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Log odds of positive lymph nodes is a robust predictor of survival and benefits from postoperative radiotherapy in stage IIIA-N2 resected non-small cell lung cancer

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Abstract

Background: The significance of postoperative adjuvant radiotherapy (PORT) on the survival of resected IIIA-N2 non–small cell lung cancer (NSCLC) remains controversial. Here, we aimed to determine the predictive value of the three nodal classifications which might aid in PORT decision-making.

Methods: A total of 4797 patients with stage IIIA-N2 resected NSCLC were identified in the Surveillance, Epidemiology and End Results (SEER) database and were grouped by whether PORT was administered. Survival analysis was used to identify the patient groups who can benefit from PORT. Multivariate analysis was performed to confirm the independent risk factors for lung cancer-specific survival (LCSS) and overall survival (OS). A validation cohort of 1184 patients from three medical centers in China were also included.

Results: PORT was not associated with better LCSS and OS in the entire cohort after propensity score matching (PSM). However, in the subgroups of positive lymph nodes 4 (PLN4), lymph node ratio 4 (LNR4), and log odds of positive lymph nodes 4 (LODDS4), PORT exhibited its role in improving LCSS ($p < 0.05$). Although the three nodal classifications were all identified as independent predictors of LCSS and OS, LODDS classification had the best discriminatory ability and prognostic accuracy for stage IIIA-N2 patients. Similar results were also obtained in the validation cohort.

Conclusions: The LODDS classification not only exhibited the best prognostic performance in predicting LCSS and OS in stage IIIA-N2 disease, but also could help tailor individualized PORT.

KEYWORDS
lymph node classification system, NSCLC, PORT, SEER, survival

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INTRODUCTION

Lung cancer is the second most frequently diagnosed cancer and the leading cause of cancer-related deaths worldwide.[1] Non–small cell lung cancer (NSCLC) is the most common histology, comprising nearly 85% of all lung cancers.[2] Notably, approximately 20% of patients with NSCLCs suffer from stage IIIA-N2 disease at their first treatment.[3] Since patients with stage IIIA-N2 NSCLCs constitute a very broad and diverse population, the optimal treatment for stage IIIA-N2 NSCLC remains controversial.[4,5]

Nowadays, surgery-based multimodal treatment has become the predominant strategy for the stage IIIA-N2 NSCLC population.[6] Interestingly, whether postoperative radiotherapy (PORT) can bring survival advantages to patients with stage IIIA-N2 disease has captured increasing attention. Due to the progress in radiation techniques, there is a growing number of evidences that PORT can benefit patients with stage IIIA-N2 NSCLC.[7–12] However, the latest multi-institutional randomized phase III trials (lung ART and PORT-c) revealed that PORT could not significantly improve disease-free survival (DFS) and overall survival (OS).[13,14] To be noted, a recent meta-analysis highlighted that PORT should be administered to resected pIIIA-N2 NSCLC having multiple N2 metastases but be withheld to those having single N2 station involvement.[15] Therefore, as proposed in the latest phase III trial,[14] further studies exploring which patients will optimally benefit from PORT are required.

Undeniably, the current eighth edition of TNM classification exhibited stronger predictive value than the seventh edition.[16,17] Disappointingly, few changes were made regarding the N descriptor in the eighth edition compared with the seventh, which failed to overcome the problem of lymph node heterogeneity. In the recent decade, the number of positive lymph nodes (PLN), reflecting the number of lymph nodes involved, has been incorporated into the latest version of the TNM staging system for esophageal,[18] gastric,[19] and colorectal cancer.[20] Meanwhile, PLN has also been proven to be a reliable prognostic factor for NSCLCs.[21] In addition, the lymph node ratio (LNR) and the log odds of positive lymph nodes (LODDS), defined as the ratio of the number of metastatic lymph nodes to the total number of lymph nodes removed, and the logarithm of the ratio of the number of metastatic lymph nodes to the number of negative lymph nodes, respectively, have also been confirmed to be promising predictors of survival in NSCLCs.[22] Nonetheless, it remains unclear whether the aforementioned three nodal classifications can help distinguish potential beneficiaries from stage IIIA-N2 patients for administration of PORT.

The present study aimed to investigate the potential value of PLN, LNR and LODDS as prognosticators for stage IIIA-N2 NSCLC using both the population-based Surveillance, Epidemiology, and End Results (SEER) database and a Chinese multi-institutional cohort, and to assess whether the three nodal classifications can help clinicians select IIIA-N2 patients whose survival might be improved by PORT.

METHODS

Data source and patient selection

The SEER data were extracted from the SEER database with SEER*Stat Software (version 8.3.9). The SEER database (https://seer.cancer.gov/) is the authoritative cancer statistics database in the United States (US), which collects data from 18 population-based registered cancer institutes, covering approximately 28% of cancer cases in the US.

