Original Study

The Value of Radiotherapy in Patients With Resectable Stage IIIA Non–Small-Cell Lung Cancer in the Era of Individualized Treatment: A Population-Based Analysis

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Abstract

Radiotherapy remains controversial for resected stage IIIA NSCLC patients. Public records of 2632 NSCLC patients were re-staged using AJCC 8th manual and analyzed using X-tile. 5+ mediastinal N2 lymph nodes metastasis, visceral pleural invasion, age >65, or larger tumor size (>3 cm) were found to be associated with a better outcome. Further well-designed trials are warranted.

Introduction: No consensus has been achieved on the benefit of radiotherapy for resected stage IIIA NSCLC patients. The division of stage IIIA has changed significantly in 2017. This study aims to explore the effects of radiotherapy on the survival of patients with resectable stage IIIA NSCLC in the new era. **Patients and Methods:** Patients diagnosed with NSCLC between 2010 and 2018 were identified in the 8th edition TNM classification from the Surveillance, Epidemiology, and End Results database. A nomogram was developed by integrating all independent predictors for lung cancer-specific survival (LCSS). The Propensity Score Matching (PSM) and subgroup analysis were applied to mitigate potential bias. Survival analyses were conducted using the Kaplan Meier curves and Cox proportional hazards regression. **Results:** A total of 2632 stage IIIA NSCLC patients were enrolled. The C-index of the nomogram for the prediction of LCSS was 0.636 (95% CI, 0.616-0.656). In the group of patients with N2 stage who featured more than 5 positive regional lymph nodes, compared with non-PORT, PORT did prolong postoperative survival time (50 vs. 31 months; $P = .005$). N2 patients with visceral pleural invasion (VPI), older (age >65), or had a larger tumor (size >3 cm) could also benefit from adjuvant radiotherapy. **Conclusion:** Treatment protocol for stage IIIA NSCLC patients should be individualized. Based on our findings, N2 patients with more than 5 positive regional lymph nodes, VPI, larger tumor size (greater than 3 cm), and older (age above 65) could benefit from adjuvant radiotherapy. Further well-designed randomized trials are warranted.

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Introduction

Lung cancer is the leading cause of cancer-related mortality in the world,[1] with non–small-cell lung cancer (NSCLC) accounting for the vast majority of cases. The features of patients with stage IIIA NSCLC are highly heterogeneous, and the treatment for this population poses an ongoing challenge in clinical practice.[2] Upfront surgery is the preferred treatment for the majority of resectable patients. However, these patients are prone to local recurrence and distant metastasis after surgery.[3] Multidisciplinary management that incorporates consideration of surgery, chemotherapy, radiotherapy, and most recently, immunotherapy, is optimal.[4]

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Perioperative chemotherapy was considered to improve the prognosis in completely resected IIIA NSCLC patients,[5-7] but 20% to 40% of patients still suffer from early recurrences.[8] Therefore, patients may require preoperative radiotherapy and postoperative radiotherapy (PORT). However, the results of a series of studies vary regarding the effect of radiotherapy in the treatment of patients with stage IIIA NSCLC.[9-12]

In stage IIIA NSCLC patients, tumor size, lymph node involvement, and comorbidities vary widely, hence, it is unfeasible to unify a treatment plan for this population. Previous studies have identified numerous clinicopathological factors that affect the impact of radiotherapy on survival.[13-15] Therefore, it is crucial for clinicians to identify the subgroup of stage IIIA patients who can benefit from PORT.

The results of some large randomized controlled clinical trials have shown that radiotherapy does not improve patient prognosis.[16,17] However, their research is based on the 7th edition AJCC/UICC classification. In the latest 8th edition AJCC/UICC classification, many patients were re-classified into a later stage. The T stage was redefined, especially in terms of tumor size, which directly affects TNM grading. Prior to 2017, tumor sizes ≤3 cm, 3 to 7 cm, and >7 cm were classified as T1, T2, and T3, respectively. Currently, tumor sizes ≤3 cm, 3 to 5 cm, and 5 to 7 cm were reclassified into T1, T2, and T3, respectively. This resulted in IIB to IIIA for T3N1M0 and IIIA to IIIB for T3N2M0.[18] Therefore, a study that takes the new stage classification into consideration is needed.

This study analyzed the characteristics and prognosis of patients with IIIA NSCLC who underwent surgery using the population-based Surveillance, Epidemiology, and End Results (SEER) database. Furthermore, we used the latest data to determine which subgroups of patients with stage IIIA NSCLC may benefit from radiotherapy.

Patients and Methods

Data Source

In this retrospective study, the data of patients with lung cancer registered from 2010 through 2018 was extracted from SEER database using SEER*Stat program (v 8.3.9). SEER is an authoritative source for cancer statistics in the United States. The SEER database collects data on cancer cases from various locations and sources throughout the United States. Data collection began in 1973 with a limited number of registries and continues to expand to include even more areas and demographics today.

The extraction conditions were as follows: "the location of the disease: lung" and "diagnosis year: 2010-2018." The following variables were extracted: patient ID, age at diagnosis, year of diagnosis, race recode, sex, pathologic grade, primary tumor site, ICD-O-3 histology code and behavior, laterality, tumor size, derived AJCC T and N stages, 8th edition AJCC classification, RX Summary–Surgery Primary Site, RX Summary–Surgery/Radiation Sequence, regional nodes positive, visceral and parietal pleural invasion recode, chemotherapy recode, cause of death to site recode, SEER cause-specific death classification, survival months, and vital status recode (study cutoff used). Based on TNM staging, tumor size and other information, we adjusted the staging of all patients to the 8th edition AJCC/UICC classification. The inclusion criteria were as follows: (1) age >18 years; (2) confirmed pathology of primary NSCLC; (3) diagnosis of stage IIIA according to the 8th edition AJCC/UICC TNM classification[18]; (4) underwent surgical treatment; (5) complete record of radiotherapy information; and (6) available lung cancer-specific survival (LCSS) follow-up data. Patients with incomplete registration information required by the research and those whose survival time was less than 1 month were excluded from this study.

