

PLNR \leq 20% may be a benefit from PORT for patients with IIIA-N2 NSCLC: a large population-based study

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Purpose: Our study was to evaluate the influence of positive lymph nodes ratio (PLNR) on survival for patients with pathological stage IIIA-N2 non-small cell lung cancer (NSCLC) after receiving postoperative radiotherapy (PORT).

Patients and methods: The chi-squared test was used to compare the patient baseline characteristics. Cox proportional hazard model was used to analyze the influence of different variables on overall survival (OS). X-tile model was applied to determine the cutoff values of PLNR. Kaplan–Meier method and log-rank test were used to compare survival differences. Based on different cutoff values of PLNR, Cox proportional hazard model was also used to analyze the influence factors on OS.

Results: Multivariate Cox regression analysis showed that PLNR ($P=0.001$) and PORT (HR=1.283; 95% CI 1.154–1.426; $P<0.001$) were significant independent prognostic factors for OS in patients with resected IIIA-N2 NSCLC. The X-tile model was used to screen three different cutoff values including PLNR \leq 20%, 20% $<$ PLNR \leq 40%, PLNR $>$ 40%. Based on these different cutoff values, we found that patients with PLNR \leq 20% receiving PORT have a better OS ($P=0.007$). Further multivariable analysis showed that PORT is an independent prognostic factor of OS only for patients with PLNR \leq 20% (HR=1.328; 95% CI 1.139–1.549; $P<0.001$).

Conclusion: PLNR \leq 20% may be a prognostic factor for patients with IIIA-N2 NSCLC receiving PORT.

Keywords: non-small cell lung cancer, postoperative radiotherapy, positive lymph node ratio, OS, prognosis, X-tile model

Introduction

Primary bronchogenic carcinoma is one of the most common malignant tumors, and the incidence and mortality of lung cancer are on the rise in China.¹ Non-small cell lung cancer (NSCLC) makes up approximately 85% of all lung cancers. The choice of guiding treatment depends on the size, type and accurate staging of tumor,² as surgery, RT, chemotherapy, targeted therapy and immunotherapy can be used for the treatment of lung cancer.³ Relevant studies have pointed out that a possible approach for IIIA-N2 patients might be a multimodality treatment.^{4–7} For these patients, surgical removal of cancerous swelling is the most commonly used method, with 5-year overall survival (OS) rates in the range of 7%–34%.⁸

For patients with completely resected IIIA-N2 NSCLC, POCT has become a recognized adjuvant therapy.^{9–11} PORT is also considered as an effective means of treatment. Previous studies have pointed out that positive lymph node and LNR were confirmed to possess a significant guiding role in the prognosis of PORT with resected IIIA-N2 NSCLC.^{12–17} However, no relevant study has focused on the relationship between positive

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lymph nodes ratio (PLNR) and postoperative radiotherapy (PORT) in IIIA-N2 NSCLC patients. In our study, we retrospectively analyzed 3,134 patients with resected stage IIIA-N2 NSCLC either receiving or not receiving PORT to identify the subgroups who benefit from PORT. This data originated from the SEER database. According to SEER database, we analyzed the relationship between PLNR and PORT on survival time in the patients with resected IIIA-N2 NSCLC.

Patients and methods

Data source

The SEER is a National Cancer Institute program and is a comprehensive source of population-based data in the United States.¹⁸ The SEER database provides detailed information regarding patient demographics, diagnosis, treatment, and survival outcomes. Using the SEER database and based on the American Joint Committee on Cancer criteria, we selected a total of 3,134 patients with pathologically resected stage IIIA-N2 NSCLC between 2004 and 2013 using the SEER*Stat 8.3.5 software. The inclusion criteria for recruiting patients were as follows: complete resection via either lobectomy or pneumonectomy, no treatment before surgery, only one primary tumor, active follow-up, available clinical information. In addition, patients with benign tumor and other ambiguous and unknown information were all excluded.