The Incidence SEER 18 Regs Custom Data (with additional treatment fields) and November 2018 Sub (1975–2016 varying) datasets were selected for analysis.[23] We extracted the data of patients diagnosed with N2M0 lung cancer registered from 2004 to 2015. The exclusion criteria were as follows: (1) incomplete information recorded; (2) no lung resection was performed or incomplete surgery information; (3) radiation sequence with surgery is not "radiation after surgery" or "no radiation and/or cancer-directed surgery"; (4) regional nodes examined or positive number is 0 or unknown; (5) small cell lung cancer; (6) tumor size is 0 or larger than 50 mm; (7) survival time is less than 3 months or unknown; and (8) patients who underwent sublobectomy.

We also screened patients with stage IIIA-N2 NSCLC who underwent surgery at three medical centers in China between January 2004 and January 2018 as an external validation dataset. The inclusion criteria were as follows: (1) patients who underwent complete resection of primary T1-2N2M0 NSCLC according to the eighth edition of TNM staging. The exclusion criteria were: (1) patients who were lost to follow-up; (2) patients whose survival was less than 3 months; and (3) patients who received induction chemotherapy and/or radiotherapy. The treatment strategy of PORT was determined by the radiation oncologist. Radiotherapy techniques included three-dimensional conformal radiotherapy (3DCRT) and conventional two-dimensional radiotherapy (2DRT). The clinical target volume (CTV) includes the bronchial stump (BS) and stations 2R, 4R, 7, and 10 to 11R for right lung cancers, while CTV for left-sided disease includes the BS and stations 2 L, 4 L, 5, 6, 7, and 10 to 11 L. The total radiation dose was 50–60 Gy, completed within 30 days, 5 days per week. A total of 1184 patients with stage IIIA-N2 disease were finally included. The last follow-up of this external validation cohort was completed in August 2021. The study was approved by the Second Affiliated Hospital of Soochow University Ethical Committee (JD-HG-2022-21).

Variables extracted from the SEER database included age at diagnosis, sex, race, marital status, histology, primary site, grade, laterality, type of surgery, radiation sequence with surgery, chemotherapy, tumor size, T stage, the number of lymph nodes examined (ELN), the number of positive lymph nodes (PLN), survival months, vital status recode, cause of death. We also manually reclassified the TNM stage according to the American Joint Committee on Cancer (AJCC) eighth edition.

Definitions of PLN, LNR, and LODDS classifications

The PLN was defined as the number of positive lymph nodes. The LNR was calculated as: $\frac{positive\ lymph\ nodes}{lymph\ nodes\ examined}$. The LODDS was calculated as: $log\frac{positive\ lymph\ nodes+0.5}{lymph\ nodes\ examined-positive\ lymph\ nodes+0.5}$. The aforementioned nodal classifications were further divided into four groups by the corresponding quartile.

Statistical analysis

Categorical variables were present as counts and percentages, means and standard deviations were used for Gaussian distributed continuous variables. Continuous variables with non-normal distribution were present as the median (interquartile range [IQR]). The clinicopathological features and outcomes between two groups were compared by Pearson chi-square tests or Fisher's exact test for categorical variables and two-sample *t*-test or Mann–Whitney U test for continuous variables. Propensity score matching (PSM) was adopted to reduce bias (R software version 4.1.1, https://www.rproject.org/). Propensity scores were calculated by logistic regression estimation, the variables that could potentially influence the outcomes of treatment, including age at diagnosis, sex, histology, grade, type of surgery, chemotherapy, T stage, ELN and PLN, were used to generate a propensity score by logistic regression. Patients in the two groups (PORT and non-PORT) were matched using 1:1 nearest neighbor-matching with a caliper of 0.01. After PSM, differences between the two groups were tested for significance.

Spearman coefficients were used to evaluate the correlations among three N classifications. To evaluate the relationships between three N classifications and lung cancer-specific mortality, the univariate Cox regression model with a restricted cubic spline function was used. Log-rank test and Kaplan–Meier method were employed to compare lung cancer-specific survival (LCSS) and OS between different subgroups. The following factors were included in the univariate Cox regression analyses: age at diagnosis, sex, race, marital status, histology, grade, laterality, primary site, T stage, type of surgery, radiation, chemotherapy, ELN, PLN, LNR, and LODDS. The significant factors were then included in the multivariate Cox regression analyses for OS and LCSS to obtain independent prognostic factors. Likelihood ratio tests and Harrell's C-index were used to assess the goodness-of-fit and discriminability of Cox models. A higher likelihood ratio chi-square score indicated better homogeneity of the models, while a higher C-index indicated better discriminatory ability.