Data Analysis

Statistical calculations were performed using IBM SPSS Statistics version 24.0 software (IBM Corp., Armonk, NY). The χ^2 test evaluated the unadjusted association between various therapies and the other clinicopathologic categorical variables of interest. Lung cancer-specific survival (LCSS) was defined as the time from the beginning of the diagnosis until the death of lung cancer or the last follow-up date. The Kaplan-Meier method with a log-rank test was employed to compare the survival of patients between the groups. The hazard ratios (HRs) were determined using univariate and multivariate Cox proportional hazards models. Propensity score matching (PSM) was applied to mitigate potential bias at baseline between the groups. Non-PORT matched in a 1:1 ratio to PORT based on the propensity score with a standard caliper width of 0.03. After matching, the degree of baseline variable balance was assessed by standardized differences. A standardized difference of 0.1 reflects a high degree of balance. The figures were illustrated using Prism 7.0 (GraphPad Software). Nomogram, C-index and calibration curve was conducted using the "rms" and "survival" packages in R version 4.1.2. X-tlie[19] software (Version 3.6.1, www.tissuearray.org) was employed to find the cut-off point of the lymph node number and age. All statistical tests were 2-sided, and $P < .05$ was considered statistically significant.

Results

Clinicopathological Characteristics of Study Cohort

This study cohort was formed by 2617 IIIA NSCLC patients based on the inclusion criteria. Of these, 1839 (70.27%) patients received surgery only, 619 (23.65%) patients received PORT, and 159 (6.07%) patients underwent preoperative radiotherapy. And we noticed that 19 patients received radiation both before and after surgery. Since they did not receive standard treatment, we decided to exclude this group. Table 1 shows the patient demographics and clinical parameters.

The tumor size and age were discretized, and segmentation points were generated according to TNM stages (T1: tumor ≤3 cm) and by X-Tile, respectively. And the optimal cut-off point for age at diagnosis was 65 as the cut-off value and for tumor size was 3 cm.

A statistically significant difference was reported in age, gender, primary site, pathologic grade, histology, N stage, positive lymph nodes, tumor size, visceral pleural invasion (VPI) and whether they were treated with chemotherapy among groups ($P< .05$). The laterality and race among the groups showed no statistical difference. Patients who had undergone surgery only (70.27%) made up the majority of the cohort included in the study, while those who underwent preoperative radiotherapy (6.07%) were the least represented.

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Table 1 Baseline Characteristics of the Study Population

Characteristics	Surgery Only ($n = 1839$)	Preoperative Radiotherapy ($n = 159$)	Postoperative Radiotherapy (PORT, $n = 619$)	χ^2	*P*
Gender					
Male	961 (52.30%)	101 (63.50%)	321 (51.90%)	7.771	.021
Female	878 (47.70%)	58 (36.50%)	298 (48.10%)		
Race					
White	1405 (76.50%)	125 (78.60%)	458 (74.00%)	12.413	.015
Black	182 (9.90%)	23 (14.50%)	59 (9.50%)		
Others	251 (13.60%)	11 (6.90%)	102 (16.50%)		
Age at diagnosis					
≤ge	773 (42.00%)	92 (57.90%)	323 (52.20%)	29.850	<.001
>65	1066 (58.00%)	67 (42.10%)	296 (47.80%)		
Pathologic grade					
Grade I	147 (8.00%)	6 (3.40%)	25 (4.00%)	42.534	<.001
Grade II	681 (37.00%)	41 (25.80%)	229 (37.00%)		
Grade III	735 (40.00%)	68 (42.80%)	241 (38.90%)		
Grade IV	41 (2.20%)	2 (1.30%)	14 (2.30%)		
Blank(s)	235 (12.80%)	42 (26.40%)	131 (17.80%)		
Laterality					
Right-origin of primary	1022 (55.60%)	97 (61.00%)	331 (53.50%)	2.975	.226
Left-origin of primary	817 (44.40%)	62 (39.00%)	288 (46.50%)		
Primary site					
Upper lobe	907 (49.30%)	116 (73.00%)	383 (61.90%)	77.657	<.001
Main bronchus	26 (1.40%)	1 (0.50%)	5 (0.80%)		
Middle lobe	79 (4.30%)	5 (3.10%)	38 (6.10%)		
Lower lobe	693 (37.70%)	33 (20.80%)	182 (29.40%)		
Others	134 (7.30%)	4 (2.50%)	11 (1.80%)		
Histology					
Adenocarcinoma	1161 (63.10%)	88 (55.30%)	426 (68.80%)	12.118	.016
Squamous cell carcinoma	509 (27.70%)	53 (33.30%)	147 (23.70%)		
Others	169 (9.20%)	18 (7.70%)	46 (7.40%)		
Visceral pleural invasion					
Yes	697 (37.90%)	28 (17.60%)	258 (41.70%)	31.554	<.001
No	1142 (62.10%)	131 (82.40%)	361 (58.30%)		
Chemotherapy					
Yes	1068 (58.10%)	155 (97.50%)	563 (91.00%)	297.789	<.001
No/Unknown	771 (41.90%)	4 (2.50%)	56 (6.70%)		
Tumor size					
≤z cm	468 (25.40%)	201 (32.50%)	182 (29.40%)	312.996	.002
>3 cm	1371 (74.60%)	418 (67.50%)	230 (37.20%)		
N stage					
N0	659 (35.80%)	45 (28.30%)	89 (14.40%)	287.112	<.001
N1	607 (33.00%)	30 (18.90%)	102 (16.50%)		
N2	573 (31.20%)	84 (52.80%)	428 (69.10%)		
No. of positive lymph nodes					
<5	1645 (89.50%)	149 (93.70%)	483 (78.00%)	60.174	<.001
≥0	194 (10.50%)	10 (6.30%)	136 (22.00%)		