Ethics statement

Our study was constructed in accordance with the Declaration of Helsinki. We received permission to access SEER program research data with the reference number 11561-Nov2016. This study was also approved by the ethics committee of the Shandong Cancer Hospital affiliated with Shandong University. This study did not involve any personal information, and therefore informed patient consent was not required.

Statistical analysis

In this study, differences of patient baseline characteristics were analyzed using the chi-squared test. Our main endpoint was OS, which was defined as the time from diagnosis to death due to any reason. Univariate and multivariate Cox regression analyses were applied to assess the prognostic factors on OS for resected IIIA-N2 NSCLC patients receiving PORT. The X-tile model was applied to determine the cutoff values of PLNR and the Kaplan–Meier method was used to calculate OS compared by means of the log-rank test. All statistical analyses were made using Statistical Product and

Service Solutions (SPSS) 22.0 software package. All statistical *P*-values were two-sided and *P*<0.05 was considered statistically significant.

Results

Patient characteristics

A total of 3,134 patients with resected stage IIIA-N2 NSCLC from the SEER database treated between 2004 and 2013 were included for analysis. Of these, 1,164 patients (37.1%) with pathological stage IIIA-N2 disease received PORT and 1970 patients (62.8%) did not receive PORT. The baseline characteristics of patients are listed in Table 1. Among patients receiving PORT, all of them were white (100%), with 51.4% patients less than 60 years of age. The PORT group was with 51% female and 49% male patients, and the ratio of patients at Grades I–II and III–IV were 46% and 54%, respectively. The adenocarcinoma was the main pathological pattern in PORT and non-PORT groups (59.4% vs 58.5%) while the proportion of T1, T2 and T3 were 30.1% vs 27.3%, 61.9% vs 65.3% and 8.4% vs 7.4%, respectively, in both groups. Our results showed that patients who received PORT were related to factors of age (*P*<0.001) and race (*P*<0.001). There were no significant differences in sex (*P*=0.522), grade (*P*=0.149), pathology (*P*=0.171) and T stage (*P*=0.141).

Table 1 Resected pathological stage IIIA-N2 NSCLC patient characteristics from SEER database

Variables	Radiation (%)	None (%)	<i>P</i> -value
Age (years)			<0.001
<65	599 (51.4)	820 (41.6)	
≥65	566 (48.6)	1,149 (58.4)	
Race			<0.001
White	1,164 (100)	1,364 (69.3)	
Black	0 (0)	312 (15.9)	
Others	0 (0)	292 (14.8)	
Sex			0.522
Male	570 (49.0)	987 (50.2)	
Female	594 (51.0)	981 (49.8)	
Grade			0.149
I–II	535 (46.0)	957 (48.6)	
III–IV	629 (54.0)	1,011 (51.4)	
Pathology			0.171
Adenocarcinoma	691 (59.4)	1,151 (58.5)	
Squamous	255 (21.9)	483 (24.5)	
Others	218 (18.7)	334 (17.0)	
T stage			0.141
T1	351 (30.1)	538 (27.3)	
T2	720 (61.9)	1,286 (65.3)	
T3	94 (8.1)	145 (7.4)	

Abbreviations: NSCLC, non-small cell lung cancer; SEER, Surveillance Epidemiology and End Results.

PLNR and survival

The primary focus of our study was to examine whether the PLNR was associated with PORT in patients with resected pathological IIIA-N2 NSCLC. Cox proportional hazards model was used to assess the prognostic value of baseline characteristics. Univariable analysis revealed that race, T stage, PORT and PLNR were significant prognostic factors for OS (all $P<0.05$). The other factors, such as age, sex, grade and pathology, did not make a significant difference to OS. In multivariable analysis, PORT (HR=1.283; 95% CI 1.154–1.426; $P<0.001$) and PLNR ($P=0.001$) were independent and significant prognostic factors for OS. Univariable and multivariable analyses of affecting factors of OS are listed in Table 2.

