Effects of Postoperative Radiotherapy on Survival of Patients With Stage IIIA Resected Non–Small Cell Lung Cancer: Analysis of the SEER Database

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ABSTRACT

Background: The role of postoperative radiotherapy (PORT) in patients with resected stage IIIA non–small cell lung cancer (NSCLC) remains controversial. The purpose of this study was to explore the effect of PORT on survival of these patients. **Methods:** Patients aged ≥ 18 years with stage IIIA NSCLC were identified in the SEER database from 2010 through 2015. Cox regression analysis was used to identify independent prognostic factors in patients with stage IIIA NSCLC. Subgroup analysis of patients stratified by N stage was also performed. Overall survival and lung cancer–related death were compared among the different groups by using Kaplan-Meier analysis and competitive risk analysis. **Results:** A total of 5,168 patients (1,711 of whom received PORT) were included in the study. In multivariable analysis, PORT was an independent prognostic risk factor for patients with N1 stage (hazard ratio [HR], 1.416, 95% CI, 1.144–1.753; $P=.001$). PORT was a favorable prognostic factor for patients with stage IIIA, N2 disease with ≥ 6 positive lymph nodes (HR, 0.742; 95% CI, 0.587–0.938; $P=.012$). Median survival time of patients with stage IIIA, N2 disease with ≥ 6 positive lymph nodes who received postoperative chemotherapy combined with PORT was significantly longer compared with those who received postoperative chemotherapy alone (32 vs 25 months, respectively; $P=.009$). The competitive risk model revealed that 3- and 5-year lung cancer–related mortality rates increased by 8.99% and 16.92%, respectively, in patients with N1 disease who were treated with PORT, whereas the 3-year mortality rate decreased by 4.67% and the 5-year mortality rate by 10.08% in patients with N2 disease and ≥ 6 positive lymph nodes who were treated using PORT. **Conclusions:** Our results revealed that PORT significantly improved overall survival and decreased lung cancer–related mortality in patients with stage IIIA, N2 disease with ≥ 6 positive lymph node metastases. PORT was not recommended for patients with N0 and N1 disease.

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Background

Non–small cell lung cancer (NSCLC) accounts for approximately 85% of patients with lung cancer.¹ The features of patients with stage IIIA disease are highly heterogeneous, and surgery is the preferred treatment, but these patients are prone to local recurrence and distant metastasis after surgery.² Multidisciplinary sequential therapy is applied in patients with stage IIIA NSCLC. Complete surgical resection of the primary lesion and mediastinal lymph node dissection are recommended for patients with operable stage IIIA NSCLC, and platinum-based adjuvant chemotherapy is currently the standard treatment of patients with good ECOG performance status after surgery.^{3,4} Postoperative chemotherapy (POCT) can improve disease-free survival and overall survival (OS) by removing the possibility of partial residual and metastatic lesions. Previous studies showed that postoperative radiotherapy (PORT) may prevent local recurrence in carefully selected patients,^{5–7} but whether PORT can bring OS benefits to patients remains controversial.

In 1998, 2,128 patients with resected NSCLC from 9 randomized trials of PORT versus surgery alone were included in a meta-analysis group. Results showed that PORT had a significant adverse effect on survival rate. Compared with surgery alone, the risk of death in the PORT group increased by 21%, reducing OS from 55% to 48%. Subgroup analyses showed that this adverse effect was greatest for patients with stage I/II, N0–N1 disease, whereas for those with stage III, N2 disease, the effect of PORT was not clear.⁸

In an early study of the application of PORT, it was found that cardiac toxicity of radiotherapy (RT) may promote the death of patients. One study that included 127 patients with stage III NSCLC who received dose-escalated RT at 70 to 90 Gy (median, 74 Gy) from 6 trials in 1996 through 2009 showed that cardiac

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events were relatively common after high-dose thoracic RT and were independently associated with heart dose.⁹

In the open-label, multicenter Adjuvant Navelbine International Trialist Association (ANITA) study performed in 101 centers in 14 countries, 232 of 840 patients with completely resected stage IB–IIIA NSCLC received PORT. Results showed that among patients with pN1 disease, PORT was associated with improved survival among those in the observation arm, whereas it had detrimental effect on survival among those in the chemotherapy arm. In contrast, PORT was associated with improved survival among patients with pN2 disease in both the chemotherapy and observation arms. These findings suggest that PORT has a positive effect in pN2 disease and a negative effect in pN1 disease among patients who receive adjuvant chemotherapy.¹⁰

Conclusions drawn in earlier studies were constrained by several important factors, such as the planning of irradiation fields, outdated radiation technology, and high toxicity and adverse effect rates. With the development of modern RT technology, can RT technology prolong OS of patients with stage IIIA disease? We tried to answer this question through a retrospective study of high-quality, population-based data. Our study provides some evidence for clinical decision-making by evaluating the impact of PORT on OS in patients with stage IIIA NSCLC.