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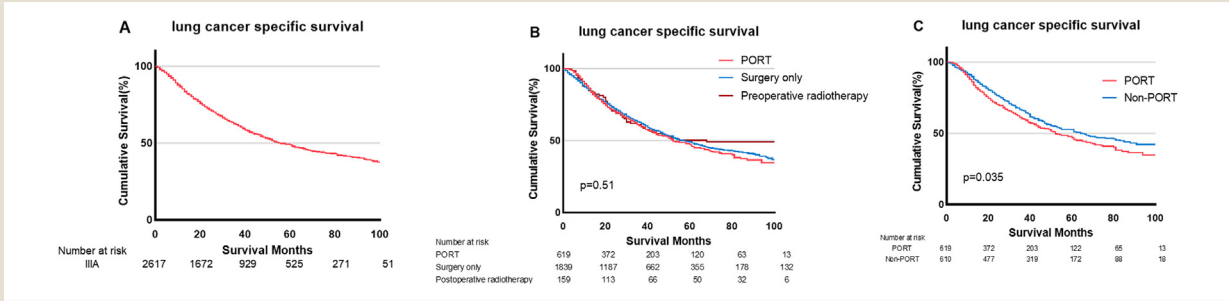
Figure 1 Kaplan-Meier analysis on LCSS of IIIA NSCLC patients. (A) With the whole population; (B) with different radiotherapy sequences. (C) LCSS for the matched study cohort. Kaplan-Meier survival analysis for matched cohort showed that PORT had shorter LCSS than non-PORT (HR = 1.197, CI, 1.089-1.427, $P = .035$).
Number at risk: The number of patients at risk in different time periods was under survival curves. Abbreviations: LCSS = lung cancer-specific survival; non-PORT = only surgery; NSCLC = nonCsmall-cell lung cancer; PORT = postoperative radiotherapy.



In addition, patients who received radiotherapy combined with surgery (more than 90%) were more likely to receive chemotherapy than patients who only received surgery (58.10%) (Table 1).

Identify Risk Factors of IIIA NSCLC Patients by Univariate and Multivariate Analysis

In the univariate Cox regression analysis of LCSS, chemotherapy was a good prognosis factor, which is consistent with previous[20] reports (HR = 0.722, 95%CI (0.639, 0.816), $P < .001$). Poor prognosis factors include age over 65, male sex, nonadenocarcinoma and squamous cell carcinoma histology, larger tumor size (>3 cm), higher histological grade, VPI, lower lobe primary lesion, and positive lymph nodes ≥5.

According to multivariate analysis, age, sex, tumor size, positive lymph nodes, VPI, primary site, pathologic grade, chemotherapy and radiotherapy with surgery variables were statistically significant ($P < .05$). The univariate and multivariate Cox regression results of LCSS prognostic factors in patients with IIIA NSCLC are listed in Table 2.

Compare the Prognosis in the Whole Study Cohort and Matched Study Cohort

In LCSS, the median follow-up time of the entire cohort was 55 months (Figure 1A). The median follow-up time for the surgery only, preoperative radiotherapy and PORT groups were 57, 68, and 52 months, respectively. Kaplan-Meier survival analysis showed no statistical difference among the groups (Figure 1B).

To assess the efficacy of radiotherapy, propensity score matching (PSM) was used. The most representative PSM was selected for patients who underwent surgery only and PORT. A total of 1220 patients were included in the analysis after PSM. All baseline characteristics were well matched, with standardized differences for all variables of 0.1 or less (Table 3). In the matched analyses, the median survival time of PORT and non-PORT groups was 52 and 65 months (HR = 1.197, CI (1.089-1.427), $P < .05$) (Figure 1C).

Subgroup Analysis to Select Postoperative Radiotherapy Candidates

Subgroup analyses were conducted to determine the populations that could benefit from postoperative radiotherapy. Age, tumor size, lymph node and VPI were independent risk factors for limited survival. A subgroup analysis of the cohort was performed based on these factors.

In patients with N0 and N1 metastasis, PORT showed shorter LCSS compare to non-PORT. The Kaplan-Meier curve is shown in Figure 2A and B. The median survival was higher in the PORT group than in the non-PORT group in N2(+) patients (58 months vs. 48 months), but the differences did not reach statistical significance (Figure 2C). In N2 patients who received chemotherapy, there is no significant difference between PORT and non-PORT ($P = .758$, Figure 2D).

