

How many ELNs are optimal for breast cancer patients with more than three PLNs who underwent MRM? A large population-based study

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Background: Few studies have focused on the optimal threshold of examined lymph nodes (ELNs) for breast cancer patients with more than three positive lymph nodes after modified radical mastectomy.

Materials and methods: The X-tile and the minimum *P*-value models were applied to determine the optimal threshold. Cox proportional hazard analysis was used to analyze the cancer-specific survival and perform subgroup analysis.

Results: The results showed that 12 ELNs was the optimal threshold for these patients, and the patients with >12 ELNs had a better cancer-specific survival benefit compared with the patients with <12 ELNs (*P*<0.001).

Conclusion: The number 12 can be selected as the optimal threshold of ELNs for breast cancer patients with >3 positive lymph nodes after modified radical mastectomy.

Keywords: breast cancer, mastectomy, ELNs, positive lymph nodes, X-tile

Introduction

Modified radical mastectomy (MRM) serves as the primary treatment strategy for early breast cancer patients.^{1,2} The status of local positive lymph nodes (PLNs) after MRM has been regarded as an important prognostic factor for patients with breast cancer.³⁻⁵ Some lymph node parameters including the ratio of PLNs and the number of negative lymph nodes have been introduced and demonstrated to assume more powerful role in predicting survival prognosis for breast cancer patients.⁶⁻⁹ In addition, the number of PLNs strongly associated with American Joint Committee on Cancer (AJCC) N stage is a critical factor to determine the strategies in adjuvant systemic therapy.¹⁰⁻¹³

Theoretically, more number of examined lymph nodes (ELNs) after MRM could increase the probability of PLNs, thus providing more accurate information on TNM stage and adjuvant therapy. However, it is worth noting that more number of ELNs is associated with an increased risk of adverse outcomes.¹⁴⁻¹⁶ Therefore, it is vitally important to find an optimal threshold of ELNs, so as to balance the two key clinical prognosis factors. It is a pity that few studies have focused on these issues of clinical significance, especially in recent years.

To address these unresolved issues, using the Surveillance, Epidemiology, and End Results (SEER)-registered database based on a large sample size and high-quality population-based US cancer registries we focused on the breast cancer patients with more than three PLNs undergoing MRM and further confirmed the relationship between

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the number of ELN and cancer-specific survival (CSS). Importantly, multiple models were applied to determine the optimal threshold for ELN count.

Materials and methods

Patient selection

The SEER Cancer Statistics Review²⁸ is published annually by the Data Analysis and Interpretation Branch of the National Cancer Institute, Bethesda, MD, USA. A total of 18 population-based cancer registries in the USA were included in the current SEER database.¹⁷ We used SEER*Stat software 8.3.2 to screen the appropriate patients with breast cancer between 2004 and 2009. Patients with the following criteria were included: female with confirmed age and only one primary tumor; the diagnosis was confirmed microscopically; and active follow-up. In addition, the breast cancer patients should have received MRM and should be with more than three PLNs removed. The breast cancer patients who underwent conserving surgery were not included in our study. All the breast cancer patients included in our study had conducted the MRM and did not have the sentinel lymph node biopsy performed. Breast cancer patients lacking information on the subgroup variables including age, race, AJCC T stage, grade, and the number of ELNs were all excluded. We also excluded the patients lacking information on the cause of death and survival months.

Ethics statement

As we have previously mentioned,¹⁸ this study was mainly based on the SEER database and was conducted in compliance with the Helsinki Declaration. We obtained permission to access the files of SEER program research data and the reference number is 11304-November 2015. 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.

Statistical analysis

We mainly analyzed the following variables: age, race, grade, AJCC T stage, and the number of ELNs. We obtained CSS from the SEER database and identified it as the terminal point of the patients. CSS is a survival measure representing survival of a specified cancer of death in the absence of other causes of death.¹⁸ The influence of ELN numbers on CSS was measured by Cox proportional hazard. We determined

the optimal threshold for the number of ELNs by the X-tile mode. Then, the optimal threshold was validated by using the minimum *P*-value model. Based on the optimal threshold, subgroup analyses of the CSS were conducted by Cox proportional hazard analysis based on different variables and presented on the forest plot.

As we have previously mentioned,¹⁸ all statistical tests were two-sided and a *P*<0.05 was considered statistically significant. The statistical software SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used for all data analyses.