All statistical analyses and plotting graphics were performed using the R software (R Foundation for Statistical Computing, version 4.0.2). For all statistical analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological characteristics of PORT and non-PORT groups

Figure 1 shows the flowchart of patient selection. After careful screening, we identified 4797 stage IIIA-N2 NSCLC patients from the SEER database. Among the 4797 patients, a total of 1829 (38.9%) patients received PORT. The baseline information was shown in Table 1, which suggested imbalance between the PORT and non-PORT groups. Therefore, PSM was performed to produce 1680 patient pairs (Table 1). After PSM, the confounding variables including age at diagnosis, sex, histology, grade, type of surgery, chemotherapy, T stage, ELN and PLN were well balanced ($p > 0.05$).

Correlations and stratifications of the three N classifications

The relationships between PLN, LNR and LODDS were shown in Figure S1. The closest correlation was demonstrated between LODDS and LNR (0.965) compared with that between LODDS and PLN (0.399). By restricted cubic spline analysis, it was revealed that the hazard ratios (HRs) of lung cancer-specific mortality increased as the PLN, LNR, and LODDS rose (Figure S2). The three N classifications were further categorized into four subgroups stratified by their respective quartiles: PLN1 (PLN = 1), PLN2 (1 < PLN ≤3), PLN3 (3 < PLN ≤5) and PLN4 (PLN >5); LNR1 (LNR ≤0.167), LNR2 (0.167 < LNR ≤0.333), LNR3 (0.333 < LNR ≤0.545) and LNR4 (LNR >0.545); LODDS1 (LODDS ≤ −0.618), LODDS2 (−0.618 < LODDS ≤ −0.331), LODDS3 (−0.331 < LODDS ≤0.052) and LODDS4 (LODDS >0.052).

PORT brought advantages to the subgroups stratified by the fourth quartiles of the three nodal classifications

The log-rank test revealed that PORT was not a significant prognostic factor for both LCSS (HR = 0.962; 95% CI: 0.874–1.060; $p = 0.44$) and OS (HR = 0.994; 95% CI: 0.912–1.084; $p = 0.90$) in the entire SEER cohort after PSM (Figure 2). Furthermore, the subgroup analyses indicated that PORT could not significantly affect LCSS in the subgroups stratified by the first three quartiles (PLN1: $p = 0.15$; LNR1: $p = 0.39$; LODDS1: $p = 0.34$; PLN2: $p = 0.61$; LNR 2: $p = 0.61$; LODDS2: $p = 0.71$; PLN3: $p = 0.79$; LNR3: $p = 0.15$; LODDS3: $p = 0.14$, Figure S3). Nonetheless, in the subgroups stratified by the fourth quartile, PORT exhibited significant advantages in improving LCSS (PLN4: $p < 0.01$; LNR4: $p < 0.01$; LODDS4: $p < 0.01$, Figure 3). As shown in Figure S4, the histogram indicated that administration of PORT always brought benefits to the 1-, 3-, and 5-year LCSS rates in the subgroups of PLN4, LNR4, and LODDS4 (1-year

