

Prognostic Factors for Surgically Resected N2 Non-small Cell Lung Cancer

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Purpose: Non-small cell lung cancers (NSCLCs) with pathologically documented ipsilateral mediastinal lymph node (LN) metastases (pN2) are a broad spectrum of diseases. We retrospectively analyzed prognostic factors for cases of pN2 NSCLC treated by surgical resection. **Methods:** Clinicopathological data were reviewed for consecutive 121 patients who underwent anatomical pulmonary resection with mediastinal LN sampling or dissection for pN2 NSCLC over a 15-year period.

Results: The 5-year survival rate for all patients was 29.9%. Clinical N status, curability, surgical procedure and adjuvant chemotherapy were favorable prognostic factors in univariate analysis, with 5-year survival rates of 35.0% for cN0/1 vs. 17.7% for cN2/3 cases; 33.1% for R0 vs. 14.7% for R1/2 resection; 31.5% for lobectomy vs. 25.0% for bilobectomy and 15.6% for pneumonectomy; and 72.7% with adjuvant chemotherapy vs. 23.8% without adjuvant chemotherapy. Survival did not differ significantly based on gender, age, smoking status, clinical T status, tumor location, histology, skip metastasis, subcarinal LN metastasis, or number of involved N2 levels. In multivariate analysis, adjuvant chemotherapy, R0 resection, and lobectomy emerged as independent favorable prognostic factors.

Conclusion: Complete resection using lobectomy and adjuvant chemotherapy are favorable prognostic factors in cases of pN2 NSCLC.

Keywords: carcinoma non-small-cell lung, thoracic surgery, survival analysis, lymph nodes

Introduction

Non-small cell lung cancers (NSCLCs) with pathologically documented ipsilateral mediastinal lymph node (LN) metastases (pN2) are a broad spectrum of diseases ranging from microscopic metastasis identified after a curative operation to bulky multiple LN metastases that

are considered to be unresectable.¹⁾ Multidisciplinary evaluation on an individual basis is necessary to establish the best treatment option for pN2 NSCLC.²⁾ Definitive chemoradiotherapy is the current mainstay treatment and surgery improves survival and is beneficial for selected patients in bi- or trimodal therapy. Thus, determination of favorable prognostic factors in pN2 NSCLC is important for appropriate selection of patients for surgery. In this study, we retrospectively analyzed prognostic factors among patients who underwent surgical resection for pN2 NSCLC over 15 years at our institution.

Materials and Methods

The study was approved by the institutional review board. Written informed consent from each patient was waived because of the retrospective nature of the study. Clinical and pathological data were collected from medical

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records of patients who underwent surgical resection for NSCLC from January 1995 to December 2009 at our hospital. A total of 121 consecutive patients were treated by anatomical pulmonary resection with mediastinal LN sampling or dissection with pathologically proven N2 involvement. This cohort represented approximately 18% of NSCLC surgical cases during the 15 years of the study.

Preoperative examinations included chest and abdominal computed tomography (CT) and brain magnetic resonance imaging with contrast medium, unless contraindicated. Positron emission tomography (PET) scans became available after October 2004. Mediastinoscopy was not performed. Therapeutic options for each patient were discussed in tumor board meetings held once a week. After 2004, adjuvant chemotherapy after complete resection was recommended for patients younger than 75 years with performance status 0-1 and no severe comorbidities according to the guideline.³⁾

Staging was defined according to the seventh tumor, node and metastasis (TNM) classification for lung cancer.⁴⁾ During the study period we adopted the Naruke map for classification of LN level.⁵⁾ The International Association for the Study of Lung Cancer (IASLC) map, which is currently used in practice, defines the whole subcarinal LN as level 7⁶⁾ and level 7 LN in the IASLC map contains both levels 7 and 10 LN in the Naruke map. Because it is difficult to define the exact location of metastatic level 10 LN through a retrospective review of pathological reports, we classified cases with level 10 LN metastasis as N1 in this study.