Cutoff determination for PLNR count and survival

The cutoff values of PLNR were determined by the X-tile model. Survival curves were measured using the Kaplan–Meier and compared by long-rank test. The different cutoff

values of PLNR on OS including low (PLNR \leq 20%), medium (20% $<$ PLNR \leq 40%) and high (PLNR $>$ 40%) were produced by X-tile (Figure 1A–C). Survival curves revealed that the patients with PLNR \leq 20% had a better OS ($P=0.007$) from PORT, as measured by Kaplan–Meier (Figure 2A). However, the difference on OS was not found between 20% $<$ PLNR \leq 40% ($P=0.944$) and PLNR $>$ 40% ($P=0.091$; Figure 2B and C).

Subgroup analysis for OS based on PLNR

Univariate and multivariate Cox regression analyses were further applied to analyze the effect of PORT on OS based on different cutoff points for PLNR. Our results showed that the patients with PLNR \leq 20% had a better OS (HR=1.328; 95% CI 1.139–1.549; $P<0.001$) after receiving PORT. However, the OS benefit was not found in patients with 20% $<$ PLNR \leq 40% and PLNR $>$ 40%. Therefore, PORT was an independent prognostic factor only in patients with PLNR \leq 20%. The subgroup analysis for OS based on different PLNR is listed in Table 3.

Table 2 Influence of different variables on OS for patients with resected pathological stage IIIA-N2 NSCLC analyzed by Cox proportional hazard model

Variables	Overall survival		
	Univariate	Multivariate	
	P-value	HR (95% CI)	P-value
Age (years)	0.915		Not included
<65			
\geq 65			
Race	<0.001		<0.001
White		Reference	
Black		0.746 (0.628–0.885)	0.001
Others		0.603 (0.492–0.740)	<0.001
Sex	0.775		Not included
Male			
Female			
Grade	0.890		Not included
I–II			
III–IV			
Pathology	0.304		Not included
Adenocarcinoma			
Squamous			
Others			
T stage	<0.001		<0.001
T1		Reference	
T2		1.250 (1.119–1.395)	<0.001
T3		1.397 (1.110–1.757)	0.004
PORT	<0.001		<0.001
Yes		Reference	
No		1.283 (1.154–1.426)	<0.001
PLNR	0.001		0.001

Abbreviations: OS, overall survival; NSCLC, non-small cell lung cancer; PORT, postoperative radiotherapy; PLNR, positive lymph nodes ratio.

Discussion

The value of PORT for completely resected IIIA-N2 NSCLC is controversial. A PORT meta-analysis conducted in 1998 has shown that PORT had a detrimental effect on survival.¹⁹ Wisnivesky et al demonstrated that PORT was not associated with improved survival for elderly patients with completely resected stage III NSCLC (HR=1.11; 95% CI 0.97–1.27; $P>0.05$).²⁰ In contrast, a growing number of more research has supported the use of modern PORT for completely resected stage IIIA-N2 NSCLC.^{21,22} Recently, several studies have suggested that patients with completely resected stage IIIA-N2 NSCLC may be a result of benefits from PORT.^{23–26} Feng et al have demonstrated that PORT was an independent prognostic factor for improved locoregional free Survival (HR=0.2, 95% CI 0.1–0.5; $P=0.001$) and improved OS (HR=0.4, 95% CI 0.2–0.7; $P=0.001$).²⁷ The Lung Adjuvant Radiotherapy Trial (LungART, NCT00410683), a randomized trial of modern PORT vs no PORT in patients with resected NSCLC, is ongoing.²⁸

Patients with stage IIIA-pN2 NSCLC are a heterogeneous group and the treatment for these patients should be individualized.²⁹ Reif et al showed that surgery alone is considered to have a more limited role in the management of stage IIIA patients.³⁰ However, many patients with locally advanced or metastatic disease lose the opportunity for surgery at the time of diagnosis.