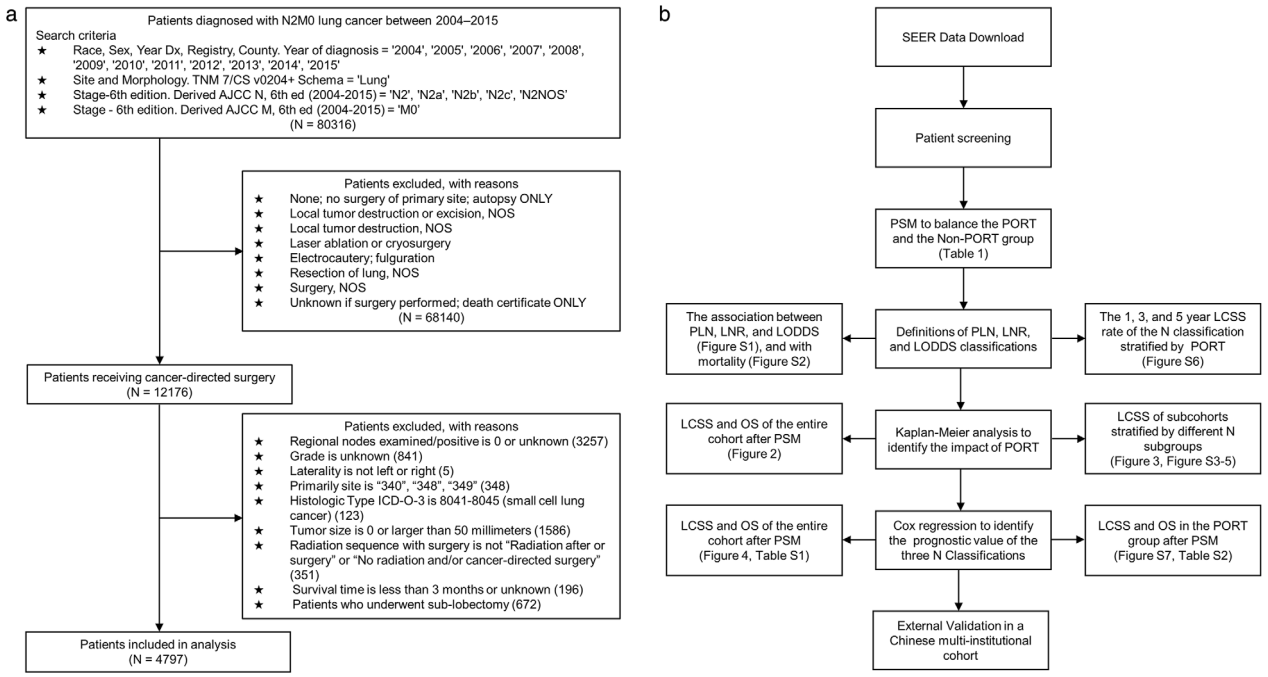

FIGURE 1 Flow chart of patient selection in the SEER database (a) and that of the entire study (b). SEER, Surveillance, Epidemiology and End Results; LCSS, lung cancer specific survival; OS, overall survival; PLN, positive lymph nodes; LNR, lymph node ratio; LODDS, log odds of positive lymph nodes; PORT, postoperative adjuvant radiotherapy; PSM, propensity score matching

LCSS: PLN4: $p = 0.04$, LNR4: $p = 0.03$, LODDS4: $p = 0.04$; 3-year LCSS: PLN4: $p = 0.01$, LNR4: $p = 0.02$, LODDS4: $p = 0.02$; 5-year LCSS: PLN4: $p = 0.01$, LNR4: $p < 0.01$, LODDS4: $p = 0.01$).

LODDS classification exhibited the best performance in predicting survival in the SEER cohort after PSM

In the SEER cohort after PSM, multivariate Cox regression analyses further confirmed that PLN, LNR and LODDS were all independent prognostic factors for LCSS and OS ($p < 0.01$, Figure 4). Next, we performed the likelihood ratio test and calculated the C-index of the three nodal classifications. As a result, the LODDS classification yielded the highest C-index (LCSS: 0.658, 95% CI: 0.645–0.671; OS: 0.673, 95% CI: 0.659–0.687, $p < 0.01$) and likelihood ratio (LCSS: 387.6; OS: 449.2, $p < 0.01$) among the three nodal classifications, which implied that the LODDS classification was more powerful in predicting survival than the others (Table S1).

LODDS classification was a robust prognosticator in the internal validation subcohort receiving PORT

A total of 1680 patients who received PORT in the SEER cohort after PSM were selected as the internal validation cohort. As shown in Figure S5, multivariate analysis indicated that the LODDS classification was consistently an independent prognostic factor for both LCSS and OS in the subcohort. Likewise, the LODDS model had the most powerful performance among the three LN models with the highest C-index (C-index. LCSS: 0.661, 95% CI: 0.643–0.679; OS: 0.667, 95% CI: 0.647–0.687. $p < 0.01$) and likelihood ratio (LCSS: 193.0; OS: 250.6. $p < 0.01$) (Table S2).

LODDS classification displayed the greatest performance in the external validation cohort

A total of 1184 eligible patients with stage IIIA-N2 resected NSCLC from three institutions in China were included as the external validation cohort. PSM was employed to balance the baseline characteristics which produced 348 pairs included in the subsequent analyses, as shown in Table S3. The Spearman rank test showed the strongest correlation between LNR and LODDS (0.973) than between LODDS and PLN (0.510) in this external cohort. Meanwhile, the HRs of LCSS also increased as the N classifications rose.

Similarly, PORT failed to improve LCSS ($p = 0.63$) and OS ($p = 0.41$) in the entire cohort (Figure S6). Moreover, PORT also exhibited advantages in LCSS and OS in the subgroups stratified by the fourth quartiles of the three N classifications (Figure S7). PORT significantly improved the 1-, 3-, and 5-year LCSS rates of the LODDS4 subgroup. (1-year LCSS: $p < 0.01$; 3-year LCSS: $p < 0.01$; 5-year LCSS: $p < 0.01$).

