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Original Article

The role of lymph node status in cancer-specific survival and decision-making of postoperative radiotherapy in poorly differentiated thyroid cancer: a population-based study

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Abstract: Objective: This study aimed to investigate the prognostic value of lymph node (LN) status for patients with poorly differentiated thyroid cancer (PDTC), and to develop a reliable nomogram to predict the 3-, 5- and 10-year cancer-specific survival (CSS) and assist the decision-making of postoperative radiotherapy (PORT). Methods: The Surveillance, Epidemiology, and End Results (SEER) database was utilized to screen eligible patients who were diagnosed between 2004 and 2016. The optimal values of age, metastatic lymph node ratio (LNR), and the number of metastatic lymph nodes (MLN) were determined and incorporated into the construction of a nomogram. The performance of the model was evaluated by generating a calibration curve and calculating the consistency index (C-index). Based on the nomogram, patients were classified into three risk cohorts. The prognostic efficacy of PORT was evaluated in each cohort. Results: A total of 522 PDTC patients were included in this study. The LN status-associated parameters (MLN and LNR) were independent risk factors for CSS of PDTC patients. Based on MLN, LNR, and other clinical characteristics (age and T stage), an individualized nomogram was constructed that showed an acceptable predictive performance. Furthermore, we proposed a novel risk-classification system to stratify PDTC patients and to assess the prognostic efficacy of PORT. Only patients in high-risk cohort were found eligible to benefit from PORT. Conclusion: LN status is statistically associated with the prognosis of PDTC patients. In addition, the individualized nomogram may be a significant tool to assist the evaluation of patients' long-term prognosis and to guide the decision-making for PORT.

Keywords: Postoperative radiotherapy, poorly differentiated thyroid cancer, lymph node status, prognosis, nomogram

Introduction

Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, accounting for 75-85% of all thyroid cancer cases. It is also the predominant cancer type in children with thyroid cancer, and in patients with thyroid cancer who have received direct external radiation to the head and neck. Anaplastic thyroid cancer (ATC) is one of the most lethal malignancies, with dismal prognosis, resistance to multimodal treatments and a median survival of only 5-6 months. Poorly differentiated thyroid cancer (PDTC) is a distinct clinical and pathological entity with intermediate features between differentiated thyroid carcinoma (DTC) and ATC [1]. The incidence of PDTC is low, and it is a major cause of mortality from non-anaplastic follicular cell-derived thyroid cancer [2]. The existing literature on PDTC is limited, with very few studies, making it difficult to form definite guidelines for the management of such tumors.

Surgery is the mainstay of treatment for patients with PTDC, and radioactive iodine (RAI) is considered postoperatively [3, 4]. Importantly, PDTC is biologically aggressive in nature with a potential to invade adjacent tissues [5], including blood vessels, nerves, trachea, larynx, and muscles. Postoperative radiotherapy (PORT) is

known as a supplementary therapy for patients with non-small-cell lung cancer (NSCLC), however, consensus regarding the therapeutic role of PORT remains controversial.

Studies [6, 7] have concentrated recently on more than just nodal positivity, including the number of positive LN, location of positive LN within the draining nodal basins, and lymph node ratio (LNR), i.e., the ratio between the numbers of positive and examined lymph nodes. A great number of MLNs and high LNR have been identified as independent predictors of prognosis in patients with gastric cancer [8], head and neck cancer [9], and pancreatic cancer [10]. Nevertheless, to date, no study has concentrated on the number of MLNs and LNR in PDTC patients.

Therefore, in the present study, we aimed to investigate the prognostic role of LN status-associated parameters (MLN and LNR) in PDTC patients who received curative surgery. Furthermore, we combined MLN, LNR, and other clinicopathological features to establish a predictive model for PDTC patients' survival, and to facilitate decision-making for PORT.

Methods

Study population

In the current study, a retrospective analysis of PDTC patients was conducted using the data extracted from the Surveillance, Epidemiology, and End Results (SEER) database, which contained nearly 34.6% of the U. S. population. Detailed descriptions related to the data could be found on the official SEER website (https://seer.cancer.gov/data/).

To acquire integrant information, the following criteria were set to identify eligible patients: (I) PDTC as a primary thyroid tumor; (II) diagnosis was confirmed by histopathology; (III) (IV) follow-up time was < 3 months; (V) unknown clinicopathological characteristics; (VI) existence of distant metastasis.

