Survival and Prognostic Factors in Resected cN2-pN2 Non-Small-Cell Lung Cancer

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Abstract

The aims of this study were to reveal the prognostic factors of cN2-pN2 and to define the criteria to select appropriate surgical candidates.

From 1982 to 1997, 40 patients with cN2 were operated on, who actually had pN2. We retrospectively analyzed the survival of these 40 patients by means of a univariate and multivariate analysis.

The overall 5-year survival rate of the cN2-pN2 patients was 21%. According to multivariate analysis, single metastatic MLN station, absence of parietal pleural involvement and low CEA level improved the prognosis. The 5-year survival rate of the patients with all of the three prognostic factors (n=6) was 67% and that of those with two prognostic factors (n=9) was 21%, compared with 0% in those with one or none (n=24) ($p<0.01$ and $p=0.05$, respectively). Even in cN2-pN2, patients with these three prognostic factors can benefit from primary surgical treatment, and can have long-term survival.

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Introduction

There is a controversy in the literature about the indication of surgical treatment for pathological N2 (pN2) non-small cell lung cancer (NSCLC). Many series have reported 5-year survival rates ranging from 10% to 41% after primary surgery (1-4) and ranging from 17% to 32% after induction therapy followed by surgery (5,6), which were not satisfactory. Particularly, preoperatively discovered pN2 (cN2-pN2), in comparison with preoperatively unsuspected pN2 (cN0-1-pN2), is mostly reported to be associated with poor results, for which surgical treatment is contraindicated (4,7). However, selected groups of patients with pN2 have been shown to survive for five or more years after surgical treatment (1-3). For patients with pN2, surgical treatment is the only modality to obtain long-term survival. The opportunity for cure should not be denied because of rigid policies in surgical indication.

This retrospective study reports the survival of 40 patients with resection of cN2-pN2. By means of a univariate and multivariate analysis, it also seeks the prognostic factors and candidates for surgery.

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Materials and Methods

a) Eligibility criteria: From September 1982 to March 1997, 94 patients clinically diagnosed to have N2 (cN2) NSCLC underwent resection at Hokkaido University Hospital. Prior to March 1997, cN2 patients (except bulky cN2) with otherwise operable NSCLC had been considered to be candidates for surgical treatment in our institution. Forty patients among this patient population who were actually with pN2 comprised this study group.

b) Demographic characteristics: The patient population consisted of 28 males and 12 females with a mean age of 61 years (range 36 to 80 years).

c) Staging classification: All patients were staged clinically according to the TNM classification of the International Union Against Cancer (UICC).

d) Diagnostic procedures: Clinical staging was preoperatively done based on information from chest roentogenography, bronchoscopy, CT scan of the chest and abdomen, magnetic resonance imaging (MRI) or CT scan of the brain, and bone scan.

e) Mediastinal staging: The clinical diagnosis of mediastinal lymph node (MLN) involvement was determined by staff radiologists and based on the CT findings. MLNs larger than 1 cm, 1.5 cm for subcarinal nodes, in short-axis diameter were defined as positive on CT (8,11). Routine mediastinoscopic examination was not performed except in patients with suspected contralateral nodal involvement.

f) Surgical technique: In all the patients, a posterolateral thoracotomy was the standard approach. The technique of resection of the primary lung tumor consisted of no less than lobectomy combined with systemic mediastinal lymphadenectomy.

g) Adjuvant therapy: Adjuvant treatment was applied in 34 patients, and doses of postoperative mediastinal radiation were 40 to 50 Gy; chemotherapeutic agents used were predominantly vindesine sulfate, cisplatin or mitomycin-C combined with fluorouracil.

h) Statistical analysis: Survival rate was calculated according to the Kaplan-Meier method. For univariate analysis, the log-rank statistics were used. A Cox regression analysis was carried out by a conditional backward procedure and processing categorical covariates with the deviation method. A significance level of 0.05 was used for adding and deleting. The data were considered significant when the p-value did not exceed 0.05.