Chemotherapy and RT have become the most important method to treat these patients. Roth et al showed that the

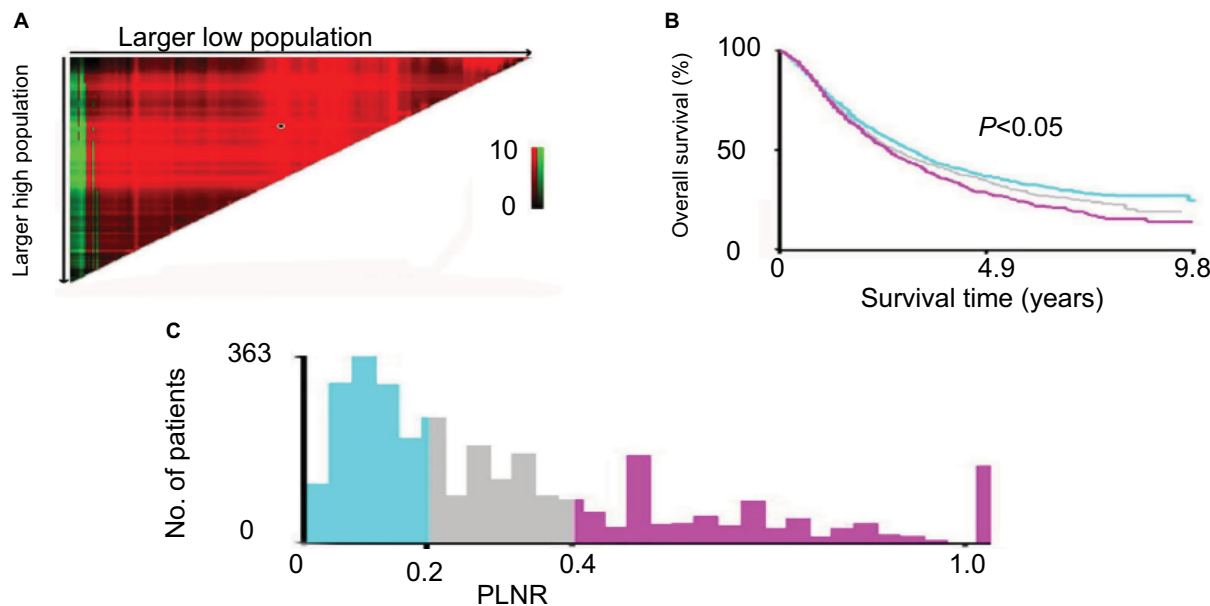


Figure 1 The optimal threshold of PLNR count for OS as determined by the X-tile model.
Notes: (A) X-tile plots based on PLNR. (B) OS curves based on the threshold ($P < 0.05$). (C) The optimal cutoff point is shown by the blue (PLNR ≤ 20%), gray (20% < PLNR < 40%) and violet panels (PLNR ≥ 40%).
Abbreviations: PLNR, positive lymph nodes ratio; OS, overall survival.