Variables and outcomes

The following variables were extracted for further analysis: age at diagnosis, race, gender, TNM stage, the number of examined lymph nodes, the number of MLNs, marital status, surgical treatment, radiotherapy record, survival time, and vital status.

Cancer-specific survival (CSS) was identified as the primary endpoint, and it was defined as the period from the date of diagnosis to death from cancer-specific death. The latest update on the follow-up date was censored to December 31, 2016.

Statistical analysis

The PDTC patients' baseline characteristics were summarized with counts and percentages and compared by the Chi-square test. The optimal cut-off values of age, MLN and LNR were determined by the X-tile program (Yale University School of Medicine, New Haven, CT, USA) with minimal *P*-value for the log-rank test. The CSS-associated potential risk factors were identified using Cox regression analysis. First, we performed univariate analysis to test the prognostic value of each factor, and factors, with *P*-value < 0.05, were included in the multivariate Cox regression analysis. Then, selected variables were employed to construct a predictive model of CSS through stepwise backward elimination method.

The predictive performance of the nomogram was evaluated using the consistency index (C-index), and the calibration curve was plotted to assess the accuracy, which could estimate the uniformity between the actual survival outcome and the model that predicted survival probability. Kaplan-Meier survival curves and log-rank test were applied to assess the prognostic value of each treatment between subgroups. A two-tailed P < 0.05 was considered statistically significant. All statistical analyses were processed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA), GraphPad Prism 8.0, and R 3.5.1 software. The X-tile software was also utilized to establish a risk-stratification model.

Results

Characteristics of study population

Data of PDTC patients who met the criteria and were diagnosed between 2004 to 2016 were extracted from the SEER database. **Table 1** shows demographic and clinical characteristics of the PDTC patients. Among 522 PDTC pa-

Table 1. Demographics and baseline characteristics of patients with PDTC

Variables	All patients (%)		Cancer-specific death (%)		Cancer-excess death (%)	
N	522		94		48	
Age						
≤ 55	280	53.6	30	31.9	8	16.7
> 55	242	46.4	64	68.1	40	83.3
Gender						
Female	319	61.1	47	50.0	20	41.7
Male	203	38.9	47	50.0	28	58.3
Race						
White	421	80.7	78	83.0	43	89.6
Black	36	7.0	5	5.3	1	2.1
Other	60	11.6	11	11.7	4	8.3
T stage						
T1-2	172	33.0	11	11.7	8	16.7
T3-4	350	67.0	83	88.3	40	83.3
MLN						
0	252	48.3	21	22.3	22	45.8
(0, 5)	164	31.4	41	43.6	15	31.3
> 5	106	20.3	32	34.0	11	22.9
LNR						
≤ 0.3	367	70.3	47	50.0	25	52.1
> 0.3	155	29.7	47	50.0	23	47.9
Number of foci						
Solitary	287	55.0	52	55.3	31	64.6
Multifocal	235	45.0	42	44.7	17	35.4
Marital status						
Married	310	59.4	55	58.5	21	43.8
Unmarried	212	40.6	39	41.5	27	56.2
PORT						
RAI	299	57.3	37	39.4	23	47.9
EBRT	66	12.6	24	25.5	4	8.3
RAI+EBRT	10	1.9	3	3.2	0	0.0
Other	7	1.3	1	1.1	2	4.2
None/Refused	140	26.8	29	30.9	19	39.6

Abbreviations: MLN, the number of metastatic lymph nodes; LNR, lymph node ratio; RAI, radioactive iodine; EBRT, external beam radiation therapy; PORT, postoperative radiotherapy.

tients, 142 died from all causes of death, including cancer-specific mortality and noncancer mortality. Among these patients, 94 patients died from PDTC, and 48 patients died from other causes, including cardiovascular disease, diabetes or suicide. In the whole cohort, the predominant patients were female (n = 319), white (n = 421), and those who received PORT (n = 382). Among cases who received PORT, the majority received RAI (n = 299; 78.3%), 17.3% of patients underwent external beam radiotherapy (EBRT), and 2.6% of patients underwent the combination of EBRT and RAI.

As shown in **Table 1**, patients who died from cancer had a higher proportion of age < 55 years compared with those who died from PDTC excess causes (31.9% vs. 16.7%). Moreover, patients who died from PDTC had a malignant tumor with larger size, and were more likely to receive PORT than those who died from non-cancer causes.