Resection curability was classified as R0, no residual tumor; R1, microscopic residual tumor; and R2, macroscopic residual tumor.⁴⁾ Overall survival was defined as the time from the day of surgery until death due to all causes. Patients who were alive at their last visit or lost during the follow-up period were regarded as censored cases. Survival curves were drawn by the Kaplan-Meier method and a log-rank test was used for comparison of survival between two groups. Multivariate analysis using Cox proportional hazard model was performed to examine the effect of several variables on survival. Analyses were performed using SPSS ver. 11.0 for Windows (SPSS Inc., Chicago, Illinois, USA) or JMP 10 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Clinical characteristics for the 121 patients are shown in **Table 1**. The tumor location was the right upper lobe

Table 1 Clinical Characteristics

Factor		Number
Gender	Male	81
	Female	40
Age	Mean, Years	66.6
	<75	96
	≥75	25
Smokers		79
Cell Type	Adenocarcinoma	87
	Squamous	29
	Others	5
Curability	R0	101
	R1/2	20
Surgical Procedure	Lobectomy	99
	Bilobectomy	12
	Pneumonectomy	10
Clinical T Factor	cT1/2	111
	cT3/4	10
Clinical N Factor	cN0/1	85
	cN2/3	36
Subcarinal LN Metastasis		54
Skip Metastasis		40
Involved Levels	Single	33
	Multiple	88
Adjuvant Chemotherapy		20

R0: no residual tumor; R1: microscopic residual tumor; R2: macroscopic residual tumor; LN: lymph node

in 35 patients, right middle lobe in three patients, right lower lobe in 32 patients, left upper lobe in 33 patients, and left lower lobe in 18 patients.

As for preoperative staging, bi-lobectomy and pneumonectomy group (n = 22) included 20 patients (90.9%) with clinical T2 or T3, while lobectomy group (n = 99) had 53 patients (53.5%). Frequency was higher in the former group ($p = 0.0013$, Fisher's exact test). In addition, bi-lobectomy and pneumonectomy group included 14 patients (63.6%) with clinical N1-3, while lobectomy group had 39 patients (39.4%). Frequency tended to be higher in the former group ($p = 0.00562$, Fisher's exact test).

The mean follow-up period for the 44 surviving patients was 4.4 years. Causes of death for the other 77 patients included the original lung cancer in 67 cases (87.0%), other causes unrelated to lung cancer in 9 cases (11.7%), and an unknown cause in one case (1.3%).

The 5-year survival rate for all patients was 29.9% (95% confidence interval, 21.3–40.2%) (**Fig. 1**). Clinical N status (**Fig. 2A**), curability (**Fig. 2B**), surgical procedure (**Fig. 2C**), and adjuvant chemotherapy (**Fig. 2D**) were prognostic factors in univariate analysis based on 5-year survival rates of 35.0% for cN0/1 vs. 17.7% for cN2/3 cases ($p = 0.0235$); 33.1% for R0 vs. 14.7% for R1/2 resection ($p = 0.0004$); 31.5% for lobectomy vs. 25.0%

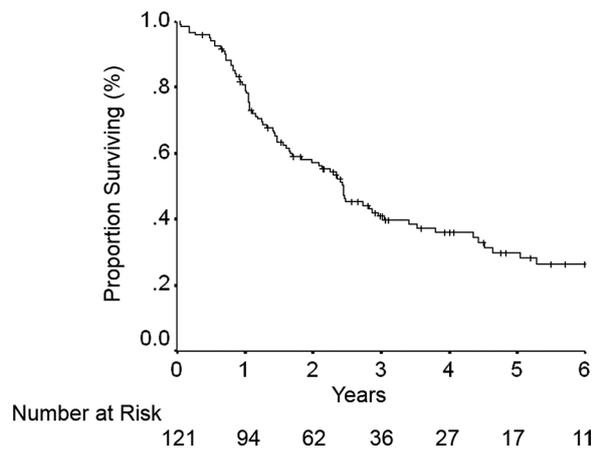


Fig. 1 Survival curve for all 121 patients. The 5-year survival rate was 29.9%.

for bilobectomy and 15.6% for pneumonectomy ($p = 0.0091$); and 72.7% with adjuvant chemotherapy vs. 23.8% without adjuvant chemotherapy ($p = 0.0022$). Survival did not differ significantly based on gender, age, smoking status, clinical T status, tumor location, histology, skip metastasis, subcarinal LN metastasis, or the number of involved N2 levels. The 5-year survival rates were 32.5% and 29.0% for single- and multi-level N2 cases, respectively ($p = 0.698$). In multivariate analysis, adjuvant chemotherapy, R0 resection, and lobectomy emerged as independent favorable prognostic factors for survival (Table 2).

