Original Article

Prognostic significance of extranodal extension in patients with pathologic N1 non-small cell lung cancer undergoing complete resection

Seung Keun Yoon[1#^], Jae Kwang Yun[2#], Geun Dong Lee[2], Sehoon Choi[2], Hyeong Ryul Kim[2], Yong-Hee Kim[2], Seung-Il Park[2], Dong Kwan Kim[2]

[1]Department of Thoracic and Cardiovascular Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Contributions: (I) Conception and design: SK Yoon, JK Yun; (II) Administrative support: DK Kim; (III) Provision of study materials or patients: GD Lee, S Choi, HR Kim, YH Kim, SI Park, DK Kim; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: SK Yoon, JK Yun, DK Kim; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Dong Kwan Kim, MD, PhD. Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea. Email: dkkim@amc.seoul.kr.

Background: The prognostic significance of extranodal extension (ENE) remains unclear in patients with pathologic N1 (pN1) non-small-cell lung cancer (NSCLC) undergoing surgery. We evaluated the prognostic impact of ENE in patients with pN1 NSCLC.

Methods: From 2004 to 2018, we retrospectively analyzed the data of 862 patients with pN1 NSCLC who underwent lobectomy and more (lobectomy, bilobectomy, pneumonectomy, sleeve lobectomy). According to their resection status and the presence of ENE, patients were classified into R0 without ENE (pure R0) (n=645), R0 with ENE (R0-ENE) (n=130), and incomplete resection (R1/R2) groups (n=87). The primary and secondary endpoints were 5-year overall survival (OS) and recurrence-free survival (RFS), respectively.

Results: The prognosis of the R0-ENE group was significantly worse than the pure R0 group for both OS (5-year rate: 51.6% *vs.* 65.4%, P=0.008) and RFS (44.4% *vs.* 53.0%, P=0.04). According to the recurrence pattern, a difference of RFS was found only for distant metastasis (55.2% *vs.* 65.0%, P=0.02). The multivariable Cox analysis revealed that the presence of ENE was a negative prognostic factor in patients who did not undergo adjuvant chemotherapy [hazard ratio (HR) =1.58; 95% confidence interval (CI): 1.06–2.36; P=0.03], but it was not in those with adjuvant chemotherapy (HR =1.20; 95% CI: 0.80–1.81; P=0.38).

Conclusions: For patients with pN1 NSCLC, the presence of ENE was a negative prognostic factor for both OS and RFS, regardless of resection status. The negative prognostic effect of ENE was significantly associated with an increase in distant metastasis and was not observed in patients who underwent adjuvant chemotherapy.

Keywords: Extranodal extension (ENE); complete resection; pathologic N1 (pN1); non-small-cell lung cancer (NSCLC); prognosis

Submitted Jan 30, 2023. Accepted for publication May 12, 2023. Published online Jun 02, 2023.
doi: 10.21037/jtd-23-150
View this article at: https://dx.doi.org/10.21037/jtd-23-150

^ ORCID: 0000-0002-2609-2148.

Introduction

The presence of extranodal extension (ENE) has been reported to be a negative prognostic factor in patients with surgically resected non-small-cell lung cancer (NSCLC) (1-3). Recently, the International Association for the Study of Lung Cancer (IASLC) proposed refined definitions of complete resection that incorporated quality standards of tumor resection and lymph node (LN) staging. In detail, complete resection (R0) is defined when all of the following criteria are satisfied: (I) a free resection margin has been proven microscopically, (II) systemic lymph node dissection (LND) or lobe-specific LND must be performed, (III) no ENE in nodes removed separately or in those at the margin of the main lung specimen, and (IV) highest mediastinal node that has been removed must be negative (4,5). Among these patients, ENE of the tumor from nodes removed separately is defined as incomplete resection (R1/R2) even if the resection margin is clear. However, this definition of R0 resection seems to be considerably stricter than the traditional definition that requires only a clear resection margin, which surgeons have adopted in the past (6,7).

Highlight box

Key finding

- For patients with pN1 NSCLC, the presence of ENE was a negative prognostic factor for both OS and RFS, regardless of resection status. The negative prognostic effect of ENE was significantly associated with an increase in distant metastasis and was not observed in patients who underwent adjuvant chemotherapy.

What is known and what is new?

- IASLC definitions of R0 resection seems to be considerably stricter than the traditional definition that requires only a clear resection margin, which surgeons have adopted in the past.
- For patients with pN1 NSCLC, the presence of ENE was a negative prognostic factor for both OS and RFS even after complete resection.
- When ENE is confirmed postoperatively in a patient with R0 resection, it should be evaluated as an R1 resection in accordance with the recommendation in IASLC.
- A negative prognostic effect of ENE was found only in patients who skipped adjuvant CTx, which might be due to an increased rate of distant metastasis.

What is the implication, and what should change now?

- Even for patients with borderline medical conditions, adjuvant CTx might be considered more actively in completely resected pN1 NSCLC with the presence of ENE.

Therefore, this study aimed to compare the long-term outcomes according to the presence of ENE in patients with completely resected pathologic N1 (pN1) NSCLC. Furthermore, we sought to compare the recurrence pattern and evaluate the effect of adjuvant therapy in these patients. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-150/rc).

Methods

Patients

We retrospectively reviewed the data of patients with pN1 NSCLC who underwent lung surgery at Asan Medical Center, Seoul, South Korea, between January 2004 and December 2018. Patients with sublobar resection (biopsy, wedge resection, and segmentectomy), distant metastasis, history of neoadjuvant treatment or who had a concurrent malignancy were excluded from this study. According to their resection status and the presence of ENE, patients were classified into R0 without ENE (pure R0), R0 with ENE (R0-ENE), and R1/R2 groups. The primary and secondary endpoints were 5-year rates of overall survival (OS) and recurrence-free survival (RFS), respectively.

The patient's diagnosis, staging, and surgical resection were all carried out following generally acknowledged protocols, which were previously detailed elsewhere (8). The pathological staging was performed retrospectively in accordance with the 8th edition of the American Joint Committee on Cancer (AJCC) (9).

According to the multidisciplinary team approach, all patients who had pN1 disease were advised to have adjuvant chemotherapy (CTx), except those who were over 75 years old or in poor physical health. For 4–6 weeks following surgery, a total of four cycles of systemic CTx with a platinum-based therapy was suggested. After targeted therapy became more common in 2008 for patients with active epidermal growth factor receptor (EGFR) mutations, tyrosine kinase inhibitors have become increasingly popular for treating recurrences following adjuvant CTx. In patients who had a complete resection, adjuvant radiation (RTx) was given at 50–54 Gy in 1.8 to 2.0 Gy fractions. Patients with a positive resection margin were administered RTx up to 55–60 Gy. Adjuvant therapy was regarded to have been administered to patients only if the scheduled treatment was completed.