Optimal cut-off values for age, MLN, and LNR

The X-tile program was utilized to identify the optimal cut-off values of MLN and LNR with minimum *P*-values for the Kaplan-Meier survival analysis and the highest values of sensitivity and specificity. The results showed that 55 was identified as the optimal cut-off value for age (P < 0.001, Supplementary Figure 1A). The cut-off value for MLN was 5 (P < 0.001, Supplementary Figure 1B). Besides, the cut-off values for LNR were 0 and 0.30 (P < 0.001, Supplementary Figure 1C). Kaplan-Meier curves and log-rank test showed significant prognostic differences between subgroups classified by age, MLN, or LNR.

Individualized construction of the nomogram

As illustrated in **Figure 1**, PDTC patients had a 1-year CSS of 95.5%, a 3-year CSS of 89.5%, and a 5-year CSS of 73.7%. Subsequently, we conducted univariate and multivariate Cox regression analyses for CSS (**Table 2**). Multivariate regression analysis identified age, TNM stage, MLN, and LNR as independent prognostic factors. For instance, compared with PDTC patients with lower LNR, patients whose LNR was > 0.3 had a higher risk of mortality (hazard ratio (HR): 1.695, 95% confidence interval (CI): 1.005-2.855, P = 0.048).

Based on the results of multivariate regression analysis, the nomogram was plotted to predict the 3-year, 5-year, and 10-year CSS for PDTC

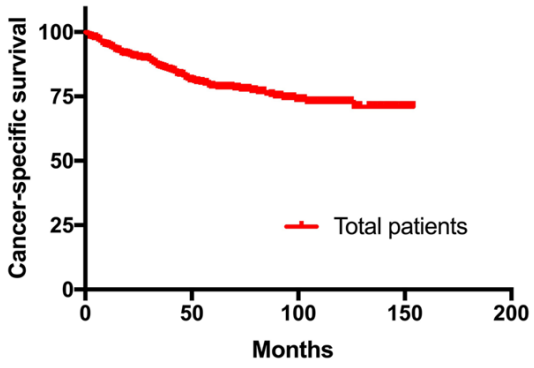

Figure 1. Kaplan-Meier curve of CSS. Cancer-specific survival plotted by Kaplan-Meier method for PDTC patients.

patients. MLN, LNR, and other clinicopathological variables (age and T stage) were finally incorporated into the establishment of nomogram (**Figure 2A**). On the basis of the point scale in the nomogram, the prognosis of each PDTC patient with different clinicopathological features could be predicted by calculating the total points.

Subsequently, our individualized nomogram was internally validated by calculating the C-index, which was 0.756 (95% CI: 0.711-0.801), indicating that our model had a good discrimination ability for CSS. Calibration was defined as the degree of uniformity between the estimated risk and the actual risk. In the current study, the calibration curve showed a satisfactory consistency between the actual probability and the predicted probability by nomogram for CSS (**Figure 2B**).

Clinical efficacy of PORT

Based on the individualized scores, a novel risk-stratification model was established for PDTC patients using the X-tile program. Patients were divided into three cohorts with different levels of prognosis, including the high-risk cohort (total score > 230, n = 145), moderate-risk cohort (total score: (95, 230), n = 228), and low-risk cohort (total score < 95, n = 143). The Kaplan-Meier survival analysis and the log-rank test indicated that the differences in prognosis between each pair of these three cohorts were statistically significant (**Figure 3A**).

Furthermore, we analyzed the clinical efficacy of PORT in the three cohorts, respectively. The results revealed that PDTC patients in high-risk cohort could benefit from PORT ($P < 0.0001$; **Figure 3C**). However, for PDTC patients in intermediate- and low-risk cohorts, the prognostic efficacy of PORT was limited (low-risk cohort: $P = 0.7367$, **Figure 3A**; intermediate-risk cohort: $P = 0.2865$, **Figure 3B**).

Discussion

PDTC represents an aggressive variant of thyroid cancer that predominantly arises from the differentiated variants of papillary and follicular thyroid carcinoma, while occasionally from normal follicular cells [1]. PDTC is a relatively rare cancer with a morbidity of 0.23-2.6% in patients with primary thyroid carcinoma [11], and its morbidity in the present study is 2.14%. A female preponderance in PDTCs has been reported by various studies [4, 12], and the proportion of female patients is here 61.1%, which is close to that reported previously.