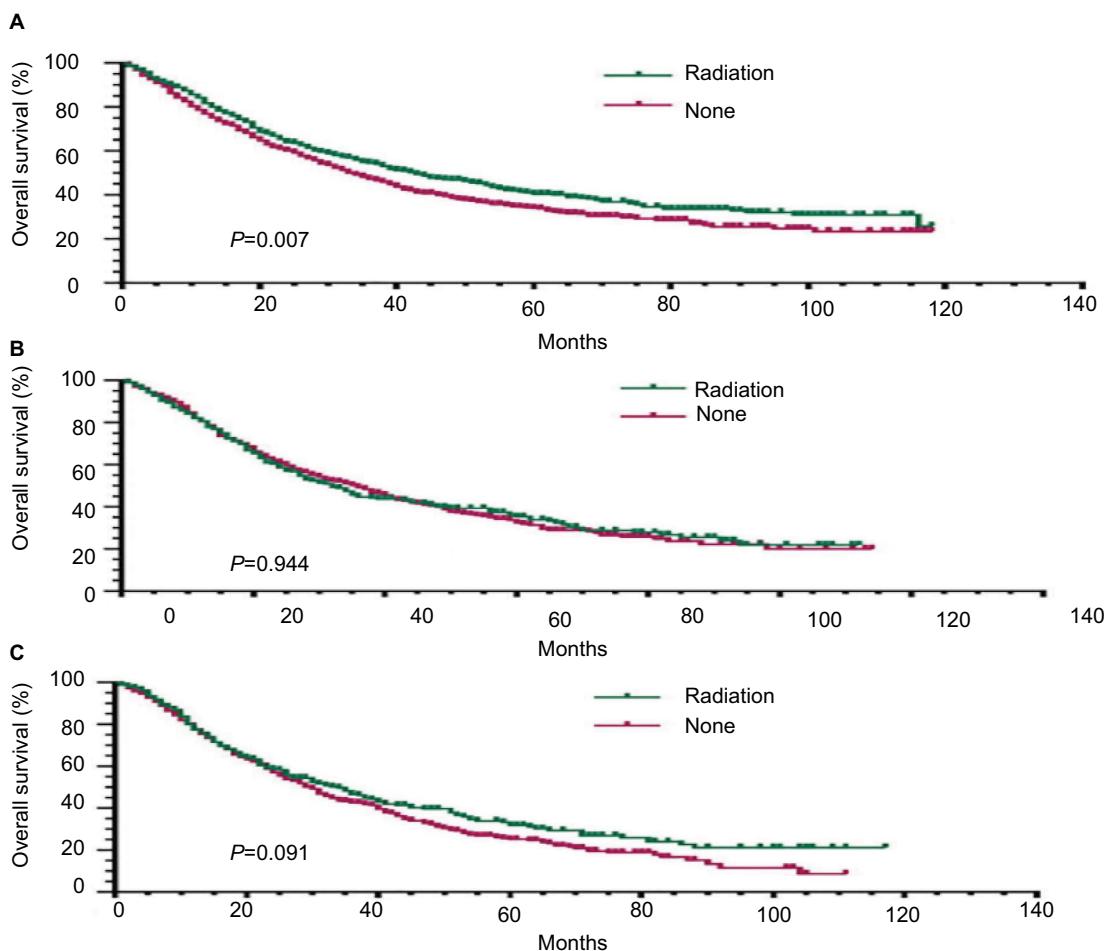


Figure 2 Prognostic survival curves according to PLNR based on different cutoff points adjusted for other variables using the Cox proportional hazard analysis in resected stage IIIA-N2 NSCLC patients receiving PORT.
Notes: The OS curves were based on the threshold. (A) OS curves for patients with PLNR ≤ 20% receiving PORT ($P = 0.007$). (B) OS curves for patients with 20% < PLNR < 40% receiving PORT ($P = 0.944$). (C) OS curves for patients with PLNR ≥ 40% receiving PORT ($P = 0.091$).
Abbreviations: PLNR, positive lymph nodes ratio; NSCLC, non-small cell lung cancer; PORT, postoperative radiotherapy; OS, overall survival.

Table 3 Subgroup analysis of OS based on PLNR for patients with resected pathological staged IIIA-N2 NSCLC analyzed by Cox proportional hazard model

Variables	OS (PLNR≤20%)		OS (PLNR 20%<PLNR≤40%)		OS (PLNR>40%)	
	Multivariate		Multivariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)		Not included		Not included		Not included
<65						
≥65						
Race		0.002		0.103		0.001
White	Reference		Reference		Reference	
Black	0.760 (0.591–0.978)	0.033	0.712 (0.505–1.003)	0.052	1.054 (0.783–1.419)	0.727
Others	0.617 (0.454–0.838)	0.002	1.122 (0.825–1.526)	0.464	0.476 (0.323–0.699)	<0.001
Sex		Not included		Not included		Not included
Male						
Female						
Grade		Not included		Not included		Not included
I–II						
III–IV						
Pathology		Not included		0.091		Not included
Adenocarcinoma			Reference			
Squamous			1.291 (1.027–1.621)	0.028		
Others			1.089 (0.834–1.421)	0.531		
T stage		0.045		Not included		0.006
T1	Reference				Reference	
T2	1.233 (1.044–1.456)	0.013			1.354 (1.107–1.656)	0.003
T3	1.495 (0.789–1.631)	0.495			1.681 (1.056–2.479)	0.027
PORT		<0.001		Not included		Not included
Yes	Reference					
No	1.328 (1.139–1.549)	<0.001				