Data on follow-up were obtained from clinic visit records

and national insurance information. The postoperative follow-up strategy was typically followed up every three months until the first 2 years of surgery, then followed up every six months for the next 3 years, and after that, an annual visit was recommended. Computed tomography (CT) was performed whenever there was a clinic visit and additionally when there were signs of recurrence. Positron emission tomography (PET) was conducted when a recurrence was suspected on CT. Treatment modalities and chemotherapeutic regimens in relapsed cases were determined by a multidisciplinary team approach, including thoracic surgeons, radiologists, and medical oncologists.

Definition of variables

In a model predicting postoperative mortality, the individual comorbidities exceed the overall number of comorbid disorders in a patient (10). The latter was regarded as a categorical variable. R0 resection was defined according to the National Comprehensive Cancer Network (NCCN) guideline: (I) free resection margin, (II) systematic node dissection or sampling, and (III) highest mediastinal node negative for tumor. R1/R2 resection was defined as positive for resection margin, unremoved positive LNs, or malignant pleural effusion (7).

On pathological specimens, LN capsular invasion or spreading of neoplastic cells beyond the LN capsule was designated as ENE. Recurrence within the surgical field, such as anastomotic site recurrence, pleura seeding, or regional and mediastinal LNs, was described as locoregional recurrence. Recurrence at all other sites of failure, including the contralateral lung or outside the hemithorax, was regarded as a distant recurrence. OS was calculated using data from the Korean National Security Death Index Database as the time interval between the date of the operation and the date of death for any reason. RFS was calculated as the period between the date of operation and the date of recurrence; Patients who did not have a recurrence at the most recent workup were regarded as recurrence-free.

Statistical analysis

For continuous variables, the independent *t*-test was used; for categorical variables, the chi-square and Fisher's exact tests were used. Means and standard deviations were used to represent continuous variables, while frequencies and percentages were used to represent categorical variables. The Shapiro-Wilk test was used to determine the normality of individual parameter distributions. The Kaplan-Meier method was used to estimate the OS and RFS, and the log-rank test was used to evaluate them. In both the univariable and multivariable analyses, the Cox proportional hazards model was utilized to evaluate the prognostic factors for OS in overall patients following adjuvant therapy classification. Following the elimination of correlated factors, independent variables with $P \leq 0.05$ in univariable analysis were included in the initial multivariate Cox model. The final multivariable model (model 1) was chosen using a backward stepwise selection procedure ($P \leq 0.10$ for entering and $P \leq 0.05$ for staying in the model). All statistical calculations were conducted using R version 4.0.4 (The R Foundation for Statistical Computing, Vanderbilt University, Nashville, TN, USA) using the survival, ggplot2, moonBook, and survminer packages. A P value less than 0.05 was considered to indicate statistical significance.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Asan Medical Center (No. 2021-1845) and individual consent for this retrospective analysis was waived.

Results

Patient characteristics

During the study period, 959 patients with surgically resected NSCLC were confirmed as pN1 disease. Among them, patients with sublobar resection (n=40), distant metastasis (n=26), neoadjuvant therapy (n=21), and concurrent malignancy (n=10) were excluded from the current study (Figure S1). Finally, 862 patients were confirmed as the final cohort. According to their resection status and the presence of ENE, there were 645 (74.8%), 130 (15.1%), and 87 (10.1%) patients with pure R0, R0-ENE, and R1/R2, respectively.

The baseline characteristics of the patients with pN1 NSCLC are summarized in *Table 1*. Compared to patients with pure R0, those with R0-ENE had a higher rate of smoking history (P=0.005), adenocarcinoma (P=0.03), and pathological multiple LN metastasis (pN1b) (P<0.001). Between patients with R0-ENE and R1/R2, there were significant differences in sex (P=0.02), smoking history

Table 1 Baseline characteristics of pN1 patients according to resection status and ENE status

Characteristics	Pure R0 (n=645)	R0-ENE (n=130)	R1/R2 (n=87)	P value (pure R0 *vs.* R0-ENE)	P value (R0-ENE *vs.* R1/R2)
Age (years)	62.1±9.5	62.0±8.6	63.9±8.3	0.90	0.10
Sex, male	465 (72.1)	105 (80.8)	81 (93.1)	0.05	0.02
Never smoker	218 (33.8)	27 (20.8)	5 (5.7)	0.005	0.004
Comorbidity				0.05	0.006
0	318 (49.3)	78 (60.0)	33 (37.9)		
1	231 (35.8)	33 (25.4)	36 (41.4)		
≥2	96 (14.9)	19 (14.6)	18 (20.7)		
Operative method				0.05	0.15
Lobectomy	498 (77.2)	86 (66.2)	45 (51.7)		
Bilobectomy	56 (8.7)	15 (11.5)	13 (14.9)		
Pneumonectomy	55 (8.5)	19 (14.6)	16 (18.4)		
Sleeve lobectomy	36 (5.6)	10 (7.7)	13 (14.9)		
Preoperative PFT values					
FEV1 (%)	86.9±15.6	84.6±15.7	78.4±15.2	0.12	0.004
DLCO (%)	86.4±18.2	87.7±19.0	80.1±18.3	0.44	0.004
Cell type				0.03	<0.001
Adenocarcinoma	256 (39.7)	68 (52.3)	65 (74.7)		
Squamous cell carcinoma	333 (51.6)	53 (40.8)	12 (13.8)		
Others	56 (8.7)	9 (6.9)	10 (11.5)		
The number of harvested LNs	29.7±11.3	32.0±12.4	30.6±13.6	0.04	0.43
Pathological T factor				0.94	0.02
pT1	147 (22.8)	28 (21.5)	13 (14.9)		
pT2	321 (49.8)	63 (48.5)	31 (35.6)		
pT3	130 (20.2)	28 (21.5)	25 (28.7)		
pT4	47 (7.3)	11 (8.5)	18 (20.7)		
Pathological TNM stage				0.60	0.006
pII	469 (72.7)	91 (70.0)	44 (50.6)		
pIII	176 (27.3)	39 (30.0)	43 (49.4)		
Adjuvant treatment				0.36	<0.001
None	174 (27.0)	35 (26.9)	13 (14.9)		
CTx	354 (54.9)	63 (48.5)	10 (11.5)		
RTx	56 (8.7)	16 (12.3)	28 (32.2)		
CRTx	61 (9.5)	16 (12.3)	36 (41.4)		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Pure R0 (n=645)	R0-ENE (n=130)	R1/R2 (n=87)	P value (pure R0 *vs.* R0-ENE)	P value (R0-ENE *vs.* R1/R2)
Subdivided node status				<0.001	0.30
pN1a	576 (89.3)	97 (74.6)	71 (81.6)		
pN1b	69 (10.7)	33 (25.4)	16 (18.4)		

Values are presented as numbers (%) or mean ± standard deviation unless otherwise indicated. ENE, extranodal extension; PFT, pulmonary function test; FEV1, forced expiratory volume in 1 s; DLCO, diffusing capacity to carbon monoxide; LNs, lymph nodes; TNM, tumor, node, and metastasis; CTx, chemotherapy; RTx, radiation therapy; CRTx, chemoradiation therapy.