Results

Postoperative survival of cN2 patients classified by the pN-stage are shown in Figure 1. The 5-year survival rate of the 40 patients with cN2-pN2 was 20.9%.

A number of factors have been studied to assess their influence on survival after resection of cN2-pN2 disease. Patients with low CEA level had 5-year survival of 35.2%; 5-year survival was nil in high CEA level (p=0.03, Table 1). Involvement of the parietal pleura, which represents invasion of chest wall, diaphragm, mediastinal pleura and parietal pericardium, had some importance; patients without involvement of parietal pleura had a better 5-year survival (25.0%) than those with involvement of parietal pleura (0%) (p=0.06, Table 2). Metastasis to subcarinal nodes was associated with poorer prognosis than no metastasis to subcarinal nodes: 5.9% vs 32.1%, respectively (p=0.03, Table 3). There was a trend towards improved survival of patients with metastasis to only one MLN station compared with those who had metastasis to two or more MLN stations: 42.9% vs 6.3%, respectively (p=0.09; Table 3). Also, a trend toward survival advantage was seen in patients who had metastasis to one or two MLNs than in those with metastasis to three or more MLNs: 32.6% vs 8.3%, respectively (p=0.07, Table 3).

For Cox model, all the prognostic factors were used as cova-

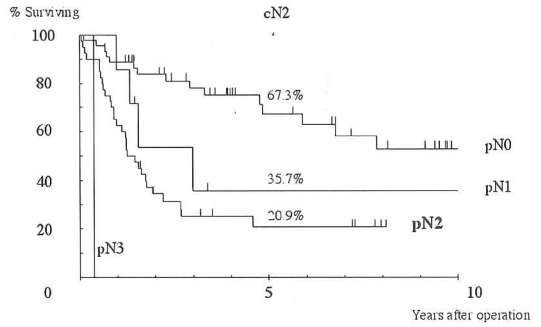

Figure 1. *Kaplan-Meiyer survival curves of clinical N2 (cN2) patients classified by the pathological N (pN) stage. Five-year survival rates are shown in the figure. [pN0, patients with cN2 but postsurgically pN0 (n=45); pN1, cN2 but postsurgically pN1 (n=8); pN2, cN2 and postsurgically pN2 (n=40); pN3, cN2 but postsurgically pN3 (n=1)].*

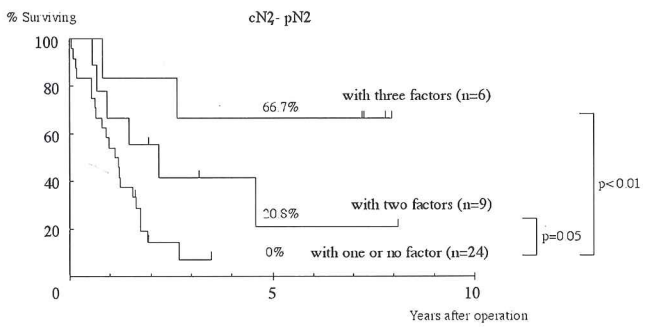

Figure 2. *Survival curves of cN2-pN2 patients with or without three prognostic factors. The three factors are single metastatic MLN station, tumor without involvement of parietal pleura and low CEA level. Five-year survival rates are shown in the figure. Survival curve of the subgroup with one or no factor (n=24) versus that of the subgroup with three factors (n=6) or two factors (n=9) show significant differences. (p<0.01 and p=0.05, respectively. Log-rank test).*

Table 1. Survival rates by clinical characteristics of the patients and types of treatment in cN2-pN2 patients (n=40)

Variable	No. of patients	Survival rates 3-year (%)	Survival rates 5-year (%)	p-value*
Total group	40	25.0	20.9	-
Age (yr)				0.11
<60	20	40.0	40.0	
≥60	20	6.9	0.0	
Sex				0.14
Male	28	33.7	26.9	
Female	12	8.3	8.3	
CEA (ng/mL)**				0.03
<2.5	16	42.2	35.2	
≥2.5	23	13.0	0.0	
SCC (ng/mL)**				0.27
<2.0	19	37.2	27.9	
≥2.0	5	20.0	20.0	
Extent of resection				0.25
Lobectomy or Bilobectomy	23	31.6	23.7	
Pneumonectomy	17	17.7	17.7	
Adjuvant therapy				0.93
Chemotherapy and/or radiotherapy	34	24.3	20.2	
No	6	33.3	0.0	

CEA, carcinoembryonic antigen; SCC, squamouse cell carcinoma antigen.