Accurate prediction of PDTC patients' prognosis is of great importance and can assist the decision making of adjuvant treatment. Previous studies have reported that LNM is associated with the prognosis of patients with thyroid carcinoma. For instance, Lei et al. found that several parameters related to LNs could significantly affect the recurrence-free survival of thyroid cancer patients, including the extent of extra-nodal invasion, diameter of the largest metastatic LN, and the number of metastatic LNs [13]. Chen et al. analyzed the prognostic value of LNM, and proposed a modified N staging system for predicting the prognosis of patients with medullary thyroid cancer [14]. Regarding the aggressiveness of PDTC, the prognostic role of LN should be investigated separately, which has been rarely studied to date.

In the present study, we utilized the X-tile program to identify the optimal cut-off values for the number of MLNs and LNR in 522 PDTC patients. It was revealed that the number of MLN > 5 and LNR > 0.3 was adversely associated with the survival outcomes of PDTC patients. The joint use of the two parameters could potentially reflect two significant features, i.e. surgical approach [15] and regional metastasis [14, 16]. These two parameters could be calculated easily, and it was reliable to predict prognosis and stratify patients based on these parameters [17]. Importantly, only LN

Table 2. Univariate and multivariate Cox analysis of cancer-specific survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age				
≤ 55	Ref		Ref	
> 55	2.792 (1.830-4.261)	0.000	2.939 (1.901-4.543)	0.000
Gender				
Female	Ref			
Male	1.278 (0.860-1.901)	0.225		
Race				
White	Ref			
Black	0.797 (0.323-1.967)	0.622		
Other	0.959 (0.511-1.799)	0.896		
T stage				
T1-2	Ref		Ref	
T3-4	4.049 (2.213-7.406)	0.000	2.584 (1.391-4.800)	0.003
MLN				
0	Ref		Ref	
(0, 5)	2.818 (1.665-4.768)	0.000	1.769 (0.925-3.383)	0.085
> 5	4.967 (2.906-8.490)	0.000	3.392 (1.718-6.697)	0.000
LNR				
≤ 0.3	Ref		Ref	
> 0.3	3.042 (2.033-4.553)	0.000	1.695 (1.005-2.855)	0.048
Number of foci				
Solitary	Ref			
Multifocal	0.812 (0.577-1.141)	0.326		
Marital status				
Married	Ref			
Unmarried	0.699 (0.471-1.037)	0.699		

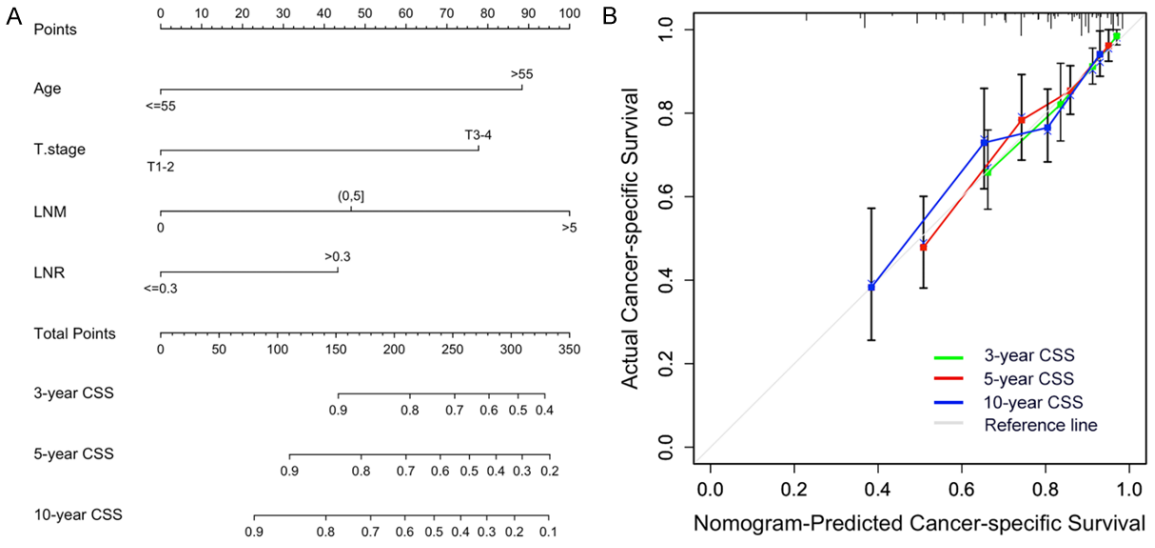

Figure 2. CSS-predicting nomogram. The individualized nomogram (A) and the calibration curve (B) for predicting 3-, 5-, and 10-year CSS for PDTC patients after curative surgery.