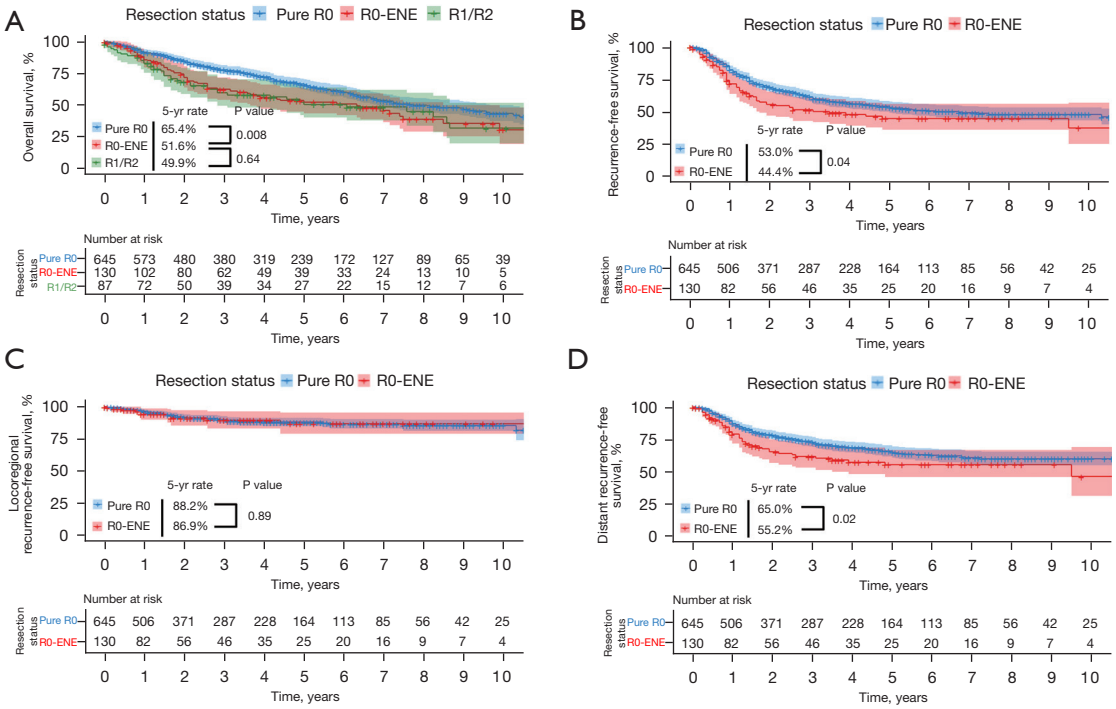

Figure 1 Overall survival (A) of patients with pN1 NSCLC based on resection status, recurrence-free survival (B) locoregional recurrence-free survival (C) distant recurrence-free survival (D) stratified by ENE status of patients pN1 NSCLC who underwent complete surgical resection. R0, complete resection; ENE, extranodal extension; R1/R2, incomplete resection; pN1 NSCLC, pathologic N1 non-small-cell lung cancer.

(P=0.004), comorbidities (P=0.006), pulmonary function (P=0.004), histologic type (P<0.001), and pathological stage (P=0.006) (*Table 1*). The detailed characteristics of the R1/R2 group was summarized in Table S1.

Survival outcomes

The mean follow-up duration was 49.8±38.0 months. During the study, 360 (41.8%) patients died. The median survival time (MST) and 5-year OS of the overall patients were 51 months [95% confidence interval (CI): 48–53 months] and 61.8%. According to the resection status, the 5-year OS rates in the pure R0, R0-ENE and R1/R2 groups were 65.4%, 51.6% and 49.9%, respectively. The R0-ENE group had significantly worse OS than the pure R0 group (P=0.008), but it was similar to the R1/R2 group (P=0.64) (*Figure 1A*). The 5-year RFS rate was significantly different between the pure R0 and R0-ENE

Table 2 Multivariable Cox analysis in patients pN1 NSCLC after complete surgical resection

Variables	Overall survival		Recurrence-free survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.03 (1.02–1.05)	<0.001		
Sex				
Female	1	ref.		
Male	1.63 (1.19–2.23)	0.002		
Cell type				
Adenocarcinoma	1	ref.	1	ref.
Squamous cell carcinoma	1.41 (1.08–1.84)	0.01	2.13 (1.66–2.75)	<0.001
Others	2.25 (1.53–3.30)	<0.001	2.11 (1.39–3.21)	<0.001
Pathological TNM stage				
pII	1	ref.	1	ref.
pIII	1.74 (1.37–2.22)	<0.001	1.93 (1.53–2.44)	<0.001
Adjuvant treatment				
None	1	ref.	1	ref.
CTx	0.49 (0.36–0.65)	<0.001	0.69 (0.54–0.89)	0.004
RTx	0.68 (0.47–0.99)	0.04	0.67 (0.44–1.02)	0.06
CRTx	0.73 (0.50–1.08)	0.11	0.68 (0.46–1.00)	0.05
Subdivided node status				
pN1a	1	ref.	1	ref.
pN1b	1.59 (1.17–2.17)	0.003	1.66 (1.25–2.20)	<0.001
Extranodal extension				
Negative	1	ref.	1	ref.
Positive	1.34 (1.00–1.78)	0.05	1.39 (1.05–1.85)	0.02

pN1, pathologic N1; NSCLC, non-small-cell lung cancer; HR, hazard ratio; CI, confidence interval; ref., reference; TNM, tumor, node, and metastasis; CTx, chemotherapy; RTx, radiation therapy; CRTx, chemoradiation therapy.

groups (53.0% *vs.* 44.4%, P=0.04) (*Figure 1B*). The 5-year OS rate and RFS rate of the R0-ENE and R1 groups were compared (Figure S2). No statistically significant differences were observed between the two groups [OS (P=0.85), RFS (P=0.22)]. According to the recurrence pattern, there was no significant difference between the pure R0 and R0-ENE groups in locoregional recurrence (P=0.89) (*Figure 1C*) but a significant difference was observed for distant recurrence (65.0% *vs.* 55.2%, P=0.02) (*Figure 1D*). In the multivariable Cox analysis, the presence of ENE was a significant prognostic factor for both OS [hazard ratio (HR) =1.34; 95% CI: 1.00–1.78; P=0.05] and RFS (HR =1.39; 95% CI: 1.05–1.85; P=0.02) for patients with completely resected pN1 NSCLC (*Table 2*, Table S2).