Results

Patient demographics

A cohort of 9,297 female breast cancer patients was selected between 2004 and 2009 from SEER database. They were followed up for a consecutive 119 months. Generally, the minimum number of ELNs among these female breast cancer patients was 4 and the maximum number of ELNs was 86. The proportion of white-raced patients and diagnosed at the age of ≥ 50 years was 78.0% and 66.2%, respectively, accounting for a large proportion among the female breast cancer patients. The ratio of breast cancer patients at Grade I, II, and III was 6.3%, 37.4%, and 56.3%, respectively. Our results also demonstrated that 61.7% of the patients were diagnosed at AJCC stage T1–2. Their clinical characteristics are presented in Table 1.

Table 1 Characteristics of patients with more than three PLNs who underwent MRM and were screened from the SEER database

Variables	Number (%)
Total	9,297 (100)
Number of ELNs	4–86
Age, years	
<50	3,146 (33.8)
≥ 50	6,151 (66.2)
Race	
White	7,253 (78.0)
Black	1,229 (13.2)
Others	815 (8.8)
Grade	
I	588 (6.3)
II	3,473 (37.4)
III	5,236 (56.3)
T stage	
T1	1,459 (15.7)
T2	4,273 (46.0)
T3	2,101 (22.6)
T4	1,464 (15.7)

Abbreviations: ELNs, examed lymph nodes; MRM, modified radical mastectomy; PLNs, positive lymph nodes; SEER, Surveillance, Epidemiology, and End Results.

The relationship between the number of ELNs and PLNs

Generally, more numbers of ELNs after MRM may increase the probability of PLNs. Pearson correlation analysis was applied to confirm the relationship. The results showed a positive significant relationship between the number of ELNs and PLNs ($P < 0.001$; Figure 1).

Number of ELNs and CSS

The association between the ELN count (as a continuous variable) and CSS was measured by Cox proportional hazard. As we expected, the number of ELNs was found to be of prognostic significance on CSS (hazard ratio [HR]: 0.992, 95% CI: 0.987–0.997, $P = 0.001$; Table 2).

Determining the optimal threshold for the number of ELNs

Next, we determined the optimal threshold for the number of ELNs by the X-tile mode. The optimal threshold was found to be 12 (Figure 2A and B). Then, the CSS curve was generated by Kaplan–Meier analyses, and the survival prognosis was evaluated by log rank χ^2 . Survival curves revealed that the patients an ELN number > 12 had a better CSS rate ($P < 0.001$; Figure 2C).

Validation of the optimal threshold of ELNs

To verify the validity of 12 as the optimal threshold of ELNs, we further analyzed individual number of ELNs from 5 to 17 using the log-rank χ^2 . The 5-year CSS was calculated based on different numbers of ELNs, respectively. The minimum P -value model was applied to validate the optimal threshold. The results showed that the patients with > 12 ELNs count had a maximum log-rank χ^2 value compared with the patients

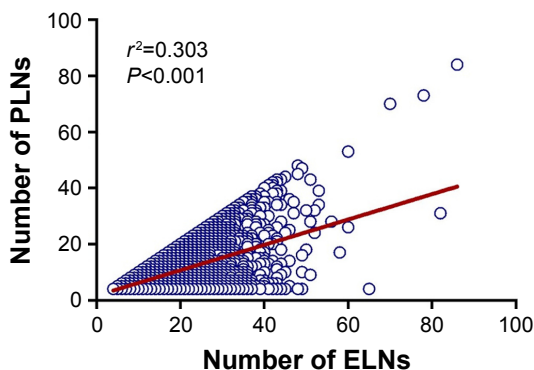


Figure 1 The relationship between the number of ELNs and PLNs demonstrated by Pearson correlation analysis ($P < 0.001$).

Abbreviations: ELNs, examined lymph nodes; PLNs, positive lymph nodes.

Table 2 The influence of different variables on CSS for breast cancer patients with more than three PLNs who underwent MRM analyzed by Cox proportional hazard model

Variables	Univariate analysis		Multivariate analysis	
	Wald χ^2	P-value	HR (95% CI)	P-value
Number of ELNs	13.782	< 0.001	0.992 (0.987–0.997)	0.001
Age, years	14.355	< 0.001		< 0.001
<50			Reference	
≥ 50			1.311 (1.214–1.415)	< 0.001
Race	0.046	0.830	Not included	
White				
Black				
Others				
Grade	268.909	< 0.001		< 0.001
I			Reference	
II			1.677 (1.360–2.067)	< 0.001
III			2.838 (2.315–3.480)	< 0.001
T stage	447.965	< 0.001		< 0.001
T1			Reference	
T2			1.584 (1.393–1.801)	< 0.001
T3			2.327 (2.033–2.663)	< 0.001
T4			3.208 (2.797–3.679)	< 0.001