In patients with stage IIIA/N2 NSCLC, on analyzing the data using the exhaustive method, X-Tile stratified this cohort into 2 groups: positive lymph nodes <5 ($n = 744$) or positive lymph nodes ≥ 5 ($n = 257$). A significant difference in survival was observed between whether patients received PORT or not in the group of N2 stage patients with ≥ 5 positive regional lymph nodes (50 vs. 31 months; $P = .005$) (Figure 2E). In the group of 744 patients with N2 stage with less than 5 positive regional lymph nodes, compared with non-PORT, PORT did not prolong postoperative survival time ($P = .212$) (Figure 2F). Among 209 patients with N2 stage who had 5 positive regional lymph nodes and received postoperative chemotherapy (POCT), PORT prolonged the median survival compared with non-PORT (50 vs. 28 months, respectively; $P = .003$) (Figure S1A). Additionally, results showed that in N2 patients with VPI, the median survival time in patients treated with PORT was significantly longer compared to surgery only (81 months vs. 46 months; $P = .011$) (Figure 3A), we also found that in IIIA/N2 patients, the older population (age >65) showed a trend of better prognosis in the PORT group ($P = .043$) (Figure 3B). Moreover, PORT prolonged the median survival time (61 vs. 44 months; $P < .001$) in N2 patients with

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Table 2 Univariable and Multivariable Analysis for LCSS Using the Cox Proportional Hazard Model in IIIA/N2 NSCLC Surgery Patients

Variables	LCSS			
	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age				
≤ge	Reference		Reference	
>65	1.617 (1.432, 1.826)	<.001	1.546 (1.363, 1.754)	<.001
Gender				
Female	Reference		Reference	
Male	1.305 (1.159, 1.470)	<.001	1.313 (1.162, 1.485)	<.001
Chemotherapy				
No	Reference		Reference	
Yes	0.722 (0.639, 0.816)	<.001	0.824 (0.632, 0.830)	<.001
Histology				
Adenocarcinoma	Reference		Reference	
Squamous cell carcinoma	1.046 (0.912, 1.200)	.519	0.893 (0.771, 1.035)	.134
Others	1.251 (1.024, 1.529)	.028	1.039 (0.837, 1.291)	.729
Pathologic grade				
Grade I	Reference		Reference	
Grade II	1.185 (0.918, 1.531)	.193	1.192 (0.918, 1.547)	.188
Grade III	1.413 (1.097, 1.821)	.070	1.420 (1.092, 1.845)	.009
Grade IV	2.009 (1.325, 3.045)	.001	1.921 (1.235, 2.989)	.004
Blank(s)	0.979 (0.708, 1.355)	.899	1.005 (0.721, 1.400)	.977
Visceral pleural invasion				
No	Reference		Reference	
Yes	1.239 (1.098, 1.397)	<.001	1.244 (1.100, 1.405)	<.001
Laterality				
Left	Reference		Reference	
Right	0.954 (0.848, 1.074)	.436	0.943 (0.834, 1.067)	.354
Primary site				
Upper lobe	Reference		Reference	
Main bronchus	1.267 (0.746, 2.154)	.382	1.688 (0.982, 2.903)	.058
Middle lobe	1.182 (0.894, 1.564)	.240	1.174 (0.880, 1.566)	.277
Lower lobe	1.265 (1.114, 1.437)	<.001	1.220 (1.069, 1.391)	.003
Others	1.187 (0.927, 1.519)	.174	1.210 (0.938, 1.561)	.142
Tumor size				
≤z cm	Reference		Reference	
>3 cm	1.197 (1.041, 1.376)	.012	1.208 (1.044, 1.3497)	.011
No. of positive lymph nodes				
<5	Reference		Reference	
≥e	1.469 (1.249, 1.727)	<.001	1.454 (1.229, 1.718)	<.001
Radiation with surgery				
Only surgery	Reference		Reference	
Preoperative radiotherapy	0.899 (0.702, 1.153)	.402	1.229 (0.944, 1.589)	.125
Postoperative radiotherapy	1.049 (0.912, 1.206)	.504	1.206 (1.036, 1.385)	.015

tumor size >3 cm (Figure 3C). In N2 patients with tumor size ≤3 cm, there was no significant difference in survival time between the 2 groups ($P = .619$) (Figure 3F). A similar conclusion was reached for N2 patients who received chemotherapy (Figure S1B-1D).

Nomogram Predicts Prognosis of Resectable Stage IIIA Patients

A nomogram predicted by LCSS was developed based on multivariate Cox regression analysis (Figure 4A). Nine prognostic factors were scored in the nomogram (gender, age, grade, chemotherapy,

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Table 3 Baseline Characteristics of the Propensity-Score Matched Population

Characteristics	Surgery Only ($n = 610$)	Postoperative Radiotherapy (PORT, $n = 610$)	*P*	SMD
Gender				
Male	290 (47.50%)	3216 (51.80%)	.137	0.085
Female	320 (52.50%)	294 (48.20%)		
Race				
White	473 (77.50%)	451 (73.90%)	.252	0.090
Black	55 (9.00%)	57 (9.30%)		
Others	82 (13.40%)	102 (16.70%)		
Age at diagnosis				
≤ge	322 (52.80%)	3219 (52.30%)	.863	0.010
>65	288 (47.20%)	291 (47.70%)		
Laterality				
Right-origin of primary	311 (51.00%)	326 (53.40%)	.390	0.049
Left-origin of primary	299 (49.00%)	284 (46.60%)		
Primary site				
Upper lobe	378 (62.00%)	376 (61.60%)	.241	0.001
Main bronchus	11 (1.80%)	5 (0.80%)		
Middle lobe	26 (4.30%)	37 (6.10%)		
Lower lobe	6178 (29.20%)	181 (29.70%)		
Others	17 (2.80%)	11 (1.80%)		
Histology				
Adenocarcinoma	440 (72.10%)	417 (68.40%)	.198	0.053
Squamous cell carcinoma	121 (19.80%)	147 (54.90%)		
Others	49 (8.00%)	46 (7.50%)		
Visceral pleural invasion				
Yes	244 (40.00%)	254 (41.60%)	.560	−0.033
No	366 (60.00%)	356 (58.40%)		
Chemotherapy				
Yes	543 (89.00%)	554 (90.80%)	.296	0.062
No/Unknown	67 (11.00%)	56 (9.20%)		
No. of positive lymph nodes				
<5	475 (77.90%)	483 (79.20%)	.577	−0.032
≥.	135 (22.10%)	127 (20.80%)		