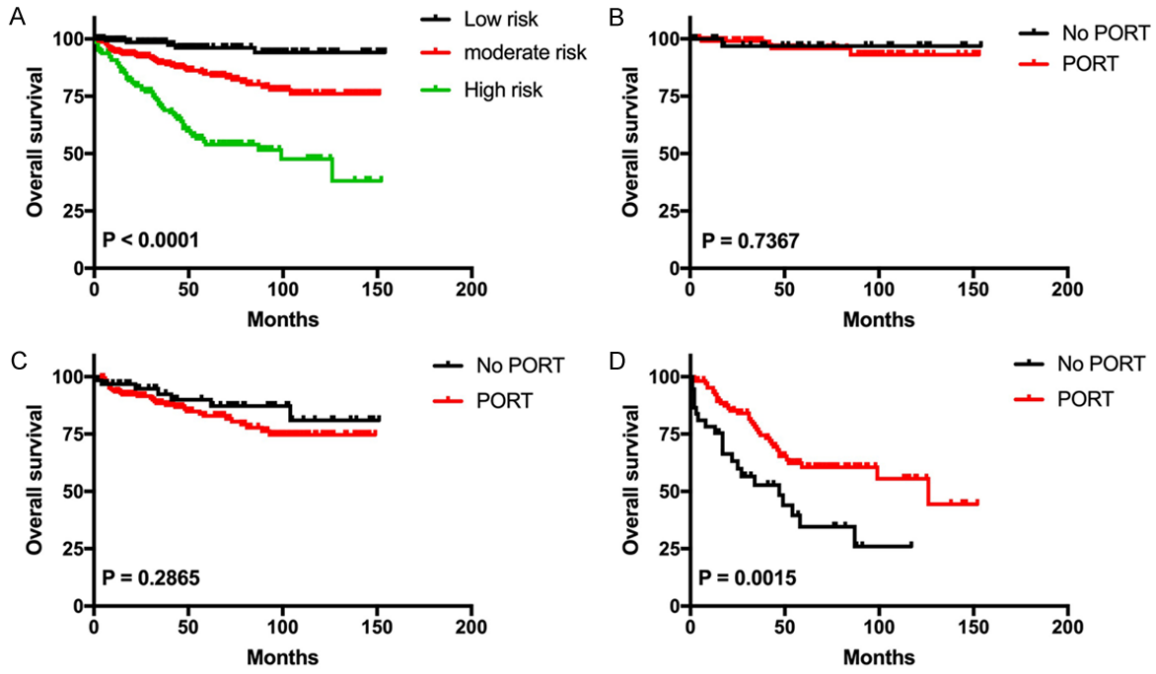

Figure 3. Prognostic effects of PORT. Cancer-specific survival curves of PDTC patients after curative surgery in total cohort (A), low-risk cohort (B), moderate-risk cohort (C), and high-risk cohort (D).

status is not sufficient to accurately predict the prognosis of PDTC patients. Previous studies have reported that age (> 45 years old), advanced T stage, and distant metastasis were correlated significantly with reduced survival in PDTC patients [4, 18]. Thus, we conducted multivariate regression analysis to explore potential prognostic factors in PDTC patients. Subsequently, we integrated all prognostic factors, including the number of MLNs, LNR, and other clinical characteristics (age and T stage) to establish an individualized nomogram for predicting the prognosis of PDTC patients.

At present, due to the poorly established therapeutic strategies after curative surgery, such as RAI, chemotherapy, and EBRT, the standard treatment guidelines for PDTC are sparse [17]. Regarding the probability of ^{131}I uptake and the low incidence of severe side effects, Sanders et al. recommended RAI for PDTC patients who received curative surgery [19]. Although PDTC has been reported to uptake ^{131}I in 85% of patients, few studies have statistically shown that RAI benefits prognosis [17]. Additionally, EBRT is typically recommended for PDTC patients with the remnant of malignant tissues postoperatively or with aggressive forms, such as an extensive extrathyroidal extension of a tumor [20]. However, retrospective studies reported that the clinical efficacy of EBRT is not statistically significant in PDTC patients, and the application of this adjuvant treatment is still questionable. The role of radiotherapy in treating PDTC remains controversial.