Abbreviations: CSS, cancer-specific survival; ELNs, examined lymph nodes; HR, hazard ratio; MRM, modified radical mastectomy; PLNs, positive lymph nodes.

with ≤ 12 ELNs ($\chi^2 = 28.85$, $P < 0.001$; Table 3). Therefore, 12 was validated as the optimal threshold for these patients. In addition, the 5-year CSS rate of the breast cancer patients with > 12 ELNs was 73.3% (Table 3). Also, the 5-year CSS rate of the breast cancer patients with ≤ 12 ELNs was 68.3% (Table 3).

Subgroup analysis for CSS

After adjusting for other prognostic factors including age, race, grade, and AJCC T stage, we analyzed the CSS of subgroup variables based on the optimal threshold. The specific results were presented on the forest plot. The results demonstrated that all the subgroup variables including age < 50 , age ≥ 50 , white race, grade II and III, and AJCC T2–4, the number of ELNs > 12 showed significant CSS benefits (age < 50 : HR: 0.851, 95% CI: 0.742–0.977, $P = 0.022$; age ≥ 50 : HR: 0.839, 95% CI: 0.768–0.917, $P < 0.001$; white race: HR: 0.842, 95% CI: 0.772–0.917, $P < 0.001$; grade II: HR: 0.825, 95% CI: 0.720–0.946, $P = 0.006$; grade III: HR: 0.843, 95% CI: 0.770–0.924, $P < 0.001$; AJCC T2: HR: 0.862, 95% CI: 0.766–0.971, $P = 0.014$; AJCC T3: HR: 0.860, 95% CI: 0.741–0.999, $P = 0.048$; AJCC T4: HR: 0.815, 95% CI: 0.704–0.944, $P = 0.006$; Figure 3).

Discussion

The number of PLNs has been demonstrated to play an important role in determining adjuvant therapy by providing

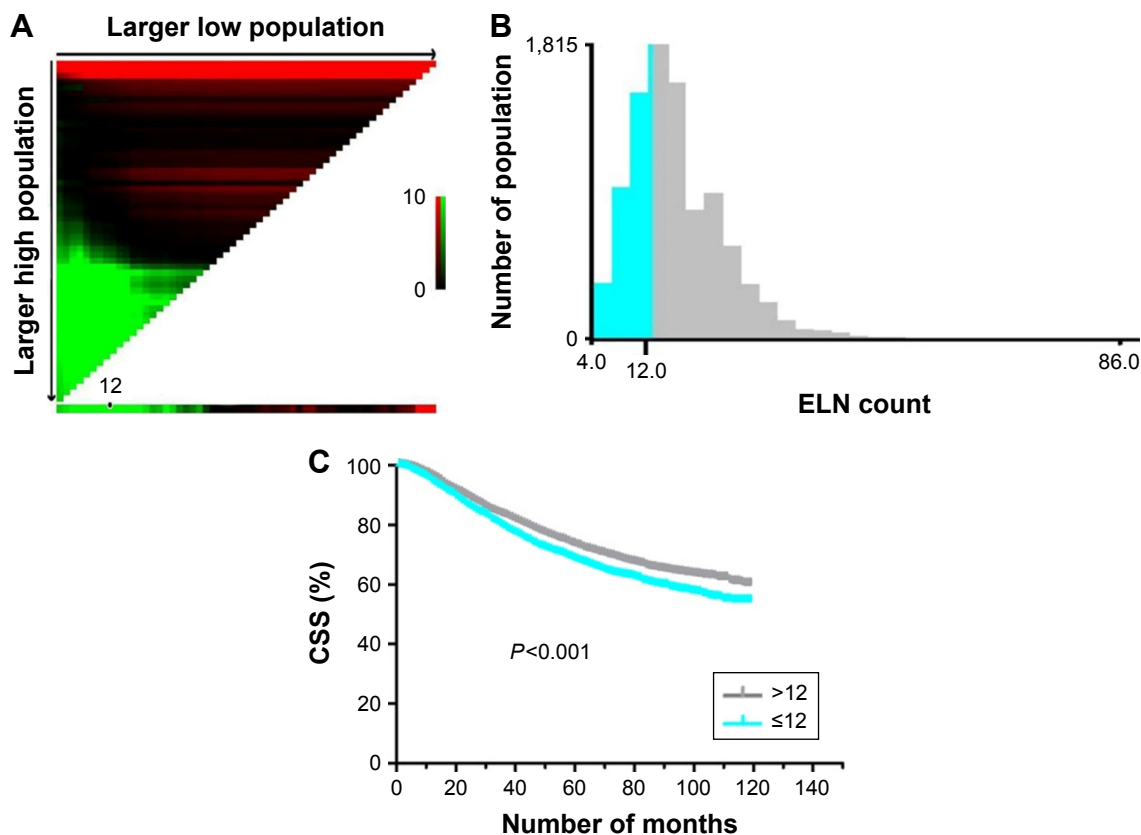


Figure 2 The optimal threshold of ELNs screened by the X-tile model.