VPI, tumor size, radiotherapy, VPI, and primary site). The 12-, 36-, and 60-month LCSS probabilities for a particular patient were calculated by cumulative scoring.

The C-index for the prediction of LCSS was 0.636 (95% CI, 0.616-0.658). The calibration curve also showed good congruence between the predicted probability and observed probability of LCSS (Figure 4B). The Hosmer-Lemeshow test showed no significant deviation between the observed and predicted LCSS ($P > .05$). We developed a web-based applet: https://xjtuwww.shinyapps.io/DynNomapp/. Doctors can input information about the patient to evaluate whether the integration of PORT can positively affect the prognosis (Figure S2A-2B).

Discussion

The 2-year survival rate of patients with stage IIIA NSCLC is only half (55%), and the 5-year survival rate is only 36%.[21] For most patients with stage IIIA, surgery is an integral part of treatment.[22] Postoperative radiotherapy and chemotherapy can reduce local recurrence and thus prolong survival.[23,24] The role of chemotherapy in multidisciplinary management of stage IIIA NSCLC has been well established, either as induction therapy or given postoperatively, this can be echoed by many clinical trials.[25,26] Moreover, with the introduction of immune checkpoint inhibitors, PD-(L)1 can prolong the disease-free survival of NSCLC patients.[4,20] However, whether the integration of radiotherapy is beneficial to patients with stage IIIA NSCLC has been a controversial topic for many years. Since the late 1990s, many randomized trials have been conducted to prove the effectiveness of radiotherapy, but the results remain to be contradictory.[27,28] The meta-analysis trial group published 9 randomized trials, which showed that radiotherapy increased the risk of death by 21% compared with surgery alone.[29] Kim et al.[30] evaluated the effect of radiotherapy on stage IIIA NSCLC and found no prolongation of OS rates (non-PORT group 58.2% vs. 49.9% PORT group, $P = .466$). At the same time, some studies implicated that patients may benefit from radiotherapy.[31,32] In this study, we initially explored the role of radiotherapy, and it seems irrelevant to survival. The Kaplan-Meier survival analysis showed no difference in patients on whether they received radiother-

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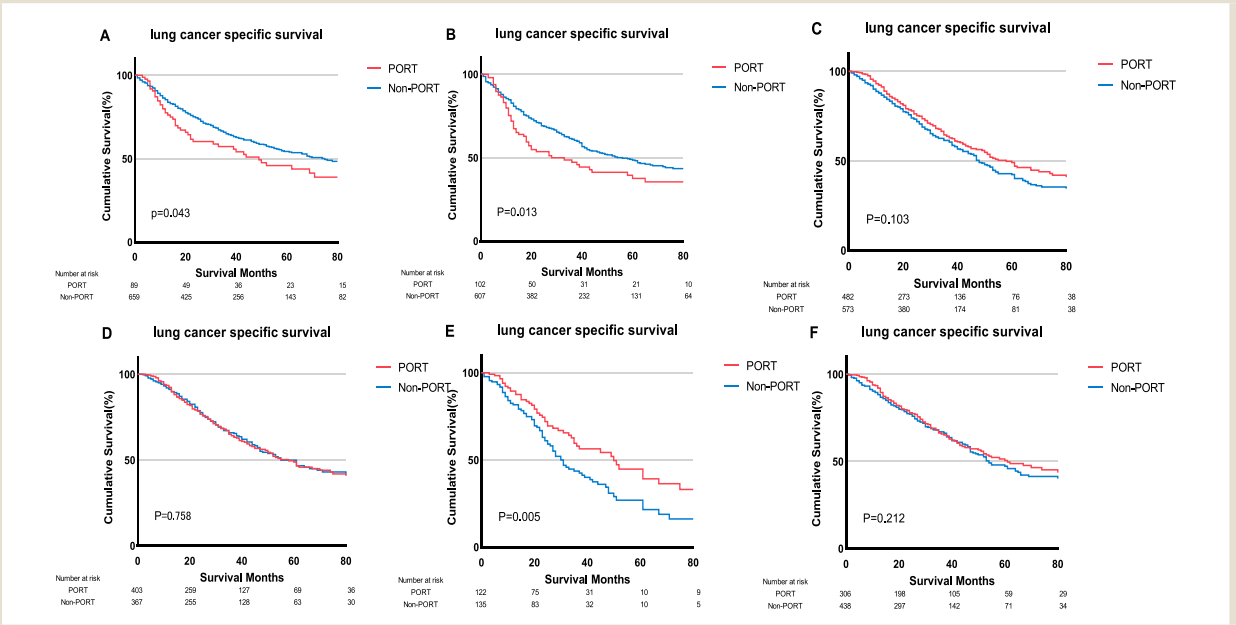
Figure 2 LCSS of patients with (A) N0 stage disease treated with PORT ($n = 89$; HR = 1.377; 95% CI, 1.099-1.961; $P = .043$) versus non-PORT ($n = 659$); (B) N1 stage disease treated with PORT ($n = 102$; HR = 1.463; 95% CI, 1.054-2.032; $P = .013$) versus non-PORT ($n = 607$); (C) N2 stage disease treated with PORT ($n = 428$; HR = 0.850; 95% CI, 0.700-1.032; $P = .103$) versus non-PORT ($n = 573$); (D) N2 stage disease treated with POCT combined with PORT ($n = 403$; HR = 1.037; 95% CI, 0.824-1.306; $P = .758$) versus POCT along ($n = 367$); (E) N2 stage disease who featured P5 positive regional lymph nodes treated with PORT ($n = 122$ HR = 0.606; 95% CI, 0.426-0.862; $P = .005$) versus non-PORT ($n = 135$); (F) N2 stage disease who featured <5 positive regional lymph nodes treated with PORT ($n = 306$ HR = 0.946; 95% CI, 0.747-1.198; $P = .212$) versus non-PORT ($n = 438$).