*The data are considered significant when the p-value does not exceed 0.05 in the log-rank test.

**The sum of the subgroups does not equal 40 because of missing data.

Table 2. Survival rates by the tumor characteristics in cN2-pN2 patients (n=40)

Variable	No. of patients	Survival rates 3-year (%)	Survival rates 5-year (%)	p-value*
Tumor site				0.70
Right	24	25.8	19.3	
Left	16	25.0	25.0	
Lobar distribution				0.40
Upper or middle lobe	24	33.1	24.8	
Lower lobe	14	14.3	14.3	
Main bronchus	2	0.0	0.0	
Tumor size (cm)				0.30
≤3	6	33.3	33.3	
>3	34	23.8	17.8	
Involvement of parietal pleura**				0.06
Absent	28	30.0	25.0	
Present	12	16.7	0.0	
Separate tumor nodules in the same lobe				0.27
Absent	34	26.3	21.0	
Present	6	16.7	16.7	
Histology of the tumor				0.31
Squamous cell carcinoma	20	37.0	27.8	
Nonsquamous cell carcinoma	20	15.0	15.0	

*The data are considered significant when the p-value does not exceed 0.05 in the log-rank test.

**Involvement of parietal pleura represents invasion of chest wall, diaphragm, mediastinal pleura and parietal pericardium.

riates. Among them, three were significantly related with survival: the number of metastatic MLN stations (multiple vs single) (p=0.02), involvement of parietal pleura (present vs absent) (p=0.02), and the preoperative CEA level (2.5 ng/ml or higher vs lower than 2.5 ng/ml) (p=0.05; Table 4). Neither metastasis to subcarinal nodes nor the number of metastatic MLNs played a significant role in the Cox model. When these three prognostic factors (i.e. a single metastatic MLN station, absence of parietal pleural involvement and a low CEA level) were combined, we observed marked survival differences among the patients with cN2-pN2 NSCLC. The 5-year survival in patients with all of three prognostic factors (n=6) was 67% and in those of two prognostic factors (n=9) was 21%, compared with 0% in those with one or none (n=24) (p<0.01 and p=0.05, respectively; Figure 2). Furthermore, four out of six (67%) patients with all of three prognostic factors survived more than seven years without any evidence of recurrence (Figure 2).

Discussion

The surgical indications for pN2-NSCLC patients are open to debate. Some authors mentioned that, among pN2, preoperatively unsuspected (cN0-1) pN2 lesions were usually subcapsular and had chances of eventual cure (1-3,9,10), while several studies showed that preoperatively discovered

Table 3. Survival rates by lymph node status in cN2-pN2 patients (n=40)

Variable	No. of patients	Survival rates 3-year (%)	5-year (%)	p-value*
Number of metastatic MLN stations				0.09
One station	16	42.9	42.9	
Two or more stations	24	12.5	6.3	
Number of metastatic MLNs**				0.07
One or two nodes	12	40.7	32.6	
Three or more nodes	27	8.3	8.3	
Metastasis to N1 nodes				0.27
Absent	18	25.4	16.9	
Present	22	25.6	25.6	
Metastasis to subcarinal nodes				0.03
Absent	23	40.1	32.1	
Present	17	5.9	5.9	

MLN, mediastinal lymph node

*The data are considered significant when the p-value does not exceed 0.05 in the log-rank test.