Methods

In this retrospective study, which was approved by the ethics committee of Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, we retrieved data from the SEER database using SEER*STAT 8.3.5 software (NCI). Permission to access the custom data file in the SEER Program was obtained (reference number 14026-Nov2018). The SEER Program has recorded information about patients with cancer in the United States over the past 40 years, including the incidence, mortality, and morbidity of millions of confirmed patients. Currently, the number of registration stations has expanded to 18. Data from registries are submitted to NCI twice per year for classification, statistical compilation, and aggregation, and cancer information of the population covered is disseminated to the United States and the rest of the world.

We extracted the data of patients with lung cancer registered from 2010 through 2015. Patients who met the following criteria were included in this study: (1) age ≥ 18 years; (2) pathologically confirmed NSCLC (histologic types selected were coded as 8012/3, 8013/3, 8022/3, 8031/3, 8032/3, 8033/3, 8035/3, 8046/3, 8050/3, 8052/3, 8070/3, 8071/3, 8072/3, 8073/3, 8074/3, 8082/3, 8083/3, 8084/3, 8123/3, 8140/3, 8200/3, 8201/3, 8250/3, 8251/3, 8252/3, 8253/3, 8254/3, 8255/3, 8260/3, 8310/3, 8323/3, 8333/3, 8430/3, 8480/3, 8481/3, 8490/3, 8550/3, 8560/3, 8570/3, 8574/3, 8980/3); (3) diagnosis of stage IIIA NSCLC

according to the 7th edition of the *AJCC Cancer Staging Manual*¹¹; (4) previous lobectomy or pneumonectomy (Site-Specific Surgery of Primary Site Code range was 30–70 according to the SEER Program Code Manual¹²); and (5) complete record of RT information (patients who received postoperative adjuvant RT or did not receive RT).

Patients with incomplete registration information required by the research and those whose survival time was <1 month were excluded from this study.

Variables extracted from the SEER database included age at diagnosis, year of diagnosis, sex, race recode, primary tumor site (main bronchus, upper lobe, middle lobe, lower lobe, overlapping lesion of lung), ICD-O-3 histology code and behavior, pathologic grade, derived AJCC T and N stages, SEER*Stat RX Summary-Surgery Primary Site, regional nodes positive, radiation sequence with surgery, chemotherapy recode, survival months, vital status recode, cause of death to site recode, SEER cause-specific death classification, and SEER other cause of death classification. SEER codes used to define the number of positive lymph nodes were as follows: 00 = all nodes examined negative; 01–89 = 1 to 89 nodes positive (code exact number of nodes positive); and 90 = ≥ 90 nodes positive.

All statistical calculations were performed using IBM SPSS Statistics version 19.0 software (IBM Corp.), and figures were drawn using GraphPad Prism 7.0 (GraphPad Software). For better analysis, all variables were converted to categorical variables. The chi-square test was used to evaluate the unadjusted association between PORT and the other clinicopathologic categorical variables of interest. OS was defined as the time from the beginning of the diagnosis until death of any cause or until the last follow-up date. The survival analysis was performed using Kaplan-Meier curves, and *P* value was determined using the log-rank method. Hazard ratios (HRs) were determined using univariate and multivariate Cox proportional hazards models. Competing risk analysis was used to calculate lung cancer-specific mortality and was conducted by Gray test using the “cmprsk” and “survival” packages in R version 3.6.0 (R Foundation for Statistical Computing). All statistical tests were 2-sided, and *P* $< .05$ was considered statistically significant.

Results

Correlation Between Clinical Parameters and PORT Use

A total of 5,168 patients met inclusion criteria and were included in this study (Figure 1). Median age at diagnosis was 68 years (range, 18–92 years). A total of 1,711 patients received PORT. The proportion of patients receiving RT differed by age, tumor location, pathologic grade, T stage, N stage, number of positive regional lymph nodes, and receipt of chemotherapy (*P* $< .001$). No significant difference in sex, year of diagnosis, race, or histology was

Figure 1. Patient selection.

Abbreviation: NSCLC, non-small cell lung cancer.

seen between patients who received PORT and those who did not (Table 1).

Univariate Analysis of Clinical Features Affecting Prognosis

Univariate survival analysis was performed for all patients. PORT and chemotherapy were favorable prognostic factors. Adverse prognostic factors included age (≥ 60 years), male sex, nonadenocarcinoma pathologic type, higher T stage, higher N stage, and ≥ 6 positive regional lymph nodes. Univariate survival analysis of patients with stage IIIA NSCLC with N0, N1, and N2 stages showed that chemotherapy was an advantageous factor for the prognosis of patients with N1 and N2 disease, whereas PORT had a beneficial effect on survival only for patients with N2 disease (supplemental eTable 1, available with this article at JNCCN.org).

