor. We further analyzed individual number of NLNs from 5 to 16 and found the patients with ≥ 5 NLNs had a maximum log-rank χ^2 value both in CSS and OS. Although the cutoff point in our study is different from other

studies, our results showed that the number of NLNs was an independent prognostic factor of CSS and OS. Patients after PMRT with higher number of NLNs had better survival, which was consistent with other studies.

The second limitation was different subgroup analysis. In our study, we found that patients with the number of >5 NLNs had better CSS and OS in all groups including different hormonal status, different AJCC T stage, different Grade stage, different year of diagnosis, and different race. Similar to our study, Wu et al^[8] found that the number of NLNs had a prognostic value in patients with different pT stages and different lymph node status. However, a study from China showed the number of NLNs had no predictive value for the efficacy with PMRT in triple-negative subtypes.^[15] Unfortunately, we did not analyze the Her2+ subgroup in our study. Interestingly, our results showed that the number of NLNs had the predictive value in breast cancer patients with negative ER and PR. The difference may result from the following aspects. First, different data sources: our study mainly analyzed the data from American in SEER database and had a larger sample size. However, other studies mainly analyze the data from China, which had a smaller sample size. Second, different variables were included in these studies. For example, the patients with Her2+ were not included and the patients with Grade stage were included in our study. Third, different cutoff point of NLNs numbers may be another attributing factor.

The third limitation was different conclusion between NLNs and non-PMRT. Recent studies showed that PMRT improved the LRFS, DFS, and OS in patients with ≤ 12 NLNs, but the survival of patients with >12 NLNs was not affected.^[14] According to this study, the patients with ≥ 4 positive lymph nodes would not benefit from PMRT if the NLNs out numbered 12. Interestingly, PMRT has become a standard adjuvant postoperative therapy for patients with at least lymph nodes invasion. However, in our study, we found all patients with ≥ 4 positive lymph nodes benefited from PMRT regardless of the number of NLNs. Therefore, the number of NLNs can be used as an important prognostic indicator for patients who underwent PMRT, but not as indicators whether to carry out PMRT for breast cancer patients.

This study also has several limitations. First, some studies have showed that the systemic therapy may bring some substantial survival benefits for PMRT.^[18-20] However, because of the absence of information on chemotherapy or targeted therapy included in the SEER database, its effect on survival could not be evaluated. Second, as a retrospective study, the study has its intrinsic defects. Third, the specific dose or methods of radiotherapy was not included in our study, which can affect the survival rate of breast cancer patients. Therefore, future prospective studies from different countries and regions are needed to further confirm these results.

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