Abbreviations: OS, overall survival; PLNR, positive lymph nodes ratio; NSCLC, non-small cell lung cancer; PORT, postoperative radiotherapy.

treatment strategy using perioperative chemotherapy and surgery was more effective than surgery alone for patients with IIIA-N2 NSCLC.³¹ Furthermore, POCT is considered a recognized treatment method for patients with resected IIIA-N2 NSCLC. In spite of this dispute, PORT was also demonstrated as an effective treatment. Feng et al showed that PORT was an independent prognostic factor for improved OS (HR=0.4, 95% CI 0.2–0.7; $P=0.001$); female sex (HR=0.5, 95% CI 0.3–0.7; $P<0.001$) and LNR>20% (HR=2.4, 95% CI 1.7–3.3; $P<0.001$) were the other factors for OS.²⁷ Wang et al demonstrated that in stage IIIA-pN2 NSCLC, the use of PORT demonstrated better survival results than no PORT for patients with positive LNs with $n>3$, but not for patients with positive LNs with $n\leq 3$.¹⁷ Other studies have reported that several clinical and pathological factors, such as the number of pathologically involved lymph node stations,^{32,33} extracapsular extension,³⁴ lymph node skip status and positive LNR^{12–16} should be considered when evaluating the risks and benefits of PORT. However, so far, there are no relative reports about the relationship between PLNR and PORT in IIIA-N2 NSCLC patients. The aim of this study is to estimate

the association between PORT and PLNR for patients with resected pathological stage IIIA-N2 NSCLC.

In the present study, we regard OS as our main end-point. The outcomes of multivariable analysis have shown that PLNR and the use of PORT were independent impact factors on OS in patients with resected IIIA-N2 NSCLC. We concluded that PLNR≤20% in patients with IIIA-N2 NSCLC may be a benefit from PORT. X-tile model was conducted to determine the optimal cutoff point.³⁵ Our study demonstrated that 20% and 40% were the proper cutoff PLNR values for OS with PORT patients. We found that the patients with PLNR less than 20% had a better OS rate. The patients with PLNR>20% had no significant difference on OS.

Why patients with a lower tumoral burden would benefit more from PORT with respect to patients with a higher number of pathological mediastinal lymph nodes? One plausible explanation is that a lower PLNR is associated with a better survival for patients with IIIA-N2 NSCLC than higher PLNR. Also, PLNR may reflect the body's immune system and the tumor–host interaction. The value of the PLNR as a predictor of PORT benefits may also be

a result of the interaction between the immune system and RT.³⁶ Another possible explanation may be that for patients with high PLNR, the toxicity of PORT is far greater than its benefits. In addition, the lower the PLNR, the number of lymph nodes that may be cleared or the number of negative lymph nodes is more. Studies have shown that the more the number of negative lymph nodes is cleaned, the better the prognosis of the patients.^{37–40}

Limitations in this study should be noted. First, this was a retrospective study from the SEER database, and not a randomized controlled clinical trial. Second, some other variables, such as smoking history, type of surgery, involved N2 stations and number of positive nodes, affecting the prognosis, were not included in the present study. Additionally, other adjuvant therapies such as chemotherapy, targeted therapy and endocrine therapy were not included in this study. Finally, due to the constraints of the SEER database, we cannot obtain specific information about the dose and segmentation of PORT and the effects of other postoperative treatments. These issues may have some effects on the results, leading to the limitations of the study, which should be explored in future studies.

To the best of our knowledge, this study is the first to demonstrate PLNR as a prognostic factor for patients with IIIA-N2 NSCLC receiving PORT. This study showed that patients with PLNR \leq 20% can benefit from PORT with improved OS. The results of this study may be of help for clinicians, surgeons and radiotherapists to choose appropriate treatment. This result requires further large-scale prospective clinical study to confirm these recommendations.

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Disclosure

The authors report no conflicts of interest in this work.

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