Multivariate Analysis of Clinical Features Affecting Prognosis

Patients With N0, N1, and N2 Stage

Multivariate survival analysis of all patients showed that age (≥ 60 years), male sex, nonadenocarcinoma pathologic type, higher T and N stages, and ≥ 6 positive regional

lymph nodes were independent risk factors for a prognosis indicating shorter survival. Chemotherapy was a favorable prognostic factor and was related to longer survival. We conducted a subgroup multivariate survival analysis according to N stage. Results showed that PORT predicted worse outcomes for patients with N1 stage (HR, 1.416; 95% CI, 1.144–1.753; $P=.001$) but had no significant impact on survival of N0 and N2 stages. Chemotherapy can prolong the survival of patients with N1 and N2 stages (supplemental eTable 2).

Patients With N2 Stage, Stratified by Number of Positive Regional Lymph Nodes

Patients with stage IIIA NSCLC with N2 stage disease are a special group that can be divided into different subgroups according to the number of positive regional lymph nodes. We divided patients with N2 stage into 2 groups according to the number of positive regional lymph nodes (< 6 or ≥ 6 positive lymph nodes). Multivariate survival analysis showed that PORT had no effect on survival in patients with stage IIIA-N2 disease with < 6 positive lymph nodes (HR, 0.993; 95% CI, 0.866–1.138, $P=.920$). Although POCT (HR, 0.618, 95% CI, 0.478–0.800; $P<.001$) and PORT (HR, 0.742; 95% CI, 0.587–0.938; $P=.012$) are both favorable prognostic factors for patients with stage IIIA-N2 disease with ≥ 6 positive lymph nodes, chemotherapy and PORT can significantly improve OS (Table 2).

OS Analysis of Subsets of Patients With N0, N1, and N2 Stages

There was no significant difference in the survival of patients with N0 stage in view of whether they received PORT ($P=.825$). A Kaplan-Meier plot for patients with N0 stage is presented in Figure 2A. A total of 1,258 patients with stage IIIA NSCLC with N1 disease were divided into 2 groups, stratified by whether they received PORT. We compared the differences of median survival in the 2 groups. Although there was no statistical difference in survival between these 2 groups, median survival of patients who received PORT was 30 months, slightly shorter than the median survival of those who did not receive PORT (34 months; $P=.255$) (Figure 2B). Among them, 769 patients with stage N1 received POCT. Compared with patients who received POCT alone, median survival of those who received POCT combined with PORT was significantly shorter (56 vs 32 months; $P=.0004$) (Figure 2C).

A total of 688 patients with stage N2 featured ≥ 6 positive regional lymph nodes and were divided into 2 groups, stratified by whether they received PORT. A significant difference in survival was seen based on whether patients received PORT (31 vs 22 months; $P<.0001$) (Figure 3A). Among them, 534 patients with

Table 1. Correlation Between Clinical Parameters and PORT Use

Clinical Parameters	Patients Who Did Not Receive PORT n (%)	Patients Who Received PORT n (%)	All Patients n (%)	P Value
Age at diagnosis				<.001
<60 y	664 (19.2)	489 (28.6)	1,153 (22.3)	
≥60 y	2,793 (80.8)	1,222 (71.4)	4,015 (77.7)	
Sex				.996
Female	1,657 (47.9)	820 (47.9)	2,477 (47.9)	
Male	1,800 (52.1)	891 (52.1)	2,691 (52.1)	
Race				.233
Black	326 (9.4)	151 (8.8)	477 (9.2)	
White	2,863 (82.8)	1,405 (82.1)	4,268 (82.6)	
Other	268 (7.8)	155 (9.1)	423 (8.2)	
Year of diagnosis				.860
2010	610 (17.7)	307 (17.9)	917 (17.7)	
2011	609 (17.6)	294 (17.2)	903 (17.5)	
2012	601 (17.4)	288 (16.8)	889 (17.2)	
2013	561 (16.2)	262 (15.3)	823 (15.9)	
2014	553 (16.0)	287 (16.8)	840 (16.3)	
2015	523 (15.1)	273 (16.0)	796 (15.4)	
Primary tumor site				<.001
Main bronchus	44 (1.3)	25 (1.5)	69 (1.3)	
Upper lobe	1,909 (55.2)	1,013 (59.2)	2,922 (56.5)	
Middle lobe	173 (5.0)	97 (5.7)	270 (5.2)	
Lower lobe	1,197 (34.6)	543 (31.7)	1,740 (33.7)	
Overlapping lesion	134 (3.9)	33 (1.9)	167 (3.2)	
Histology				.059
Adenocarcinoma	2,310 (66.8)	1,193 (69.7)	3,503 (67.8)	
Squamous cell	956 (27.7)	420 (24.5)	1,376 (26.6)	
Others	191 (5.5)	98 (5.7)	289 (5.6)	
Pathologic grade ^a				<.001
I	235 (6.8)	82 (4.8)	317 (6.1)	
II	1,409 (40.8)	700 (40.9)	2,109 (40.8)	
III	1,565 (45.3)	751 (43.9)	2,316 (44.8)	
IV	49 (1.4)	32 (1.9)	81 (1.6)	
Unknown	199 (5.8)	146 (8.5)	345 (6.7)	
T stage				<.001
T1	531 (15.4)	368 (21.5)	899 (17.4)	
T2	1,029 (29.8)	733 (42.8)	1,762 (34.1)	
T3	1,186 (34.3)	448 (26.2)	1,634 (31.6)	
T4	711 (20.6)	162 (9.5)	873 (16.9)	
N stage				<.001
N0	482 (13.9)	101 (5.9)	583 (11.3)	
N1	1,037 (30.0)	221 (12.9)	1,258 (24.3)	
N2	1,938 (56.1)	1,389 (81.2)	3,327 (64.4)	
POCT				<.001
No	1,511 (43.7)	165 (9.6)	1,676 (32.4)	
Yes	1,946 (56.3)	1,546 (90.4)	3,492 (67.6)	
Positive lymph nodes				<.001
<6	3,024 (87.5)	1,371 (80.1)	4,395 (85.0)	
≥6	433 (12.5)	340 (19.9)	773 (15.0)	