Notes: (A) X-tile plots based on the number of ELNs. (B) The optimal cut-off point stressed by the gray and green panels. (C) The CSS curves based on the threshold ($P < 0.001$).

Abbreviations: CSS, cancer-specific survival; ELNs, examined lymph nodes.

accurate information on N stage of TNM stage for breast cancer patients.^{10–13} The number of PLNs has been applied by the AJCC staging system to classify the breast cancer patients with 1–3 PLNs as pN1 stage, 4–9 PLNs as pN2 stage, and ≥ 10 PLNs as pN3 stage.^{19,20} In fact, National Comprehensive Cancer Network and several other studies have regarded radiotherapy after MRM as standard treatment only for breast cancer patients with more than three PLNs.^{12,21} Therefore, the number of three has been viewed a key point to determine adjuvant therapy for patients with breast cancer after MRM. Based on these scenarios, we only screened the appropriate breast cancer patients with more than three PLNs undergoing MRM. Theoretically, the number of PLNs depends on the number of ELNs. In other words, more numbers of ELNs would increase the probability of PLNs. As we expected, the relationship between the number of ELNs and PLNs has been reflected in Figure 1.

From the point of view of adjuvant treatment, more number of ELNs could reduce the proportion of understaged patients and provide more breast cancer patients with adjuvant therapy

after MRM. Several studies have also shown that the number of ELNs has an intimate correlation with the survival benefit of patients.^{22,23} However, from the point of view of adverse outcomes with lymph node surgery, more number of ELNs could inevitably lead to more complications including pain, infection, seroma formation, restricted shoulder mobility, and sometimes even lymphedema.^{14–16} Importantly, more number of ELNs will destroy the immune microenvironment and affect the organism's immunity function negatively.^{24,25} Therefore, it is very important to strike a balance between increasing the detection rate of PLNs and reducing the incidence of complications. However, few studies have focused on the key clinical problem. In our study, using the SEER database, patients who underwent MRM and with more than three PLNs were only enrolled, and we regarded CSS as our main end point. As previously described,¹⁸ the X-tile model was used to determine the optimal threshold of ELNs. In fact, the X-tile plots can provide a single, global assessment of every possible way of dividing a population into low- and high-level marker expression. In addition, the X-tile can

Table 3 Univariate analysis to evaluate the influence of different cut-off points on CSS for breast cancer patients with more than PLNs who underwent MRM

Cut-off	Number	5-year CSS	Log rank χ^2	P-value
≤5	165	60.8	8.47	0.004
>5	9,132	72.0		
≤6	342	62.1	15.10	<0.001
>6	8,955	72.2		
≤7	570	63.9	22.40	<0.001
>7	8,727	72.3		
≤8	848	65.1	20.63	<0.001
>8	8,449	72.5		
≤9	1,276	66.6	18.40	<0.001
>9	8,021	72.6		
≤10	1,731	67.1	24.43	<0.001
>10	7,566	72.9		
≤11	2,246	67.8	26.03	<0.001
>11	7,051	73.1		
≤12	2,792	68.3	28.85	<0.001
>12	6,505	73.3		
≤13	3,398	69.0	23.19	<0.001
>13	5,899	73.4		
≤14	3,981	69.7	21.55	<0.001
>14	5,316	73.4		
≤15	4,607	70.6	9.92	<0.001
>15	4,690	73.1		
≤16	5,173	70.6	12.19	<0.001
>16	4,124	73.4		
≤17	5,719	70.8	8.81	0.003
>17	3,578	73.5		

Abbreviations: CSS, cancer-specific survival; MRM, modified radical mastectomy; PLNs, positive lymph nodes.

produce corrected *P*-values using several Monte Carlo simulations: cross-validation takes our dataset, randomly splits it into two halves, and finds the optimal cut-off point of one half and then divides the other half according to this cut-off point. Then, it finds the optimal cut-off point of the second half and similarly divides the first.²⁶ The results showed that the number 12 can be regarded as the optimal threshold for these breast cancer patients. In order to ensure the accuracy of the results, another model named minimum *P*-value method applied in others studies^{9,27} was used to further validate the feasibility of using 12 as the optimal threshold for ELN count. Our finding may give some suggestions and references to surgical specialists or pathologists to determine the appropriate number of lymph nodes to be dissected.