Discussion

The indications for surgery for pN2 NSCLC are uncertain. Two randomized trials, the EORTC-08941 study and the Intergroup trial 0139, have evaluated the role of surgery for pN2 NSCLC, but neither study provided strong support for this treatment.^{7,8} The EORTC-08941 study was limited in this respect because of inclusion of patients with unresectable stage IIIA-N2 NSCLC.⁷ The Intergroup trial 0139 demonstrated improved progression-free survival in patients who received concurrent chemoradiotherapy followed by surgery, but found no difference in overall survival between bimodal and trimodal therapy. An unplanned exploratory analysis in the Intergroup trial 0139 showed significantly improved overall survival with addition of lobectomy to chemoradiotherapy compared to chemoradiotherapy alone, whereas the same survival benefit was not seen in patients who underwent pneumonectomy.⁸

The results of these two trials suggest that surgery may be beneficial for selected patients with pN2 NSCLC. Therefore, we conducted this retrospective study to determine favorable prognostic factors for the purpose of appropriate selection of patients who may be most suitable for surgery. The significant prognostic factors repeatedly reported in previous studies of pN2 NSCLC are complete resection, lower T status, single-level N2 involvement, and clinical N0 or N1 status determined by CT.⁹⁻¹⁵ All of these factors were included in the current analysis of resection cases.

The 5-year survival rate for all pN2 NSCLC cases in our study was 29.9%, which is comparable to the survival rates in previous reports ranging from 18% to 31%.⁹⁻¹⁴ Our R0 resection rate of 83.5% was also consistent with the 82.5% rate found in a Japanese lung cancer registry study in 2004.¹⁶ Our results clearly show that thorough preoperative and intraoperative evaluations are needed to ensure complete surgical resection of pN2 NSCLC because successful R0 resection is a significant prognostic factor. Survival after bilobectomy or pneumonectomy was poor in our study. The 5-year survival rate for pneumonectomy cases was 15.6% in our study within ranges of previous studies.¹ Previous results are inconsistent because of multiple confounding factors such as a high T status and bulky N1 nodes for cases treated with pneumonectomy and the meta-analyses did not demonstrate that the surgical procedure was a repeated significant prognostic factor.¹ Some author insisted that pneumonectomy offered a reasonable outcome.¹ Based on these findings, we believe that bilobectomy or pneumonectomy should not be a contraindication for N2 NSCLC if complete resection is possible, but an alternative treatment such as sleeve lobectomy is preferable.

After the International Adjuvant Lung Cancer Trial showed that cisplatin-based adjuvant chemotherapy improved survival in 2004, adjuvant chemotherapy has become standard for surgically resected stage II-IIIa NSCLC.¹⁷ Pooled analysis including five trials of cisplatin-based adjuvant chemotherapy showed an absolute benefit of 5.4% at 5 years.¹⁸ Adjuvant radiotherapy for completely resected pathological stage IIIa NSCLC is not performed at our institution. Multivariate analysis in our study showed that adjuvant chemotherapy was a favorable prognostic factor for survival, with an associated improvement of the 5-year survival rate of 48.9%, which is well beyond previously reported benefits of adjuvant chemotherapy. This result deserves further consideration, but might have been biased by selection of patients with