Abbreviations: POCT, postoperative chemotherapy; PORT, postoperative radiotherapy.

^aPathologic grades: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated, anaplastic.

Table 2. Multivariate Analysis of Clinical Features Affecting Prognosis of Patients With N2 Stage

Parameters	≥6 Positive Lymph Nodes (n=688)			<6 Positive Lymph Nodes (n=2,639)		
	HR	95% CI	P Value	HR	95% CI	P Value
PORT						
No		Ref			Ref	
Yes	0.742	0.587–0.938	.012	0.993	0.866–1.138	.920
Age at diagnosis						
<60 y		Ref			Ref	
≥60 y	1.320	1.023–1.704	.033	1.317	1.119–1.550	.001
Sex						
Female		Ref			Ref	
Male	1.328	1.069–1.651	.011	1.529	1.347–1.736	<.001
Race						
Black		Ref			Ref	
White	1.113	0.781–1.586	.555	1.158	0.924–1.452	.203
Other	1.100	0.671–1.802	.706	0.810	0.586–1.119	.201
Year of diagnosis						
2010		Ref			Ref	
2011	0.975	0.727–1.307	.866	1.037	0.872–1.234	.680
2012	0.911	0.667–1.244	.557	1.070	0.891–1.285	.472
2013	0.828	0.578–1.187	.304	0.980	0.797–1.204	.847
2014	0.787	0.526–1.179	.246	0.850	0.662–1.092	.203
2015	0.777	0.415–1.453	.430	0.829	0.548–1.254	.375
Primary tumor site						
Main bronchus		Ref			Ref	
Upper lobe	0.821	0.356–1.895	.644	1.830	0.812–4.124	.145
Middle lobe	0.837	0.327–2.141	.710	1.951	0.826–4.604	.127
Lower lobe	0.999	0.431–2.314	.998	2.185	0.968–4.930	.060
Overlapping lesion	1.674	0.614–4.564	.314	2.195	0.886–5.438	.089
Histology						
Adenocarcinoma		Ref			Ref	
Squamous cell	0.974	0.735–1.291	.855	1.261	1.089–1.460	.002
Others	1.135	0.680–1.893	.629	1.358	1.051–1.753	.019
Pathologic grade ^a						
I		Ref			Ref	
II	1.101	0.646–1.876	.724	0.954	0.719–1.267	.747
III	1.482	0.868–2.531	.150	1.096	0.825–1.456	.527
IV	0.952	0.333–2.726	.928	1.239	0.704–2.183	.457
Unknown	1.289	0.646–2.572	.471	0.899	0.609–1.327	.591
T						
T1		Ref			Ref	
T2	1.030	0.779–1.363	.834	1.235	1.061–1.436	.006
T3	1.373	0.995–1.896	.054	1.601	1.338–1.917	<.001
POCT						
No		Ref			Ref	
Yes	0.618	0.478–0.800	<.001	0.569	0.495–0.655	<.001

Abbreviations: HR, hazard ratio; POCT, postoperative chemotherapy; PORT, postoperative radiotherapy.

^aPathologic grades: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated, anaplastic.

Figure 2. Overall survival of patients with (A) N0 stage disease treated with PORT (n=101; HR, 1.041; 95% CI, 0.723–1.500; $P=.825$) versus without PORT (n=482); (B) N1 stage disease treated with PORT (n=221; HR, 1.123; 95% CI, 0.911–1.384; $P=.255$) versus without PORT (n=1,037); and (C) N1 stage treated with POCT combined with PORT (n=182; HR, 1.550; 95% CI, 1.177–2.039; $P=.0004$) versus POCT alone (n=587).

Abbreviations: HR, hazard ratio; POCT, postoperative chemotherapy; PORT, postoperative radiotherapy.

stage N2 received POCT. Median survival of patients who received POCT combined with PORT was significantly longer than for those who received POCT alone (32 vs 25 months; $P=.009$) (Figure 3B).