To evaluate the effectiveness of adjuvant treatment, subgroup analysis was performed of patients with pN1 NSCLC after complete resection. The 5-year OS rates were 72.4%, 63.3%, 54.9%, and 46.4% in the CTx group, chemoradiation (CRTx) group, RTx group, and no treatment group, respectively (*Figure 2*). Patients who underwent CTx or CRTx had comparable prognoses, which were superior to those who underwent RTx or no adjuvant therapy (*Figure 2A*). The 5-year RFS rates were 45.3% in the no treatment group, 52.6% in the CTx group, 55.8% in

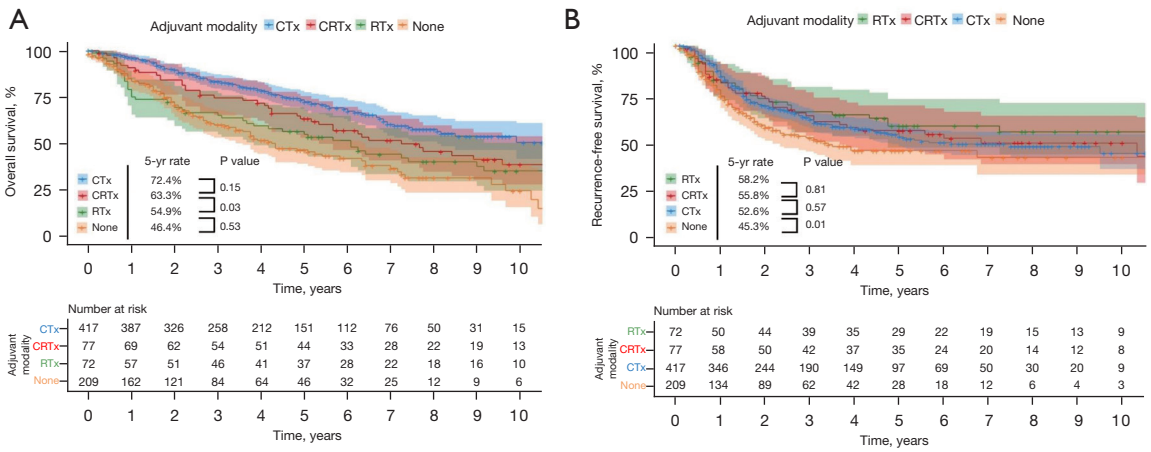

Figure 2 Overall survival (A) and recurrence-free survival (B) based on adjuvant treatment modality of patients pN1 NSCLC after R0 resection. CTx, chemotherapy; CRTx, chemoradiation therapy; RTx, radiation therapy; pN1 NSCLC, pathologic N1 non-small-cell lung cancer; R0, complete resection.

the CRTx group, and 58.2% in the RTx group (*Figure 2B*). The 5-year OS rate and RFS rate was shown in R0-ENE group based on adjuvant treatment modality (Figure S3).

Patients with completely resected pN1 NSCLC were divided according to the performance of adjuvant CTx. In patients who underwent adjuvant CTx, a significant difference between the pure R0 group and R0-ENE group was not found for both OS (P=0.38) and RFS (P=0.28) (*Figure 3A,3B*). Meanwhile, among patients without adjuvant CTx, the presence of ENE was significantly associated with poor OS (P=0.004) (*Figure 3C*), and the RFS had a marginally significant difference (P=0.06) (*Figure 3D*). According to the univariate Cox analysis, the presence of ENE was not a prognostic factor in patients who underwent adjuvant CTx (HR =1.20; 95% CI: 0.80–1.81; P=0.38) (Table S3). However, it was an independent risk factor for patients who did not undergo adjuvant CTx after adjustment for several cofactors through multivariable Cox analysis (HR =1.58; 95% CI: 1.06–2.36; P=0.03) (*Table 3*).

Discussion

In this study, we demonstrated that the presence of ENE was significantly associated with inferior outcomes for both OS and RFS, although complete resection was performed in patients with pN1 NSCLC. Significant differences between pure R0 and R0-ENE were not observed for locoregional recurrence but were for distant metastasis. When patients were divided according to the performance of adjuvant CTx, the prognostic impact of ENE was significant in patients who skipped adjuvant CTx even after adjustment with several cofactors through multivariate Cox analysis. However, it was not significant in patients who underwent adjuvant CTx.

Several studies have reported that the presence of ENE is an important prognostic factor in patients with surgically resected NSCLC (2,11,12). However, those studies performed their analysis without stratification of patients according to resection status. Thus, the clinical impact of ENE in patients whose resection margin is clear remained unclear. In the present study, the importance of ENE was investigated by dividing the patients into three groups according to their resection status: pure R0, R0-ENE, and R1/R2. The findings in this study are in line with previous studies that reported the prognostic significance of ENE and, at the same time, verify for the first time the recently proposed definition of R1 resection status by the IASLC (4,13).

In pN1 NSCLC with a clear resection margin, the significant difference of RFS associated with the presence of ENE was attributed to distant recurrence rather than locoregional recurrence (*Figure 1C,1D*). This means the R0-ENE group might have a relatively more advanced status than the pure R0 group even in the same pathological stage. In fact, the proportion of patients with multiple N1 metastases (pN1b) was significantly higher in the R0-ENE group than the pure R0 group, which is reported as a negative prognostic factor compared to a single N1 metastasis (pN1a) (14,15). However, the presence of ENE