apy or not ($P = .69$). This may indicate that radiotherapy cannot benefit the entire stage IIIA population for the heterogeneity of this cohort. The need to be further stratified the population to explore the relationship between radiotherapy and prognosis is still unmet.

So, PSM was adopted although it may not eliminate all confounding variables.[33] In observational research, they are typically more practical and statistically more effective than multivariate Cox statistical methods.[34] There is a broader debate about the use of PORT. Based on these factors, the application of PSM in this study provides new information about the impact of PORT on patients with resectable IIIA NSCLC. Notably, the results obtained demonstrate that, for resectable IIIA NSCLC patients, the survival time of those who received PORT is significantly shorter than that of the non-PORT counterparts. In the 8th edition AJCC/UICC classification, a large number of patients were reclassified into a later stage, from IIB to IIIA for T3N1 and from IIIA to IIIB for T3N2.[18] Adding the old stage IIB patients into this analysis would be expected to further shrink the potential benefit and perhaps further decrease DFS and OS. However, the positive effects of PORT remain, probably due to the relevant small population of T3N1 patients.

Subgroup analyses were necessary to identify potential populations that could benefit from PORT. The first section of the survey was concerned with N stage. N staging may be a key indicator in determining the efficacy of radiotherapy. Similar to prior studies,[32,35] PORT may not be required for patients with N0 and N1.

The treatment of stage IIIA/N2 NSCLC has been controversial. In 2006, the ANITA study[36] show that postoperative radiotherapy improved the 5-year survival of IIIA N2 patients regardless of chemotherapy status (Chemotherapy group: 47% vs. 34%; Control group: 21% vs. 17%). The publication of the results of this study led to a series of similar subsequent studies. Recently, numerous researchers[35,37,38] have analyzed the role of PORT in N2 patients using the SEER database, demonstrating that PORT could improve survival. Mikell et al.[39] evaluated the benefits of PORT through NCBD database. PORT was associated with improved OS in pN2 patients who were treated on linear accelerators in 3D conformal radiotherapy era. This study is a conducted analysis of NCDB database. It provided information that we believe may be crucial to the outcome of PORT, ie, the specific treatment modality and dose applied for patients. But the benefit for this group of patients was indirectly confirmed by prospective studies. Recently, the Lung-ART[17] study and the PROT-C study[16] revealed that in patients with stage IIIA/N2 NSCLC, PORT did not provide an OS benefit. The difference in 3-year DFS and OS in Lung-ART study was not statistically significant. These studies point out that PORT cannot be recommended as the standard of care in patients with stage IIIA N2 NSCLC.

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Figure 3 LCSS of N2 (A) and VPI patient treated with PORT ($n = 157$; HR = 0.649; 95% CI, 0.465-0.906; $P = 0.011$) versus non-PORT ($n = 204$); (B) patient who age >65 treated with PORT ($n = 201$; HR = 0.778; 95% CI, 0.600-0.953; $P = 0.043$) versus non-PORT ($n = 321$); and (C) patient who tumor sizes >3 cm treated with PORT ($n = 255$; HR = 0.700; 95% CI, 0.536-0.914; $P = .003$) versus non-PORT ($n = 308$).