In the group of 2,639 patients with N2 stage who featured <6 positive regional lymph nodes, median survival of patients who received PORT was 47 months, significantly longer than for those who did not receive PORT (41 months; $P=.002$) (Figure 4A). Among 694 patients with N2 stage who had <6 positive regional lymph nodes and did not receive POCT, PORT prolonged median survival compared with those who received surgical treatment only (41 vs 28 months, respectively; $P=.009$) (Figure 4B). Among 1,945 patients with N2 stage who had <6 positive regional lymph nodes and received POCT, PORT did not show a significant advantage in influencing OS ($P=.237$) (Figure 4C).

Competitive Risk Analysis of Cancer-Related Death

We analyzed the death outcomes using a competitive risk model. Causes of death were divided into cancer-related and non-cancer-related. Results showed that the cancer-related death of patients with N1 stage treated with PORT was significantly higher than that of patients who did not receive PORT. The 3- and 5-year mortality rates increased by 8.99% and 16.92%, respectively, in patients with stage N1 who were treated with PORT ($P=.005$) (Figure 5A). For patients with N2 stage with ≥ 6 positive lymph nodes, cancer-related mortality was significantly lower among patients treated with PORT compared with the non-PORT group, with results showing that the 3-year mortality rate decreased by 4.67% and the 5-year mortality rate decreased by 10.08% ($P=.022$) (Figure 5B). There was no difference in cancer-related mortality caused by PORT in both N0 and N2 stages in patients with <6 positive lymph nodes (N0, $P=.987$; N1, $P=.238$) (Figure 5C, D).

Figure 3. Overall survival of patients with N2 stage disease who featured ≥ 6 positive regional lymph nodes (A) treated with PORT (n=323; HR, 0.637; 95% CI, 0.518–0.784; $P<.0001$) versus without PORT (n=365) and (B) treated with POCT combined with PORT (n=305; HR, 0.726; 95% CI, 0.564–0.934; $P=.009$) versus POCT alone (n=229).

Abbreviations: HR, hazard ratio; POCT, postoperative chemotherapy; PORT, postoperative radiotherapy.

Figure 4. Overall survival of patients with N2 stage disease who featured <6 positive regional lymph nodes (A) treated with PORT (n=1,066; HR, 0.825; 95% CI, 0.729–0.933; $P=.002$) versus without PORT (n=1,573); (B) not treated with POCT who received PORT (n=81; HR, 0.613; 95% CI, 0.450–0.834; $P=.009$) versus surgical treatment only (n=613); and (C) treated with POCT combined with PORT (n=985; HR, 1.094; 95% CI, 0.942–1.271; $P=.237$) versus POCT alone (n=960).

Abbreviations: HR, hazard ratio; POCT, postoperative chemotherapy; PORT, postoperative radiotherapy.

Discussion

For patients with stage IIIA NSCLC, risks of recurrence and death remain high even after complete resection. Nearly 30% of patients had local recurrence or regional lymph node metastasis within 5 years after surgery.² Because previous studies have confirmed the positive effect of POCT, NCCN Guidelines recommend POCT as a standard treatment for patients with stage IIIA NSCLC.¹³ PORT, as a local treatment, can destroy residual tumors and local subclinical lesions, thus reducing the recurrence rate.^{14,15} Therefore, PORT can theoretically improve the therapeutic effect. The effect of PORT on the survival of patients with stage IIIA NSCLC is still controversial, however.

Based on our retrospective analysis of large population-based data, we attempted to answer the clinical question of whether additional PORT prolongs OS for patients with stage IIIA NSCLC under the condition that POCT is the standard treatment. Although our study was retrospective and therefore bias was inevitable, we tried to minimize this bias through a large data analysis and statistical methodology. Among patients with N1 stage, we found that PORT can increase the cancer-related mortality and can have a harmful effect on these patients, and was associated with a significant decrease in survival. For patients with <6 positive lymph node metastases who did not receive POCT, however, RT can improve survival time, and for patients with ≥ 6 positive lymph node metastases, POCT combined with PORT can prolong survival time and reduce the risk of cancer-related death compared with POCT alone.

Among patients with stage IIIA NSCLC with T4N0 disease who had no regional lymph node metastases, PORT, as an additional local treatment, had no significant effect on survival. Meanwhile, no difference in lung

cancer-related mortality was seen between patients with stage IIIA NSCLC with T4N0 disease who received PORT and those without PORT treatment. Therefore, PORT is not necessary for this group of patients with stage IIIA NSCLC.

Similar to previous studies,¹⁶ PORT was harmful to patients with N1 stage NSCLC. The 3- and 5-year cancer-related mortality rates increased by 8.99% and 16.92%, respectively, in patients with stage N1 who were treated using PORT in our study. Adverse impacts on survival may be attributed to the adverse effects of PORT. In our opinion, PORT can increase mortality and shorten the survival time of patients with N1 stage. Because there was no recorded information regarding local recurrence of lung cancer in the SEER database, the effect of PORT on local control rate was not analyzed in our study.