Multivariate Cox regression analyses further confirmed the LODDS classification as an independent prognostic

TABLE 1 Baseline characteristics of the SEER cohort before and after PSM

	Before PSM				After PSM			
Characteristic	**Overall ($n = 4797$) n (%)**	**No radiation ($n = 2968$) n (%)**	**Radiation ($n = 1829$) n (%)**	***p*-value**	**Overall ($n = 3360$) n (%)**	**No radiation ($n = 1680$) n (%)**	**Radiation ($n = 1680$) n (%)**	***p*-value**
Age at diagnosis				<0.001				0.879
Median (IQR)	67 (59,74)	68 (60,75)	66 (58,72)		66 (58,72)	66 (58,73)	66 (59,72)	
Range	12–90	12–90	28–88		22–89	22–89	28–88	
Sex				0.248				0.917
Male	2172 (45.3)	1324 (44.6)	848 (46.4)		1524 (45.4)	760 (45.2)	764 (45.5)	
Female	2625 (54.7)	1644 (55.4)	981 (53.6)		1836 (54.6)	920 (54.8)	916 (54.5)	
Race				0.313				0.563
White	3911 (81.5)	2429 (81.8)	1482 (81.0)		2740 (81.5)	1373 (81.7)	1367 (81.4)	
Black	459 (9.6)	289 (9.7)	170 (9.3)		302 (9.0)	156 (9.3)	146 (8.7)	
Other	427 (8.9)	250 (8.4)	177 (9.7)		318 (9.5)	151 (9.0)	167 (9.9)	
Marital status				<0.001				1.000
Married	2898 (60.4)	1734 (58.4)	1164 (63.6)		2132 (63.5)	1066 (63.5)	1066 (63.5)	
Unmarried	1899 (39.6)	1234 (41.6)	665 (36.4)		1228 (36.5)	614 (36.5)	614 (36.5)	
T stage				0.398				0.650
T1	2792 (58.2)	1742 (58.7)	1050 (57.4)		1950 (58.0)	982 (58.5)	968 (57.6)	
T2	2005 (41.8)	1226 (41.3)	779 (42.6)		1410 (42.0)	698 (41.5)	712 (42.4)	
Histology				0.203				0.784
Adenocarcinoma	2834 (59.1)	1733 (58.4)	1101 (60.2)		2032 (60.5)	1008 (60.0)	1024 (61.0)	
Squamous cell carcinoma	827 (17.2)	534 (18.0)	293 (16.0)		550 (16.4)	282 (16.8)	268 (16.0)	
Others	1136 (23.7)	701 (23.6)	435 (23.8)		778 (23.2)	390 (23.2)	388 (23.1)	
Grade				0.642				0.917
I/II	2516 (52.4)	1565 (52.7)	951 (52.0)		1774 (52.8)	889 (52.9)	885 (52.7)	
III/IV	2281 (47.6)	1403 (47.3)	878 (48.0)		1586 (47.2)	791 (47.1)	795 (47.3)	
Laterality				0.487				0.917
Right	2604 (54.3)	1599 (53.9)	1005 (54.9)		1842 (54.8)	923 (54.9)	919 (54.7)	
Left	2193 (45.7)	1369 (46.1)	824 (45.1)		1518 (45.2)	757 (45.1)	761 (45.3)	
Primary site				0.100				0.518
Upper lobe	2957 (61.6)	1802 (60.7)	1155 (63.1)		2110 (62.8)	1043 (62.1)	1067 (63.5)	
Middle lobe	255 (5.3)	152 (5.1)	103 (5.6)		174 (5.2)	84 (5.0)	90 (5.4)	
Lower lobe	1585 (33.0)	1014 (34.2)	571 (31.2)		1076 (32.0)	553 (32.9)	523 (31.1)	
Type of surgery				<0.038				0.198
Lobectomy	4528 (94.4)	2785 (93.8)	1743 (95.3)		3218 (95.8)	1617 (96.2)	1601 (95.3)	
Pneumonectomy	269 (5.6)	183 (6.2)	86 (4.7)		142 (4.2)	63 (3.8)	79 (4.7)	
Chemotherapy				<0.001				1.000
Yes	3397 (70.8)	1767 (59.5)	1630 (89.1)		3965 (88.2)	1483 (88.3)	1482 (88.2)	
No/unknown	1400 (29.2)	1201 (40.5)	199 (10.9)		395 (11.8)	197 (11.7)	198 (11.8)	
ELN				0.370				0.788
Median (IQR)	10 (6,16)	10 (6,16)	10 (6,16)		10 (6,15)	10 (6,15)	10 (6,16)	
Range	1–84	1–84	1–63		1–84	1–84	1–63	
PLN				<0.001				0.116
Median (IQR)	3 (1,5)	2 (1,4)	3 (2,5)		3 (1,5)	3 (1,5)	3 (2,5)	
Range	1–41	1–41	1–38		1–36	1–24	1–36	
Cause of death				<0.001				0.076
Lung cancer	2385 (49.7)	1523 (51.3)	862 (47.1)		1639 (48.8)	852 (50.7)	787 (46.8)	