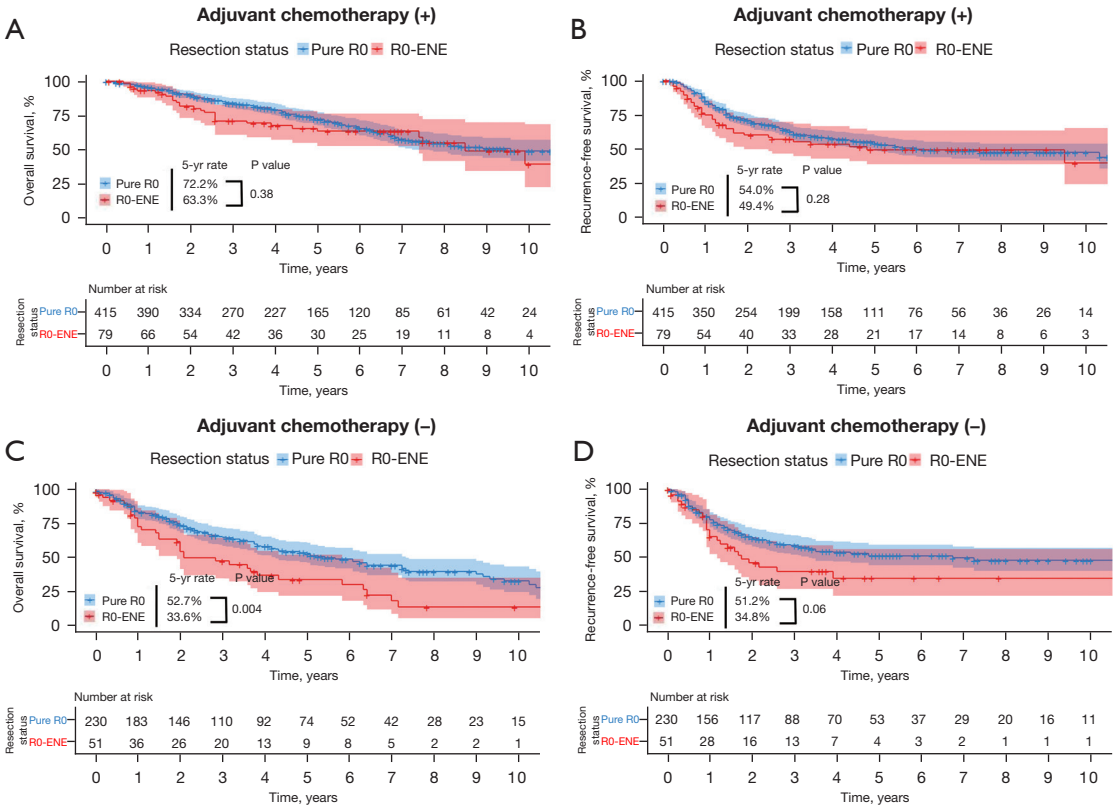

Figure 3 Overall survival (A) and recurrence-free survival (B) based on the ENE status of patients pN1 NSCLC who underwent adjuvant chemotherapy after R0 resection. Overall survival (C) and recurrence-free survival (D) based on the ENE status of patients pN1 NSCLC who did not receive adjuvant chemotherapy after R0 resection. R0, complete resection; ENE, extranodal extension; pN1 NSCLC, pathologic N1 non-small-cell lung cancer.

was still an independent prognostic factor after adjustment by cofactors including subdivided node status (pN1b *vs.* pN1a) in patients with completely resected pN1 NSCLC (HR =1.34; 95% CI: 1.00–1.78; P=0.05) (*Table 2*). Given the different prognosis according to the type of adjuvant therapy, we divided the patients into two groups by whether adjuvant CTx was performed. As a result, a significant prognostic impact of ENE was shown in patients without adjuvant CTx (P=0.004) (*Figure 3C*), but not in those who underwent adjuvant CTx (P=0.38) (*Figure 3A*), which is closely related to distant recurrence.

According to the NCCN guideline, adjuvant CTx is recommended as category 1 for patients with stage IIB (T1abc-T2ab, N1) after R0 resection, and resection + CTx or CRTx is recommended for R1 patients. Similarly, for stage IIIA (T3N1) patients, CTx is recommended after R0 resection, and CRTx is recommended for R1/R2 patients (7). However, for several reasons, these patients could not receive adjuvant therapy in the real world. Previous studies have reported that only 46% to 68% of patients with pN1 NSCLC undergo adjuvant CTx or CRTx, consistent with guideline recommendations (16,17). In our study, 36.3% (281/775) of patients with completely resected pN1 NSCLC did not receive adjuvant CTx, up to 39.2% (51/130) in the R0-ENE group. Reasons for skipping adjuvant CTx among eligible patient include older age (23.5%, n=12/51), poor performance status (23.5%, n=12/51), underlying comorbidities (21.6%, n=11/51), and patient refusal (19.6%, n=10/51). However, considering that the presence of ENE acts as a negative prognostic factor in pN1 NSCLC without adjuvant CTx, we think adjuvant CTx should be recommended more aggressively in R0-ENE than the pure R0 group.

This study has several limitations. First, this study is

Table 3 Multivariable Cox analysis for overall survival after complete surgical resection of patients pN1 NSCLC with and without adjuvant chemotherapy

Variables	Overall survival			
	Adjuvant chemotherapy (+)		Adjuvant chemotherapy (–)	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.03 (1.01–1.06)	<0.001	1.03 (1.01–1.06)	0.002
Sex, male	1.62 (1.06–2.48)	0.03		
Histology				
Adenocarcinoma	1	ref.		
Squamous cell carcinoma	1.59 (1.11–2.27)	0.01		
Others	2.64 (1.52–4.56)	0.001		
Pathological TNM stage				
pII	1	ref.	1	ref.
pIII	1.66 (1.19–2.33)	0.003	1.79 (1.27–2.52)	<0.001
Subdivided node status				
pN1a			1	ref.
pN1b			1.99 (1.25–3.16)	0.004
Extranodal extension				
Negative			1	ref.
Positive			1.58 (1.06–2.36)	0.03

pN1, pathologic N1; NSCLC, non-small-cell lung cancer; HR, hazard ratio; CI, confidence interval; ref., reference; TNM, tumor, node, and metastasis.

a retrospective study conducted in a single institution. Therefore, external validation through multi-center and large sample-size studies is needed in the future. Second, the association with adjuvant treatment cannot be evaluated in more detail due to the lack of data on the specific protocols applied for CTx, RTx and CRTx. Third, there is a lack of data for cancer-related mortality. Fourth, although the detailed status of ENE could affect prognosis, only the presence or absence of ENE was used as prognostic factor (18,19). It is because when referring to the pathology reports of the patients who participated in this study, detailed information on ENE status could not be obtained. However, there are still only a few studies on which methods of describing the extent of ENE are most appropriate for NSCLC (12,20). Therefore, follow-up studies are needed regarding the detailed status of ENE. Fifth, there are significantly more pN1b patients in the R0-ENE group. Although the status of LN metastasis had no significant correlation with OS in the subgroup analysis, the relatively small sample size for pN1b ENE (+) patients (N=33) may have reduced statistical power (Figure S4). Therefore, further research is needed to overcome these limitations.

Conclusions

For patients with pN1 NSCLC, the presence of ENE was a negative prognostic factor for both OS and RFS even after complete resection. When ENE is confirmed postoperatively in a patient with R0 resection, it should be evaluated as an R1 resection in accordance with the recommendation in IASLC. A negative prognostic effect of ENE was found only in patients who skipped adjuvant CTx, which might be due to an increased rate of distant metastasis. Consequently, even for patients with borderline medical conditions, adjuvant CTx might be considered more actively in completely resected pN1 NSCLC with the presence of ENE.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-150/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-150/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-150/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-150/coif). SC serves as an unpaid editorial board member of *Journal of Thoracic Disease* from October 2022 to September 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Asan Medical Center (No. 2021-1845) and individual consent for this retrospective analysis was waived.