PORT is controversial for patients with N2 stage. Wisnivesky et al¹⁷ suggested that PORT did not improve the survival of elderly patients with NSCLC with N2 lymph node metastasis. A meta-analysis of adjuvant PORT concluded that the effect of PORT on patients with stage IIIA-N2 disease was not clear.⁸ Other researchers, however, hold the opposite view. A total of 8,928 patients with NSCLC with stage III-N2 in 11 studies were included in a meta-analysis.¹⁸ This meta-analysis showed a trend of improving OS associated with the use of PORT. Several studies have shown that PORT can prolong survival and reduce local recurrence in patients with N2 lymph node metastasis after surgery.^{19–22} The ANITA study showed that PORT increased the 5-year survival rate of patients with stage IIIA-N2 NSCLC from 34% to 47%.²³ Our study findings suggest that patients with stage IIIA-N2 disease after radical resection should be carefully evaluated before treatment with PORT is initiated. For patients with <6 lymph node metastases, PORT could prolong survival compared with no adjuvant therapy after surgery if these

Figure 5. Competitive risk analysis for cancer-related death of patients with (A) N1 stage disease caused by PORT ($P=.005$); (B) N2 stage disease who featured ≥ 6 positive lymph nodes caused by PORT ($P=.022$); (C) N0 stage disease caused by PORT ($P=.987$); and (D) N2 stage disease who featured < 6 positive lymph nodes caused by PORT ($P=.238$).

Abbreviation: PORT, postoperative radiotherapy.

patients did not undergo POCT for some reason. PORT can be used as an effective supplementary treatment to surgery. Compared with surgery alone, use of PORT could be converted into survival benefit by reducing the local recurrence rate. Therefore, we suggest that for patients who cannot tolerate POCT, and whose physical condition permits, PORT could be used as a recommended therapy. However, we found no difference in survival between PORT combined with POCT and POCT alone. Treatment involving PORT combined with POCT might offset the survival advantage because of significant adverse effects.

Patients included in our study underwent either lobectomy or pneumonectomy. The range of lymph nodes dissected in patients with stage IIIA-N2 disease

was 1 to 90 or more, and the median number of lymph nodes dissected was 12. The number of positive lymph nodes recorded was analyzed in our study, and was considered to be one of the reliable indicators of prognosis in patients with lung cancer; more lymph node metastases predicted poorer outcome.^{24,25} Lally et al¹⁶ showed that PORT increased the 5-year survival rate of patients with N2 stage from 20% to 27% and reduced the risk of death by 14.5%. In a study of 2,691 patients with known histologies of pathologic stage IIIA (N2) NSCLC, Herskovic et al²⁶ concluded that improved survival was associated with receipt of PORT. Our study provided a more detailed categorization of patients with stage IIIA-N2 disease who benefited from PORT, and our findings suggest that patients with stage N2 undergoing PORT

should be carefully selected. Results indicated that PORT was necessary for patients with ≥ 6 lymph node metastases and could reduce the risk of cancer-related death, that PORT and POCT can increase survival time compared with POCT alone (32 vs 25 months; $P=.009$), and that PORT was an independent prognostic protective factor (HR, 0.742; 95% CI, 0.587–0.938; $P=.012$). Through competitive risk analysis, we concluded that for patients with N2 stage with ≥ 6 positive lymph node metastases, the cancer-related mortality rate decreased by 4.67% and the 5-year mortality rate decreased by 10.08% with PORT.

For patients with stage IIIA-N2 disease, the risks of local recurrence and distant metastasis are higher than in other patients with stage IIIA disease, and therefore surgery alone is not enough. Especially for patients with stage IIIA-N2 disease with ≥ 6 positive lymph nodes, local and systemic treatment should be strengthened to reduce recurrence and metastasis and to prolong survival. PORT has a beneficial effect on survival by eliminating local micrometastasis and reducing the local recurrence and cancer-related death rates. POCT can prevent systemic micrometastasis and recurrence to improve the survival period.

Conclusions

Currently, prospective randomized controlled studies of PORT for patients with resectable stage IIIA NSCLC are mostly single-center, have small sample sizes, and have different doses and ranges of RT, which reduce the effectiveness of the evidence. Our study was based on a population-based cohort to provide more evidence for the application of PORT in patients with operable stage IIIA NSCLC, but further prospective clinical trials are needed.

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Supplemental online content for:

Effects of Postoperative Radiotherapy on Survival of Patients With Stage IIIA Resected Non–Small Cell Lung Cancer: Analysis of the SEER Database