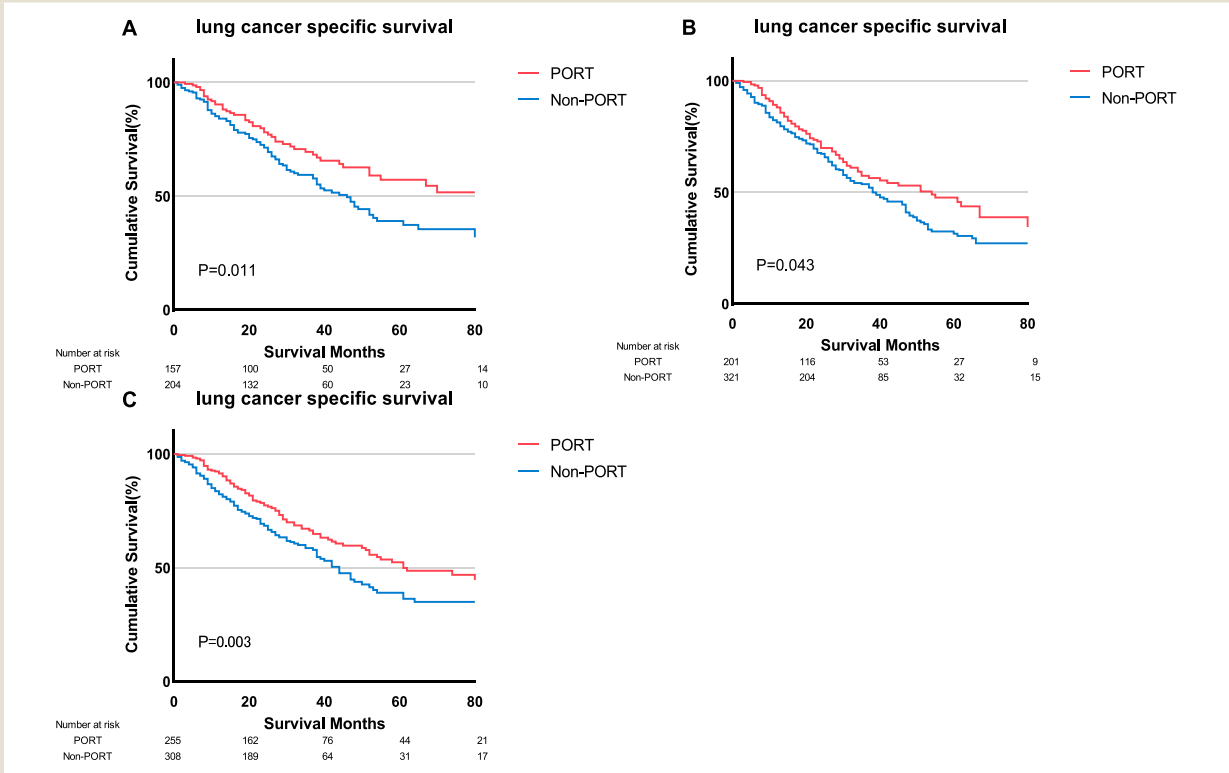
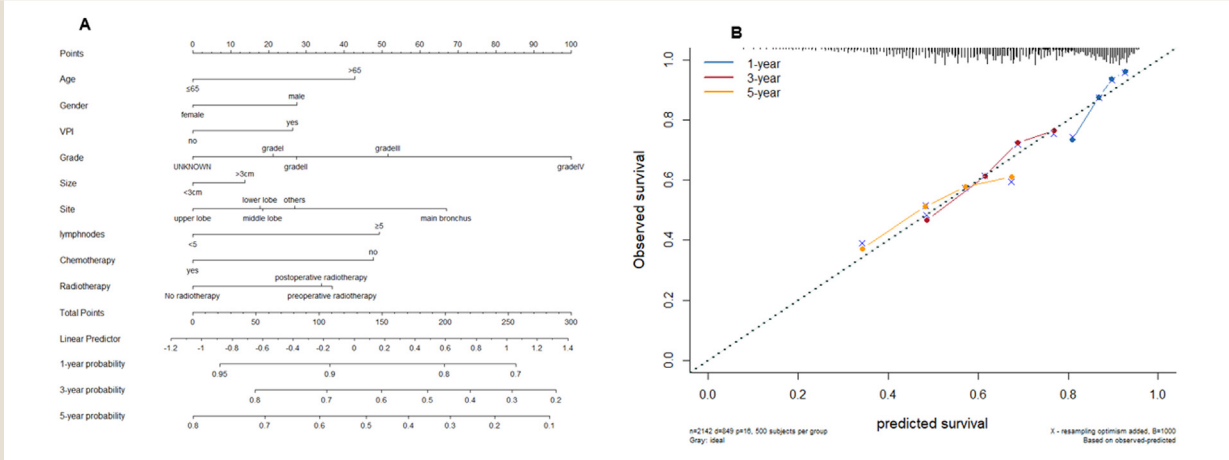


Figure 4 (A) Nomogram developed from our data for predicting 12-, 36-, and 60-month LCSS in NSCLC stage IIIA patients after surgical resection. (B) Calibration curve of the nomograms. a: 12-, 36-, and 06-month LCSS nomogram calibration curves. The results showed good agreement between prediction and observation in probability.



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Nevertheless, we believe PORT can still benefit some IIIA N2 patients. Previous clinical trials were based on the 7th edition TNM classification, but in the 8th edition classification, patients with IIIA/N2 excluded tumor size larger than 5 cm, invasion of chest wall, phrenic nerve, pericardium or separate tumor nodule(s) in the same lobe. the composition of stage IIIA patients has changed in the new edition, which may affect treatment decisions. Therefore, it makes sense to screen the population that may benefit from radiotherapy based on clinical characteristics in the 8th classification.

Our study identified several groups of stage IIIA patients who may benefit from radiotherapy. Although AJCC classification did not use the number of lymph nodes as a determining factor, the number of positive lymph nodes has proven to have an important relationship with the prognosis.[40,41] Yoo et al.[42] showed that the number of positive lymph nodes is an independent prognostic factor of OS. Haager et al.[43,44] investigated the relationship between lymph node ratio (LNR) and survival of IIIA N2 patients with chemotherapy; they suggested that higher LNR had a worse prognosis. Consequently, it can be decided whether to use radiotherapy or not according to this factor. This is also resonated in the present study, patients with <5 positive lymph nodes, we found no difference in LCSS between PORT and non-PORT. Due to potentially significant toxicity, the oncologic benefit of radiotherapy may be offset. However, according to our findings, PORT was necessary for patients with ≥ 5 positive lymph nodes and could reduce the risk of cancer-related death. Meanwhile, VPI and tumor size have been reported to be poor prognostic factors in patients with NSCLC. Andrea et al.[45] proposed chemotherapy should be strongly recommended in NSCLC patients with positive nodes or tumors ≥ 4 cm with pleural invasion based on SEER database. Kaplan-Meier survival analysis showed that PORT shared better LCSS with non-PORT in N2 patients with VPI or tumor size >3 cm. In addition, we found that PORT prolonged the survival time of N2 patients with age over 65. Radiotherapy may have its unique advantages in elderly patients. The nutritional status of tumors in elderly patients may be worse than that in younger patients, providing radiotherapy enough space and time to control local conditions. This may be one of the factors, and the specific reasons may need further investigation.