Based on the novel risk-stratification model, we found that only patients classified as high-risk could mainly benefit from PORT, and the survival outcomes of patients with low- and moderate-risk were not markedly improved after receiving PORT. Consequently, this model could guide the decision-making of adjuvant therapy for PDTC patients after curative surgery. This could provide a greater beneficial rate and a more reliable clinical choice than none or all patients undergoing PORT as recommended by other studies.

To our knowledge, this is the first comprehensive research aiming to investigate the role of LN status in the survival prediction and the decision-making of postoperative treatment in PDTC patients. Due to the retrospective nature of the present study, there are a number of limitations. Firstly, the SEER database lacks the information related to the positive margin rate, perineural invasion, blood and/or lymphatic

invasion, and comorbidities, which may influence the survival outcomes of patients. The proposed model is expected to be improved by incorporating more prognostic factors. Secondly, the majority of patients in our study were Caucasian, and our results may be generalized, at least in the USA, while external validations among non-US populations are warranted, especially in the Asian population. What's more, the details of PORT for each patient were not provided, and we failed to specify the clinical benefit of RAI or EBRT for PDTC patients. Therefore, further prospective studies are warranted to confirm our findings, and to improve our decision-making system for postoperative adjuvant treatment.

Conclusions

In this population-based study, the prognostic value of LN status, i.e. the number of MLNs and LNR, was investigated for PDTC patients. The combination of LN status and other clinicopathological features (age and T stage) could estimate the prognosis of PDTC patients with satisfactory performance. Furthermore, based on the nomogram, we proposed a novel risk-stratification system to guide the decision-making for PORT.

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Disclosure of conflict of interest

None.