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eTable 1: Univariate Analysis of Clinical Features Affecting Prognosis

eTable 2: Multivariate Analysis of Clinical Features Affecting Patient Prognosis

eTable 1. Univariate Analysis of Clinical Features Affecting Prognosis

	All Patients			N0			N1			N2		
Parameters	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
Total, n	5,168			583			1,258			3,327		
PORT												
No	Ref			Ref			Ref			Ref		
Yes	0.871	0.796–0.953	.003	1.041	0.726–1.494	.826	1.123	0.918–1.374	.260	0.796	0.715–0.887	<.001
Age at diagnosis												
<60 y	Ref			Ref			Ref			Ref		
≥60 y	1.389	1.248–1.545	<.001	0.987	0.676–1.441	.946	1.394	1.134–1.713	.002	1.483	1.299–1.693	<.001
Sex												
Female	Ref			Ref			Ref			Ref		
Male	1.480	1.359–1.162	<.001	1.463	1.104–1.940	.008	1.345	1.138–1.590	<.001	1.526	1.373–1.697	<.001
Race												
Black	Ref			Ref			Ref			Ref		
White	1.139	0.980–1.323	.089	1.034	0.674–1.585	.879	0.968	0.712–1.318	.838	1.192	0.988–1.438	.067
Other	0.817	0.656–1.017	.071	0.513	0.221–1.190	.120	0.636	0.405–0.999	.050	0.904	0.693–1.179	.457
Year of diagnosis												
2010	Ref			Ref			Ref			Ref		
2011	0.964	0.856–1.085	.544	0.745	0.510–1.089	.129	0.918	0.726–1.161	.475	1.021	0.881–1.183	.782
2012	0.954	0.842–1.080	.454	0.789	0.524–1.188	.256	0.926	0.727–1.180	.534	0.990	0.848–1.157	.901
2013	0.882	0.768–1.014	.077	0.653	0.411–1.037	.071	0.934	0.720–1.211	.606	0.901	0.755–1.075	.246
2014	0.796	0.675–0.940	.007	0.826	0.489–1.396	.475	0.735	0.538–1.003	.052	0.815	0.660–1.006	.057
2015	0.762	0.582–0.996	.047	0.492	0.175–1.383	.179	0.796	0.495–1.280	.347	0.801	0.567–1.130	.206
Primary tumor site												
Main bronchus	Ref			Ref			Ref			Ref		
Upper lobe	0.899	0.618–1.308	.877	1.513	0.211–10.884	.680	0.901	0.537–1.512	.693	1.007	0.570–1.782	.980
Middle lobe	0.808	0.531–1.229	.319	1.565	0.207–11.809	.664	0.517	0.282–1.180	.132	1.022	0.553–1.889	.945
Lower lobe	1.079	0.740–1.572	.694	1.881	0.261–13.573	.531	0.930	0.550–1.571	.786	1.266	0.715–2.244	.419
Overlapping lesion	1.289	0.842–1.974	.243	2.709	0.362–20.243	.332	1.078	0.587–1.980	.808	1.521	0.787–2.937	.212
Histology												
Adenocarcinoma	Ref			Ref			Ref			Ref		
Squamous cell	1.328	1.210–1.457	<.001	1.543	1.149–2.071	.004	1.112	0.938–1.317	.222	1.403	1.241–1.585	<.001
Others	1.503	1.272–1.776	<.001	1.582	0.960–2.606	.072	1.706	1.243–2.341	.001	1.425	1.149–1.767	.001
Pathologic gradea												
I	Ref			Ref			Ref			Ref		
II	1.040	0.859–1.259	.688	0.934	0.580–1.502	.777	0.862	0.573–1.296	.476	1.030	0.805–1.319	.813
III	1.343	1.112–1.621	.002	1.665	1.059–2.617	.027	1.014	0.680–1.513	.946	1.300	1.018–1.660	.035
IV	1.620	1.140–2.301	.007	1.476	0.510–4.270	.473	1.357	0.728–2.531	.336	1.529	0.948–2.466	.082
Unknown	0.913	0.701–1.190	.502	0.571	0.245–1.330	.194	0.904	0.516–1.584	.723	0.936	0.674–1.301	.694
T stage												
T1	Ref			—			—			T1: Ref		
T2	1.249	1.096–1.423	.001	—	—	—	—	—	—	1.252	1.099–1.427	.001
T3	1.567	1.376–1.784	<.001	—	—	—	T3: Ref			1.725	1.480–2.011	<.001
T4	1.121	0.963–1.305	.140	—	—	—	1.102	0.914–1.330	.310	—	—	—
N stage												
N0	Ref			—			—			—		
N1	1.648	1.404–1.935	<.001	—	—	—	—	—	—	—	—	—
N2	1.372	1.183–1.591	<.001	—	—	—	—	—	—	—	—	—
POCT												
No	Ref			Ref			Ref			Ref		
Yes	0.592	0.543–0.645	<.001	0.986	0.745–1.305	.922	0.443	0.377–0.521	<.001	0.556	0.498–0.622	<.001
Positive lymph nodes												
<6	Ref			—			Ref			Ref		
≥6	1.569	1.410–1.747	<.001	—	—	—	1.622	1.223–2.152	.001	1.595	1.414–1.799	<.001

Abbreviations: HR, hazard ratio; POCT, postoperative chemotherapy; PORT, postoperative radiotherapy.