In addition, we have attempted to explore the association between risk factors and the prognosis of patients who underwent radiotherapy. We identified age, sex, tumor size, positive lymph nodes, VPI, primary site, pathologic grade, chemotherapy, and radiotherapy with surgery as independent prognostic factors for LCSS. Based on the controversy of radiotherapy, patients with resectable IIIA NSCLC were accurately included as the study participants. According to the clinical significance and statistical methods, we included 9 prognostic factors and used X-tile to determine the grouping of the variables. We also reported the prediction of individual survival probability of patients to avoid the influence of additional unmeasurable factors related to the health status of patients. This nomogram can be effectively applied in clinical practice with good discrimination (the C-index was 0.636 (95% CI, 0.616-0.656)) and excellent calibration. In this study, a new model was established, and clinicians can easily conduct an individualized survival prediction for stage IIIA NSCLC patients who underwent surgery in clinical practice. For clinicians to use it more directly and conveniently, we have also developed a web-based applet: https://xjtuwww.shinyapps.io/DynNomapp/. Doctors can input the information of the patient to evaluate whether the integration of PORT can positively affect prognosis. Users can make a judgment by entering the clinical and pathological characteristics of patients and it can generate the predicted survival curve (Figure S2A). Moreover, users can choose the length of follow-up time to predict the survival rate and 95% confidence interval at various time points (Figure S2B).

As techniques continue to evolve, certain high-risk N2 patients may benefit from new technologies. Remick et al.[46] first reported the role of proton beam therapy (PBT) in NSCLC patients with better prognosis and less toxicity. Besides, in the era of immunotherapy and following the CheckMate-816[4] report of neoadjuvant nivolumab with chemotherapy in resected stage III patients, Checkmate-816 has verified the clinical value of neoadjuvant combination immunotherapy for NSCLC. This mode will definitely change the dominant position of chemotherapy in the perioperative period, and the personalized scheme of multidisciplinary management will become a new trend in the near future. The effect of radiotherapy and chemotherapy plus immunotherapy should also be further evaluated. Additionally, on the basis of detecting postoperative minimal residual diseases by analyzing circulating tumor DNA, patients with a high risk of disease recurrence can be better identified[47] and may thus be candidates for aggressive treatment such as PORT.

It is worthy to point out some limitations in this research. First, the details of radiotherapy, such as the dose of radiotherapy, and techniques of radiotherapy (3D conformal radiotherapy or intensity-modulated radiation therapy (IMRT)), are not indicated in the database. New radiotherapy techniques, such as PBT and IMRT, may potentially reduce complications and improve OS. However, the old dose method may weaken the value of radiotherapy in NSCLC patients. Second, because the evaluation index was LCSS, many patients who died from reasons unrelated to lung cancer or had no records were excluded, and selection bias was inevitable. Third, local recurrence data does not exist in SEER database, so the relationship between radiotherapy and recurrence was not investigated. Fourth, due to the retrospective nature and limitations of SEER database, it is impossible to assess the proportion of patients treated with PORT. If these are high-risk patients, and the survival rate is the same as that of patients who have not received PORT, this may be an active intervention for these patients. Finally, although the nomogram, which predicts the potential survival benefit, has an important reference value, it should not be regarded as the sole criterion for decision-making. Additionally, cardiovascular events, R0/R1 resection, etc., are prognostic factors that should be considered for PORT. Therefore, more well-designed study cohorts are required to further validate our conclusions.

Based on the above, the role of PORT needs to be re-examined and investigated. Due to the limitations inherent in the database, and the nature of this study, the level of evidence remains weak, and further trials and real-world prospective cohorts are warranted.

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Conclusion

Lung-Art and PORT-C studies do not mean that radiotherapy is useless for all stage IIIA NSCLC patients. Combined with our results, we suggest that a comprehensive assessment is crucial to determine whether radiotherapy is needed in stage IIIA patients. Based on the results obtained, IIIA/N2 patients with ≥5 positive regional lymph nodes could benefit from postoperative radiotherapy. N2 patients with VPI, older age or larger tumor size may also benefit from postoperative radiotherapy. Patients with stage IIIA should not be recommended for radiotherapy indiscriminately, and the method for providing a basis for radiotherapy intervention merits further investigation.

Clinical Practice Points

- We restaged all data to the 8th edition classification and evaluated the effect of radiotherapy on survival in operable IIIA NSCLC patients.
- Our study identified specific populations that could benefit from radiotherapy.
- IIIA/N2 patients with ≥5 positive regional lymph nodes could benefit from postoperative radiotherapy.
- N2 patients with VPI, older age, or larger tumor size may also benefit from postoperative radiotherapy.

Data Availability Statements

The datasets pertaining to this study are available in the Surveillance, Epidemiology, and End Results (SEER) Program database.

Disclosure

The authors have stated that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2022.09.011.

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