References

1. Liu W, Shao Y, Guan B, et al. Extracapsular extension is a powerful prognostic factor in stage IIA-IIIA non-small cell lung cancer patients with completely resection. Int J Clin Exp Pathol 2015;8:11268-77.
2. Lee YC, Wu CT, Kuo SW, et al. Significance of extranodal extension of regional lymph nodes in surgically resected non-small cell lung cancer. Chest 2007;131:993-9.
3. Moretti L, Yu DS, Chen H, et al. Prognostic factors for resected non-small cell lung cancer with Pn2 status: implications for use of postoperative radiotherapy. Oncologist 2009;14:1106-15.
4. Rami-Porta R, Wittekind C, Goldstraw P, et al. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25-33.
5. Rami-Porta R, Wittekind C, Goldstraw P. Complete Resection in Lung Cancer Surgery: From Definition to Validation and Beyond. J Thorac Oncol 2020;15:1815-8.
6. Brierley JD, Gospodarowicz MK, Wittekind C. UICC TNM Classification of Malignant Tumours. 8th edition. Oxford: Wiley-Blackwell, 2017:10-1.
7. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. J Natl Compr Canc Netw 2021;19:254-66.
8. Yun JK, Lee GD, Choi S, et al. The addition of radiotherapy to adjuvant chemotherapy has a combinatorial effect in Pn2 non-small cell lung cancer only with extranodal invasion or multiple N2 metastasis. Lung Cancer 2021;155:94-102.
9. Detterbeck FC, Boffa DJ, Kim AW, et al. The Eighth Edition Lung Cancer Stage Classification. Chest 2017;151:193-203.
10. Bernard A, Rivera C, Pages PB, et al. Risk model of in-hospital mortality after pulmonary resection for cancer: a national database of the French Society of Thoracic and Cardiovascular Surgery (Epithor). J Thorac Cardiovasc Surg 2011;141:449-58.
11. Moon DH, Choi JH, Yang HC, et al. Size and extranodal extension of metastatic lymph nodes in lung adenocarcinoma. J Thorac Dis 2020;12:6514-22.
12. Luchini C, Veronese N, Nottegar A, et al. Extranodal extension of nodal metastases is a poor prognostic moderator in non-small cell lung cancer: a meta-analysis. Virchows Arch 2018;472:939-47.
13. Edwards JG, Chansky K, Van Schil P, et al. The IASLC Lung Cancer Staging Project: Analysis of Resection Margin Status and Proposals for Residual Tumor Descriptors for Non-Small Cell Lung Cancer. J Thorac Oncol 2020;15:344-59.
14. Yun JK, Lee GD, Choi S, et al. Comparison between lymph node station- and zone-based classification for the future revision of node descriptors proposed by the

International Association for the Study of Lung Cancer in surgically resected patients with non-small-cell lung cancer. Eur J Cardiothorac Surg 2019;56:849-57.
15. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:1675-84.
16. Farrow NE, An SJ, Speicher PJ, et al. Disparities in guideline-concordant treatment for node-positive, non-small cell lung cancer following surgery. J Thorac Cardiovasc Surg 2020;160:261-71.e1.
17. Toubat O, Atay SM, Kim AW, et al. Disparities in Guideline-Concordant Treatment for Pathologic N1 Non-Small Cell Lung Cancer. Ann Thorac Surg 2020;109:1512-20.
18. Almulla A, Noel CW, Lu L, et al. Radiologic-Pathologic Correlation of Extranodal Extension in Patients With Squamous Cell Carcinoma of the Oral Cavity: Implications for Future Editions of the TNM Classification. Int J Radiat Oncol Biol Phys 2018;102:698-708.
19. Shaw RJ, Lowe D, Woolgar JA, et al. Extracapsular spread in oral squamous cell carcinoma. Head Neck 2010;32:714-22.
20. Bhattacharya P, Mukherjee R. Lymph node extracapsular extension as a marker of aggressive phenotype: Classification, prognosis and associated molecular biomarkers. Eur J Surg Oncol 2021;47:721-31.

Cite this article as: Yoon SK, Yun JK, Lee GD, Choi S, Kim HR, Kim YH, Park SI, Kim DK. Prognostic significance of extranodal extension in patients with pathologic N1 non-small cell lung cancer undergoing complete resection. J Thorac Dis 2023;15(6):3245-3255. doi: 10.21037/jtd-23-150

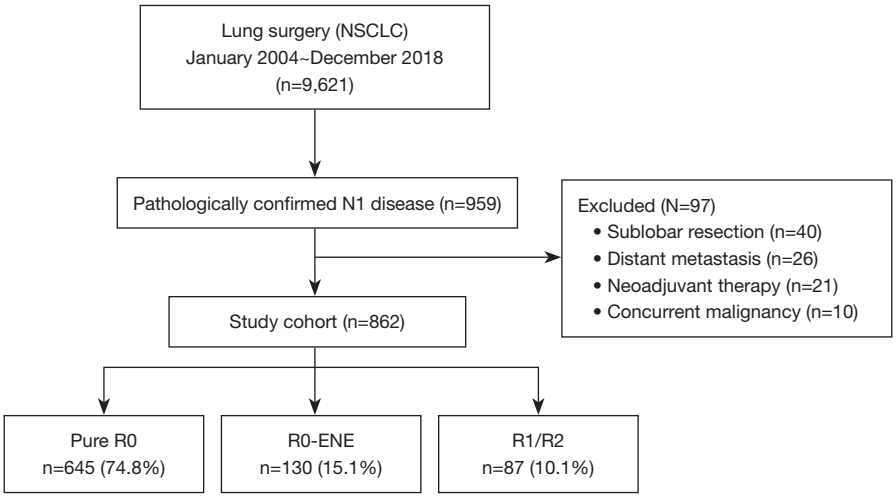

Figure S1 Flow diagram of patient inclusion in the study. NSCLC, non-small-cell lung cancer; R0, complete resection; ENE, extranodal extension; R1/R2, incomplete resection.