(Continues)

TABLE 1 (Continued)

Characteristic	Before PSM				After PSM			
	Overall ($n = 4797$) n (%)	No radiation ($n = 2968$) n (%)	Radiation ($n = 1829$) n (%)	*p*-value	Overall ($n = 3360$) n (%)	No radiation ($n = 1680$) n (%)	Radiation ($n = 1680$) n (%)	*p*-value
Alive	1712 (35.7)	986 (33.2)	726 (39.7)		1287 (38.3)	616 (36.7)	671 (39.9)	
Others	700 (14.6)	459 (15.5)	241 (13.2)		434 (12.9)	212 (12.6)	222 (13.2)	
Follow-up, months				0.485				0.181
Median (IQR)	31 (17,60)	31 (16,61)	32 (18,59)		32 (17, 61)	33 (17,63)	31 (17,59)	
Range	3–154	3–154	3–154		3–154	3–154	3–154	

Abbreviations: ELN, examined lymph nodes; IQR, interquartile range; LNR, lymph node ratio; LODDS, log odds of positive lymph nodes; PLN, positive lymph nodes; PSM, propensity score matching; SEER, Surveillance, Epidemiology and End Results.

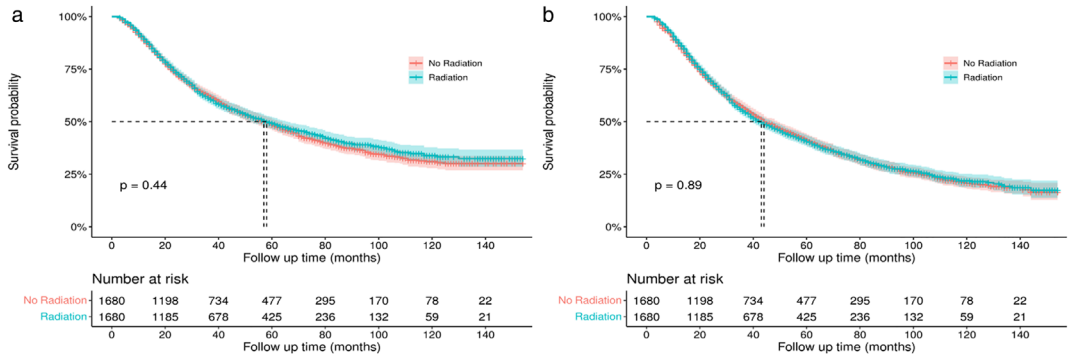

FIGURE 2 Kaplan–Meier survival curves of long-term LCSS (a) and OS (b) of patients in the PORT group and non-PORT group in the SEER cohort after PSM. SEER, Surveillance, Epidemiology and End Results; LCSS, lung cancer-specific survival; OS, overall survival; PORT, postoperative adjuvant radiotherapy; PSM, propensity score matching

factor for OS and LCSS in the external validation cohort (Figure S8). Additionally, the likelihood ratio tests and Harrell's C-index also demonstrated that the LODDS classification exhibited the greatest potential in predicting clinical outcomes (C-index, LCSS: 0.714, 95% CI: 0.681–0.747; OS: 0.710, 95% CI: 0.681–0.739; likelihood ratio LCSS: 138.2, OS: 170.9. $p < 0.01$) (Table S4).

DISCUSSION

So far, the roles of PORT remain under debate in stage IIIA-N2 NSCLC patients. Robinson et al.[11] demonstrated that PORT increased 5-year OS of pN2 patients who underwent complete resection and adjuvant chemotherapy. Herskovic et al.[24] drew a similar conclusion using a prospective nationwide oncology outcomes database. The effect of PORT on improving local control and prolonging survival in resectable stage IIIA-N2 NSCLC was further confirmed by Sakib et al.[25] In addition, our previous study also revealed that pN2 patients with extracapsular lymph node involvement receiving lobectomy and lymphadenectomy might benefit from PORT.[26] However, there is no denying that different results have been reported during the past few years. The Lung ART trial (ESMO 2021) showed PORT reduced the risk of mediastinal relapse in pN2 NSCLC patients but could not significantly increase DFS.[13] Moreover, PORT was proved to be ineligible as a significant prognostic factor for OS.[13] In another phase III randomized clinical trial,[14] 394 patients with IIIA-N2 NSCLC were enrolled, of whom PORT significantly improved DFS whereas failed to prolong OS.