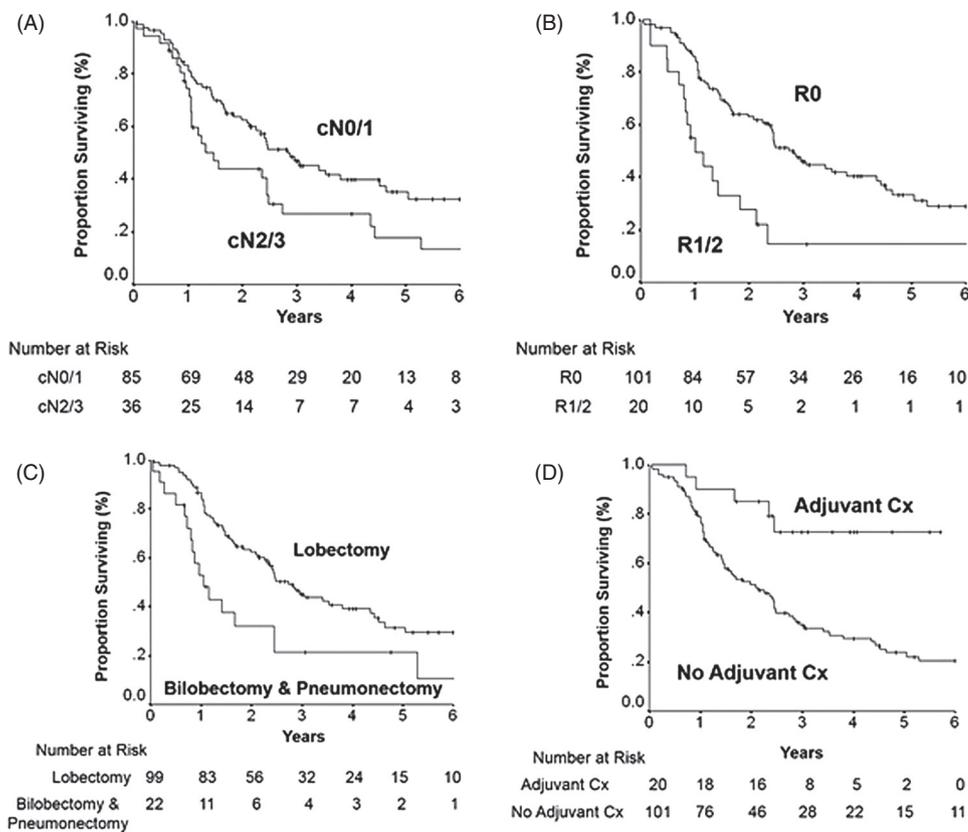


Fig. 2 (A) Survival curves according to clinical N categories. The 5-year survival rates were 35.0% for cN0/1 vs. 17.7% for cN2/3 cases ($p = 0.0235$). (B) Survival curves according to curability status. The 5-year survival rates were 33.1% for R0 vs. 14.7% for R1/2 resection ($p = 0.0004$). (C) Survival curves according to surgical procedure. The 5-year survival rates were 31.5% for lobectomy vs. 21.4% for bilobectomy and pneumonectomy combined ($p = 0.0056$). (D) Survival curves according to use of adjuvant chemotherapy. The 5-year survival rates were 72.7% with adjuvant chemotherapy vs. 23.8% without adjuvant chemotherapy ($p = 0.0022$). Cx: Chemotherapy.

Table 2 Multivariate Analysis

Factor	Hazard Ratio	95% Confidence Interval		<i>p</i> Value
Adjuvant Chemotherapy	3.663	1.471	9.119	0.005
Curability	2.152	1.210	3.827	0.009
Surgical Procedure	2.008	1.151	3.502	0.014

a good performance status and no serious comorbidities who were generally more suitable for receiving adjuvant chemotherapy. Shukuya, et al. reported administration of adjuvant chemotherapy in only 19 of 55 patients (34.5%) who underwent surgery for pathological stage IIA–IIIA NSCLC, with the other patients either refusing treatment or having no indication for treatment.¹⁹⁾

Several studies have found that multi-level N2 involvement and number of involved nodal zones are poor prognostic factors for survival in pN2 NSCLC patients, as indicated by the IASLC staging project.^{20,21)} In contrast,

single-level N2 involvement is a favorable prognostic factor even in patients with bulky, namely greater than 2 cm in short-axis diameter, N2 NSCLC.²²⁾ However, our results showed overlap of survival curves for single- and multi-level N2 NSCLC. In the ECOG 3590 trial, which was a randomized prospective trial of adjuvant therapy for patients with completely resected stage II or stage IIIA NSCLC, Keller, et al. found that mediastinal LN dissection identified more patients with multi-level N2 involvement compared to systematic sampling, while stage classifications were the same.²³⁾ Therefore, the quality of

our surgical evaluations of mediastinal LN metastases may have affected the results of the current study.

Another limitation of the study was the lengthy time-frame, during which major changes in therapeutic strategies and important advances in radiological modalities occurred. NCSLC with clinical N2 involvement was primarily treated surgically during the early years of the study, but chemoradiotherapy has now become the standard treatment based on the latest available evidence.²⁾ In addition, PET scans and adjuvant chemotherapy were not established practices at the beginning of the study period.

Conclusion

Our retrospective study showed that adjuvant chemotherapy, complete resection, and surgery by lobectomy are favorable prognostic factors for overall survival of patients with pN2 NSCLC. These results provide useful information for decisions on surgical resection of pN2 NSCLC in a multidisciplinary treatment approach.

Disclosure Statement

The authors declare that there is no conflict of interest.

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