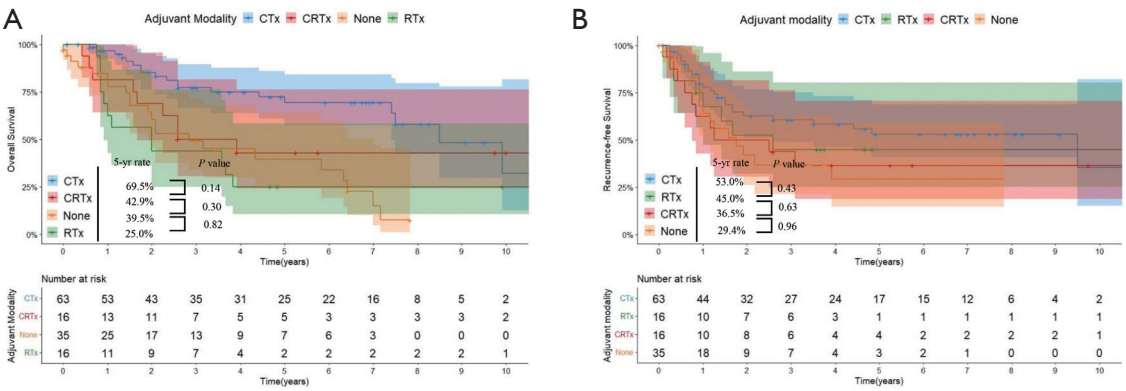

Figure S2 Overall survival (A) recurrence-free survival (B) of the R0-ENE and R1 groups. CTx, chemotherapy; CRTx, chemoradiation therapy; RTx, radiation therapy; R0-ENE, R0 with ENE; ENE, extranodal extension; R0, complete resection; R1, incomplete resection.

https://dx.doi.org/10.21037/jtd-23-150

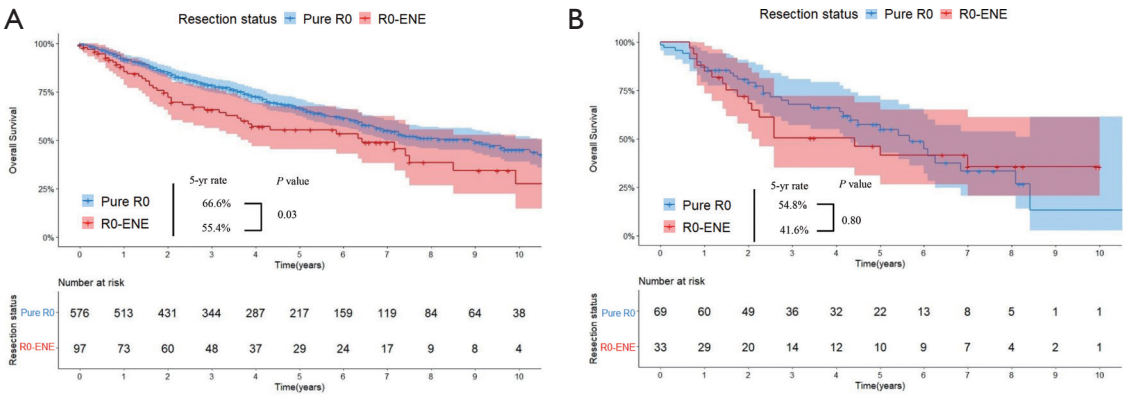

Figure S3 Overall survival (A) recurrence-free survival (B) based on adjuvant treatment modality of patients with pN1 NSCLC diagnosed R0-ENE. pN1 NSCLC, pathologic N1 non-small-cell lung cancer; R0-ENE, R0 with ENE; ENE, extranodal extension; R0, complete resection.

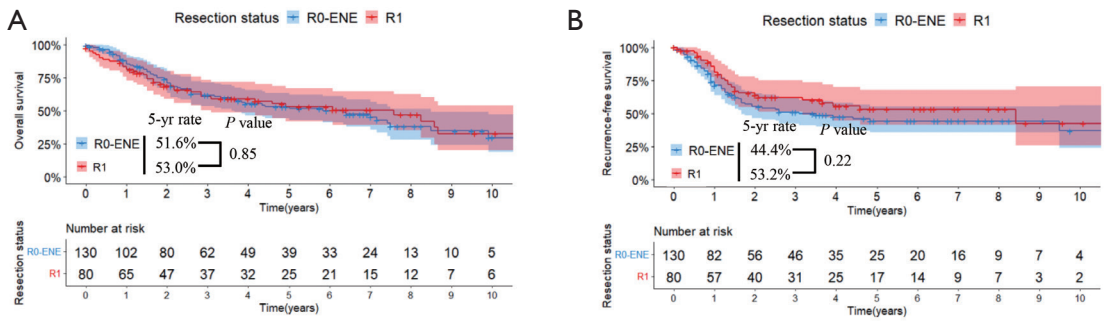

Figure S4 Overall survival of patients pN1a (A) and pN1b (B) NSCLC who underwent R0 resection. R0, complete resection; ENE, extranodal extension; R1, incomplete resection; pN1, pathologic N1; NSCLC, non-small-cell lung cancer.

https://dx.doi.org/10.21037/jtd-23-150

Table S1 Baseline characteristics of incomplete resection patients

Characteristics	R1 (N=80)	R2 (N=7)	P value
Age (years)	63.7±8.4	66.3±6.0	0.43
Sex, male	75 (95.0)	6 (85.7)	0.98
Never smoker	4 (5.0)	1 (14.3)	0.87
Comorbidity			0.41
0	32 (40.0)	1 (14.3)	
1	32 (40.0)	4 (57.1)	
≥2	16 (20.0)	2 (28.6)	
Operative method			0.26
Lobectomy	39 (48.8)	6 (85.7)	
Bilobectomy	13 (16.2)	0 (0.0)	
Pneumonectomy	15 (18.8)	1 (14.3)	
Sleeve lobectomy	13 (16.2)	0 (0.0)	
Preoperative PFT values			
FEV1 (%)	78.7±14.9	74.6±19.0	0.50
DLCO (%)	79.9±18.0	82.3±23.2	0.74
Cell type			0.54
Adenocarcinoma	59 (73.8)	6 (85.7)	
Squamous cell carcinoma	12 (15.0)	0 (0.0)	
Others	9 (11.2)	1 (14.3)	
The number of harvested LNs	30.8±13.5	28.7±16.1	0.70
Pathological T factor			0.97
pT1	12 (15.0)	1 (14.3)	
pT2	28 (35.0)	3 (42.9)	
pT3	23 (28.8)	2 (28.6)	
pT4	17 (21.2)	1 (14.3)	
Pathological TNM stage			1.00
pII	40 (50.0)	4 (57.1)	
pIII	40 (50.0)	3 (42.9)	
Adjuvant treatment			0.44
None	12 (15.0)	1 (14.3)	
CTx	8 (10.0)	2 (28.6)	
RTx	27 (33.8)	1 (14.3)	
CRTx	33 (41.2)	3 (42.9)	
Subdivided node status			0.83
pN1a	66 (82.5)	5 (71.4)	
pN1b	14 (17.5)	2 (28.6)	