The inconsistent findings on the effect of PORT may be also associated with different status of patients with stage IIIA-N2 disease, as well as different radiation techniques and doses administered in the aforementioned studies. It has been reported that a number of clinicopathological factors such as age, gender, grade, T-stage, chemotherapy and LNR, were all independent risk factors for patients with poor prognosis.[15,27–29] Notably, recent years witnessed an increase in retrospective studies to explore potential candidates with stage IIIA-N2 disease for PORT.[12,28–33] Furthermore, it was common that the number or ratio of positive nodes was identified as a predictor of responses to PORT in previous studies.[12,28,29,33,34] For instance, Gao et al.[12] found that PORT only exhibited its role in improving survival in stage IIIA-N2 NSCLC with PLN ≥6. By using the SEER database, Zeng et al.[28] found that p-N2 patients with LNR ≥0.5 could benefit from PORT. A recent study suggested that patients with LNR >1/3 and poor differentiation of primary tumor might be ideal

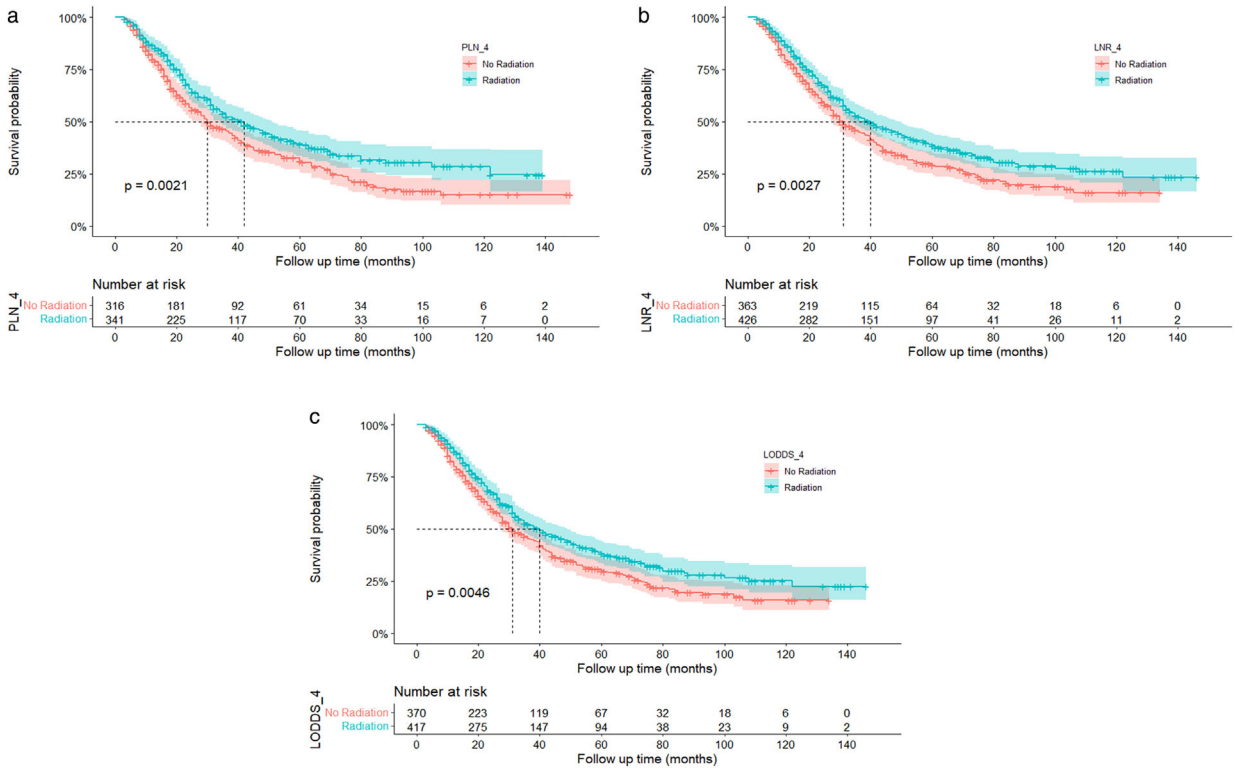

FIGURE 3 Kaplan–Meier survival curves of long-term LCSS of patients in the PORT group and non-PORT group from the SEER cohort after PSM stratified by PLN4 (a), LNR4 (b), and LODDS4 (c). SEER, Surveillance, Epidemiology and End Results; PORT, postoperative adjuvant radiotherapy; LCSS, lung cancer-specific survival; PLN, positive lymph nodes; LNR, lymph node ratio; LODDS, log odds of positive lymph nodes; PSM, propensity score matching