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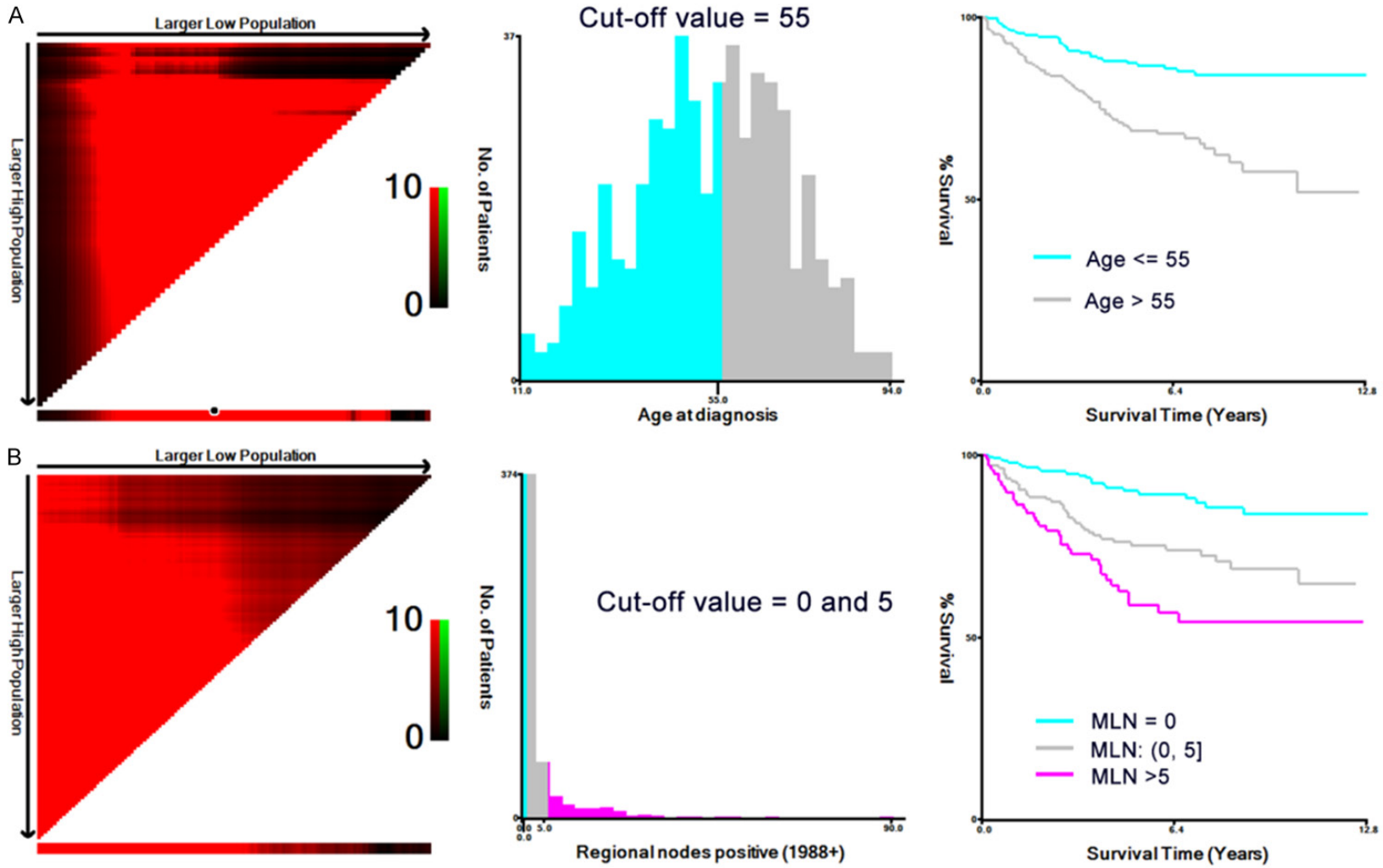
A
Larger Low Population
Larger High Population
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Cut-off value = 55
No. of Patients
Age at diagnosis
% Survival
Age <= 55
Age > 55
Survival Time (Years)
B
Larger Low Population
Larger High Population
10
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Regional nodes positive (1988+)
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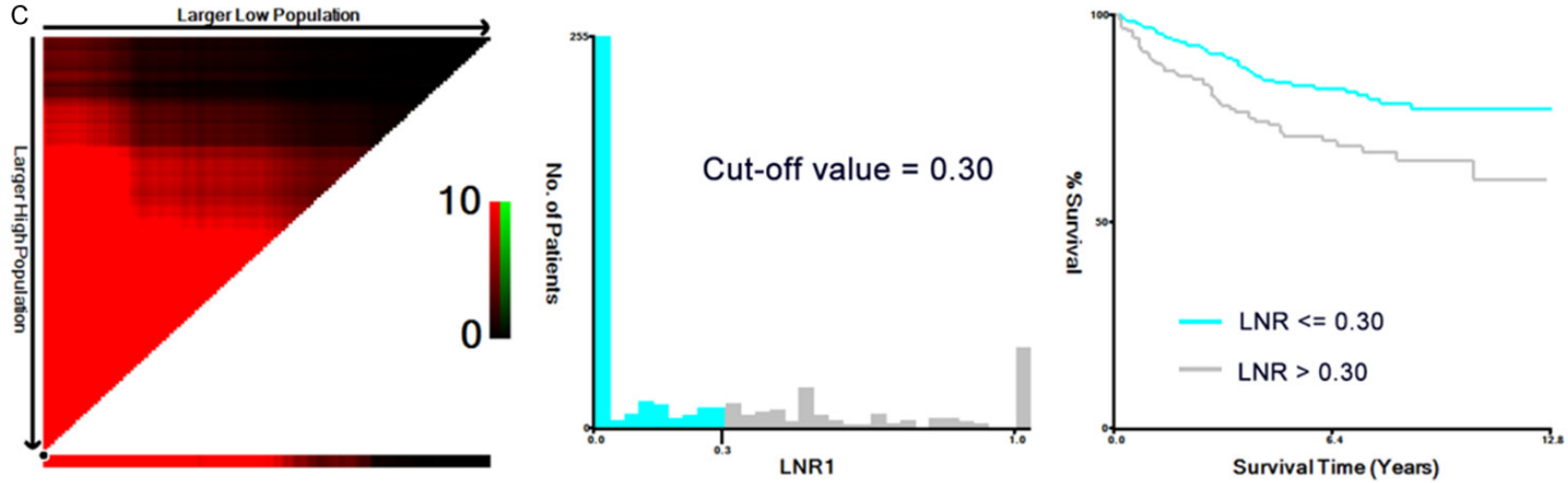

Supplementary Figure 1. Results of the X-tile analysis. The optimal cutoff values of age (A), MLN (B), and LNR (C) determined by the X-tile software.