Strength and limitations

To our knowledge, this study is currently the largest study focusing on such a clinical problem using huge and realistic data. We sought to emphasize that breast cancer patients with more than three PLNs after MRM should reasonably determine the number of ELNs based on the survival prognosis and adverse reaction. Undeniably, this study also has several limitations. First, some important factors that affected prognosis, such as adjuvant therapy, estrogen receptor/progesterone receptor status, HER-2, and so on, were not included in our study. In fact, the X-tile and minimum *P*-value model were applied to determine the optimal threshold for breast cancer patients with more than three PLNs after MRM in our

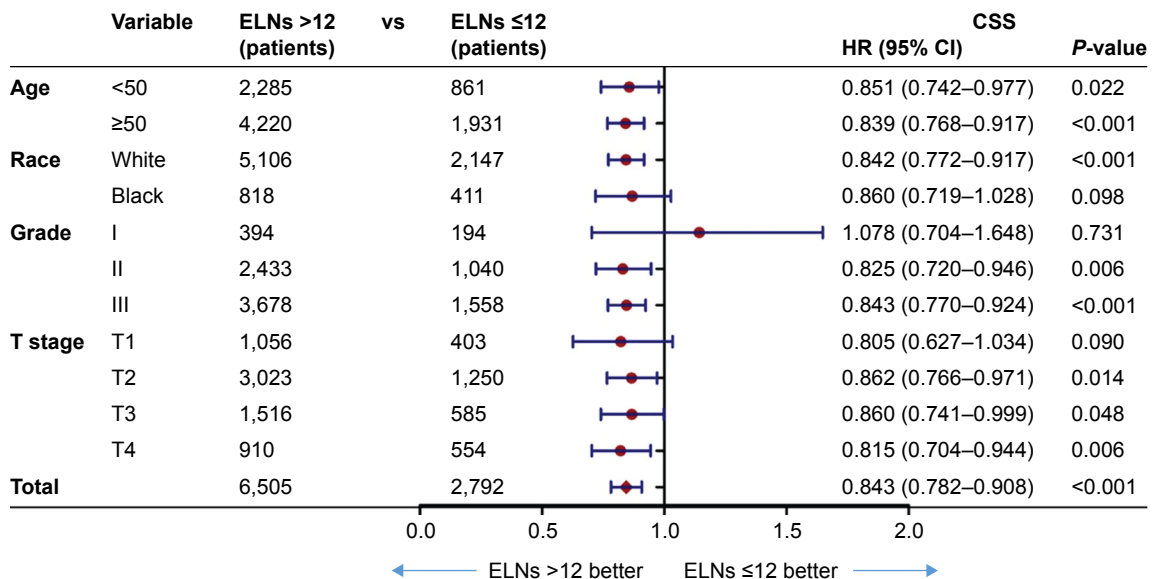


Figure 3 The forest plot of the number of ELNs on CSS based on all the subgroup variables conducted by the Cox proportional hazard model. **Abbreviations:** CSS, cancer-specific survival; ELNs, examined lymph nodes; HR, hazard ratio.

study. The variables including the number of ELNs, survival month, and CSS status were the three key factors to determine the optimal threshold. Although the important factors affecting prognosis, such as adjuvant therapy, estrogen receptor/progesterone receptor status, HER-2, and so on, were not included in our study, the final conclusion is largely unaffected. Of course, sufficient subgroup analyses would render our research more individualized and instructive.

In conclusion, our results showed that the number of 12 can be selected as the optimal threshold for ELNs for these patients. In addition, in clinical practice, we should determine the best ELN number for patients to conduct individual lymphadenectomies taking into account other factors and based on our results. Therefore, our results do not mean that a new lymphadenectomy will be performed or the lymphadenectomy is not done if the patients have <12 ELNs after MRM. Of course, further randomized controlled study and sufficient subgroup analyses are needed to validate our conclusion.

Acknowledgments

This study was supported jointly by the National Natural Science Foundation of China (No. 81603348), China Postdoctoral fund (No. 21300075311104), and Shandong postdoctoral innovation special fund (No. 201602012).

Disclosure

The authors report no conflicts of interest in this work.

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