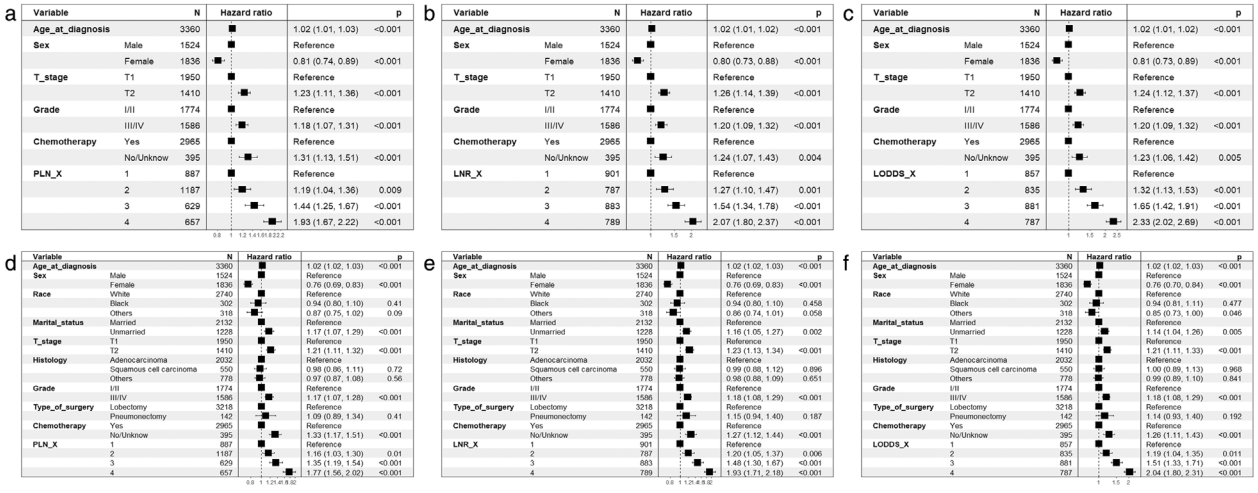

FIGURE 4 Multivariate Cox regression analyses for long-term LCSS (a, b, c) and OS (d, e, f) of the SEER cohort after PSM. SEER, Surveillance, Epidemiology and End Results; LCSS, lung cancer specific survival; OS, overall survival; PLN, positive lymph nodes; LNR, lymph node ratio; LODDS, log odds of positive lymph nodes; PSM, propensity score matching

beneficiaries from PORT.[35] However, most of the aforementioned studies had a limited sample size with external validation unavailable, nor did they compared different nodal classifications in predicting survival in stage IIIA-N2 disease.

In our present study, PORT brought no survival advantage to the SEER cohort after PSM, which was consistent with the previous studies.[13,14,36] Similar results were observed in most subgroups stratified by the quartiles of the three nodal classifications. Surprisingly, the long-term LCSS

was significantly prolonged by PORT in the PLN4, LNR4, and LODDS4 subgroups, which further indicated the heterogeneity of stage IIIA-N2 disease, and suggested that the N classifications can be used to identify populations suitable for PORT. To the best of our knowledge, it has been the first study to investigate the value of the three N classifications in selecting patients with stage IIIA-N2 NSCLC for PORT using both the SEER cohort and a Chinese population cohort. In the context of the unavailability of metastatic lymph node count in the eighth edition TNM staging system, Xu et al. reported that the number of involved nodal stations could be used to provide a more accurate prognosis for patients with resected NSCLC,[37] which also highlighted the importance of the number of positive nodes in predicting survival. As an indicator reflecting both the number of negative nodes and PLN, LODDS has been demonstrated to have better prognostic value in predicting survival of lung cancer,[21] head, and neck squamous cell carcinoma,[38] and esophageal squamous cell carcinoma.[39,40] Given that the current N descriptor could not reflect the positive number of lymph nodes, it might be of paramount significance to incorporate such an index into the N descriptor in future staging systems.

Some limitations should be acknowledged in our study. First, this was a retrospective study based on the SEER database and a Chinese multi-institutional cohort with a timespan of more than 10 years. During this period, a number of changes might occur not only in the treatment strategies, but also in the radiation and surgical techniques. Therefore, performance and selection biases were inevitable in our study. Second, unavailability of several potentially prognostic factors in the SEER database restrained the reliability of our results, such as surgical margin status, chemotherapy regimen, radiation dose, and duration of treatments. Finally, since the SEER database lacks information on the external invasion of the tumor, we reclassified the T stages by tumor size according to AJCC eighth edition, which may result in potential biases. In summary, our results should be interpreted with caution, and prospective large-scale trials should be launched to validate the potential of the LODDS classification.

In conclusion, PORT was not associated with improved survival in the entire cohort with stage IIIA-N2 resected NSCLC. The LODDS classification not only exhibited the best prognostic performance in predicting LCSS and OS in stage IIIA-N2 disease, but could also help tailor individualized PORT.

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CONFLICT OF INTEREST

Declarations of interest: none.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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