Values are presented as numbers (%) or mean ± standard deviation unless otherwise indicated. R1/R2, incomplete resection. PFT, pulmonary function test; FEV1, forced expiratory volume in 1s; DLCO, diffusing capacity to carbon monoxide; LNs, lymph nodes; TNM, tumor, node, and metastasis; CTx, chemotherapy; RTx, radiation therapy; CRTx, chemoradiation therapy.

https://dx.doi.org/10.21037/jtd-23-150

Table S2 Univariable Cox analysis of patients pN1 NSCLC after complete surgical resection

Variables	Overall survival		Recurrence-free survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.05 (1.03–1.06)	<0.001	1.00 (0.99–1.01)	0.70
Sex				
Female	1	ref.	1	ref.
Male	1.52 (1.15–2.01)	0.003	0.84 (0.66–1.06)	0.14
Smoking history				
No	1	ref.	1	ref.
Yes	1.37 (1.06–1.77)	0.02	0.79 (0.63–0.99)	0.04
Comorbidity				
0	1	ref.	1	ref.
1	1.15 (0.90–1.46)	0.28	0.86 (0.68–1.09)	0.21
≥2	1.24 (0.90–1.71)	0.18	0.90 (0.65–1.24)	0.50
Operative method				
Lobectomy	1	ref.	1	ref.
Bilobectomy	1.12 (0.78–1.61)	0.54	0.78 (0.52–1.17)	0.23
Pneumonectomy	1.01 (0.71–1.44)	0.97	0.74 (0.50–1.10)	0.13
Sleeve lobectomy	0.63 (0.35–1.13)	0.12	0.43 (0.23–0.80)	0.008
Preoperative PFT values				
FEV1	0.99 (0.99–1.00)	0.07	1.00 (0.99–1.01)	0.87
DLCO	0.99 (0.98–0.99)	<0.001	1.00 (0.99–1.00)	0.24
Cell type				
Adenocarcinoma	1	ref.	1	ref.
Squamous cell carcinoma	0.93 (0.74–1.18)	0.56	1.95 (1.53–2.48)	<0.001
Others	1.90 (1.30–2.77)	0.001	2.00 (1.32–3.03)	0.001
Pathological T factor				
pT1	1	ref.	1	ref.
pT2	1.04 (0.77–1.41)	0.78	1.14 (0.85–1.52)	0.39
pT3	1.89 (1.36–2.63)	<0.001	1.98 (1.43–2.74)	<0.001
pT4	1.66 (1.05–2.60)	0.03	1.38 (0.87–2.19)	0.17
Pathological TNM stage				
pII	1	ref.	1	ref.
pIII	1.80 (1.42–2.27)	<0.001	1.67 (1.33–2.10)	<0.001
Adjuvant treatment				
None	1	ref.	1	ref.
CTx	0.42 (0.32–0.55)	<0.001	0.73 (0.57–0.94)	0.02
RTx	0.71 (0.49–1.01)	0.06	0.64 (0.42–0.98)	0.04
CRTx	0.60 (0.42–0.86)	0.005	0.71 (0.48–1.06)	0.09
Subdivided node status				
pN1a	1	ref.	1	ref.
pN1b	1.54 (1.14–2.08)	0.005	1.95 (1.48–2.57)	<0.001
Extranodal extension				
Negative	1	ref.	1	ref.
Positive	1.45 (1.10–1.91)	0.009	1.34 (1.02–1.77)	0.04

pN1, pathologic N1; NSCLC, non-small-cell lung cancer; HR, hazard ratio; CI, confidence interval; ref., reference; PFT, pulmonary function test; FEV1, forced expiratory volume in 1s; DLCO, diffusing capacity to carbon monoxide; TNM, tumor, node, and metastasis; CTx, chemotherapy; RTx, radiation therapy; CRTx, chemoradiation therapy.

https://dx.doi.org/10.21037/jtd-23-150

Table S3 Univariable Cox analysis for overall survival in patients pN1 NSCLC with and without adjuvant chemotherapy after complete surgical resection

Variable	Overall survival			
	Adjuvant chemotherapy (+)		Adjuvant chemotherapy (–)	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.04 (1.02–1.06)	<0.001	1.03 (1.01–1.05)	0.004
Sex				
Female	1	ref.	1	ref.
Male	1.61 (1.09–2.38)	0.02	1.49 (1.01–2.22)	0.05
Smoking history				
No	1	ref.	1	ref.
Yes	1.29 (0.91–1.82)	0.15	1.46 (1.00–2.13)	0.05
Comorbidity				
0	1	ref.	1	ref.
1	1.14 (0.80–1.61)	0.47	0.93 (0.66–1.32)	0.69
≥2	1.62 (1.06–2.48)	0.03	0.77 (0.47–1.25)	0.29
Operative method				
Lobectomy	1	ref.	1	ref.
Bilobectomy	0.98 (0.59–1.63)	0.94	1.31 (0.77–2.22)	0.32
Pneumonectomy	0.84 (0.48–1.47)	0.54	1.01 (0.63–1.62)	0.97
Sleeve lobectomy	0.46 (0.19–1.13)	0.09	0.94 (0.44–2.03)	0.88
Preoperative PFT values				
FEV1	0.99 (0.98–1.01)	0.28	1.00 (0.99–1.01)	0.32
DLCO	0.99 (0.98–1.00)	0.03	0.99 (0.98–1.00)	0.002
Cell type				
Adenocarcinoma	1	ref.	1	ref.
Squamous cell carcinoma	1.12 (0.80–1.56)	0.51	0.89 (0.63–1.26)	0.52
Others	2.56 (1.49–4.40)	<0.001	1.35 (0.80–2.28)	0.27
Pathological T factor				
pT1	1	ref.	1	ref.
pT2	0.89 (0.60–1.33)	0.58	1.30 (0.832–2.03)	0.25
pT3	1.70 (1.08–2.68)	0.02	2.13 (1.32–3.46)	0.002
pT4	1.90 (1.05–3.44)	0.03	1.43 (0.71–2.88)	0.32
Pathological TNM stage				
pII	1	ref.	1	ref.
pIII	1.93 (1.39–2.67)	<0.001	1.59 (1.13–2.23)	0.005
Subdivided node status				
pN1a	1	ref.	1	ref.
pN1b	1.34 (0.89–2.03)	0.16	1.62 (1.15–2.26)	0.005
Extranodal extension				
Negative	1	ref.	1	ref.
Positive	1.20 (0.80–1.81)	0.38	1.75 (1.19–2.57)	0.004

pN1, pathologic N1; NSCLC, non-small-cell lung cancer; HR, hazard ratio; CI, confidence interval; ref., reference; PFT, pulmonary function test; FEV1, forced expiratory volume in 1s; DLCO, diffusing capacity to carbon monoxide; TNM, tumor, node, and metastasis.

https://dx.doi.org/10.21037/jtd-23-150