^aPathologic grades: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated; anaplastic.

eTable 2. Multivariate Analysis of Clinical Features Affecting Patient Prognosis

Parameters	All Patients			N0			N1			N2		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
Total, n	5,168			583			1,258			3,327		
PORT												
No	Ref			Ref			Ref			Ref		
Yes	1.028	0.930–1.136	.589	0.981	0.662–1.455	.925	1.416	1.144–1.753	.001	0.926	0.823–1.042	.201
Age at diagnosis												
<60 y	Ref			Ref			Ref			Ref		
≥60 y	1.262	1.131–1.408	<.001	0.886	0.593–1.326	.557	1.223	0.987–1.517	.066	1.324	1.155–1.518	<.001
Sex												
Female	Ref			Ref			Ref			Ref		
Male	1.411	1.293–1.541	<.001	1.354	0.996–1.842	.053	1.317	1.111–1.562	.002	1.467	1.316–1.637	<.001
Race												
Black	Ref			Ref			Ref			Ref		
White	1.054	0.906–1.226	.497	0.903	0.585–1.395	.647	0.947	0.692–1.297	.735	1.131	0.936–1.368	.203
Other	0.777	0.623–0.969	.025	0.397	0.168–0.938	.035	0.741	0.469–1.172	.201	0.869	0.664–1.137	.306
Year of diagnosis												
2010	Ref			Ref			Ref			Ref		
2011	0.968	0.859–1.090	.586	0.740	0.498–1.100	.137	0.971	0.766–1.232	.810	1.023	0.883–1.187	.759
2012	0.962	0.849–1.090	.540	0.802	0.528–1.219	.301	0.937	0.732–1.199	.604	1.016	0.869–1.188	.843
2013	0.928	0.807–1.067	.294	0.701	0.438–1.121	.138	0.988	0.758–1.287	.928	0.948	0.794–1.132	.557
2014	0.842	0.713–0.994	.042	0.941	0.549–1.614	.826	0.852	0.623–1.166	.317	0.840	0.679–1.038	.106
2015	0.783	0.598–1.025	.075	0.545	0.193–1.536	.251	0.898	0.555–1.451	.659	0.805	0.570–1.136	.217
Primary tumor site												
Main bronchus	Ref			Ref			Ref			Ref		
Upper lobe	1.056	0.722–1.545	.779	1.571	0.214–11.516	.657	0.883	0.519–1.502	.646	1.337	0.750–2.382	.325
Middle lobe	0.998	0.651–1.530	.994	1.788	0.230–13.931	.579	0.563	0.272–1.166	.122	1.420	0.762–2.646	.270
Lower lobe	1.213	0.828–1.778	.322	2.083	0.282–15.373	.472	0.898	0.523–1.540	.696	1.601	0.897–2.856	.111
Overlapping lesion	1.412	0.919–2.167	.115	3.609	0.471–27.647	.217	0.903	0.488–1.670	.744	1.843	0.951–3.572	.070
Histology												
Adenocarcinoma	Ref			Ref			Ref			Ref		
Squamous cell	1.140	1.033–1.258	.009	1.242	0.891–1.730	.201	1.017	0.853–1.212	.849	1.196	1.051–1.361	.006
Others	1.373	1.149–1.641	<.001	1.176	0.664–2.083	.578	1.509	1.067–2.135	.020	1.311	1.045–1.645	.019
Pathologic gradea												
I	Ref			Ref			Ref			Ref		
II	0.941	0.776–1.143	.541	0.876	0.535–1.434	.598	0.854	0.565–1.291	.453	1.003	0.781–1.287	.983
III	1.141	0.940–1.384	.182	1.487	0.904–2.445	.118	0.950	0.633–1.426	.806	1.185	0.923–1.521	.184
IV	1.274	0.883–1.837	.195	1.229	0.374–4.040	.734	1.164	0.604–2.244	.651	1.162	0.709–1.904	.551
Unknown	0.845	0.646–1.107	.221	0.436	0.183–1.039	.061	0.717	0.405–1.269	.254	0.987	0.705–1.381	.938
T												
T1	Ref			—			—			Ref		
T2	1.188	1.041–1.356	.010	—	—	—	—	—	—	1.189	1.041–1.357	.011
T3	1.538	1.317–1.796	<.001	—	—	—	Ref			1.551	1.327–1.814	<.001
T4	1.731	1.356–2.210	<.001	—	—	—	1.107	0.913–1.343	.300	—	—	—
N												
N0	Ref			—			—			—		
N1	1.964	1.582–2.438	<.001	—	—	—	—	—	—	—	—	—
N2	2.339	1.800–3.040	<.001	—	—	—	—	—	—	—	—	—
POCT												
No	Ref			Ref			Ref			Ref		
Yes	0.553	0.503–0.608	<.001	0.876	0.642–1.196	.405	0.435	0.366–0.517	<.001	0.574	0.508–0.649	<.001
Positive lymph nodes												
<6	Ref			—			Ref			Ref		
≥6	1.607	1.437–1.797	<.001	—	—	—	1.577	1.181–2.105	.002	1.654	1.464–1.868	<.001

Abbreviations: HR, hazard ratio; POCT, postoperative chemotherapy; PORT, postoperative radiotherapy.

^aPathologic grades: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated, anaplastic.