**The sum of the subgroups does not equal 40 because of missing data.

Table 4. Covariates related to survival in the Cox model in cN2-pN2 (n=39)*

Variable	Hazard ratio	95% CI	p-value**
Number of metastatic MLN stations			
Multiple vs single	3.13	1.24 - 7.88	0.02
Involvement of parietal pleura			
Present vs absent	2.90	1.20 - 7.05	0.02
CEA (ng/mL)			
≥ 2.5 vs < 2.5	2.26	1.01 - 5.06	0.05

CI, confidence interval; MLN, mediastinal lymph node; CEA, carcinoembryonic antigen

*The sum of the group does not equal 40 because CEA level is unknown in one case.

**p-value in the Cox model.

(cN2) pN2 lesions presented ominous findings and surgical treatment was contraindicated (4,7). On the other hand, numerous studies have consistently documented better survival of selected patients with pN2 after surgical treatment and survival of longer than five years without any evidence of recurrence (1-3). Watanabe et al. (11) have advocated that, even in cN2-pN2, curative resection should always be undertaken to obtain 5-year survival rates as high as 20%. Since definitive surgery is the only means for reasonable hope for cure, it is worthwhile selecting the cN2-pN2 patients who would benefit from surgical treatment and defining realistic criteria for this selection.

Since CEA level is a well-known prognostic factor (12,13), we routinely measured CEA level. In a large number of patients with NSCLC, CEA level demonstrated a TNM staging independent prognostic factor (13). All of 23 patients with a preoperative value of 2.5 ng/mL or higher died within three years after surgical treatment, whereas five patients (31%) out of 16 with CEA level lower than 2.5 ng/mL survived more than five years.

Among the examined lymph node characteristics, the number of metastatic MLN stations influenced survival in the Cox model. Previous reports also point out that involvement of a single MLN station brought about significantly better survival than that of multiple MLN stations (1-3,14-16). Metastasis to subcarinal nodes documented a parameter for the prognosis, but was conflicting. Although some reported significant survival benefit in patients without metastatic subcarinal nodes (14), others found no significant difference in survival (15, 16). In this study, when CEA level was excluded, the Cox model revealed that metastasis to subcarinal nodes was also a significant factor.

In most reports, lower pathological T (pT)-stage is associated with significantly better 5-year survival (2,15). Since pT-stage contains a variety of prognostic components, we evaluated three components, namely, tumor size, whether the tumor involves parietal pleura or not, and whether separate tumor nodules are in the same lobe or not. In the Cox model, involvement of parietal pleura was the only component in pT-categories that significantly influenced survival.

When the three prognostic factors, namely, a single metastatic MLN station, absence of parietal pleural involvement and a low CEA level were combined, patients with cN2-pN2 achieved 66.7% 5-year survival by primary resection.

For evaluation of tumor extent as well as mediastinal staging, thoracoscopy is reported to be a useful modality in NSCLC (15). Thoracoscopy allowed us to determine the extent of the primary tumor; a biopsy could be performed if necessary to confirm tumor invasion, and suspicious MLN lesions could be sampled. If patients are diagnosed to have good prognosis by surgery, they should subsequently undergo resection. And if not so, they should undergo induction chemotherapy protocols followed by surgical treatment.

We conclude from this study that evidently there is a selected group of patients despite cN2-pN2 who can be effectively treated by primary surgery with prolonged survival.

References

1. Tanaka F, Yanagihara K, Otake Y, et al. Prognostic factors in resected pathologic (p-) stage IIIA-N2, non-small cell lung cancer. Ann Surg Oncol 2004;11:612-8.
2. Yano T, Fukuyama Y, Yokoyama H, et al. Long-term survivors with pN2 non-small cell lung cancer after a complete resection with a systemic mediastinal node resection. Eur J Cardiothorac Surg 1998;14:152-5.
3. Inoue M, Sawabata N, Takeda S, et al. Results of surgical intervention for p-stage IIIA (N2) non-small cell lung cancer: acceptable prognosis predicted by complete resection in patients with single N2 disease with primary tumor in the upper lobe. J Thorac Cardiovasc Surg 2004; 127:1100-6.
4. Cybulsky IJ, Lanza LA, Ryan MB, et al. Prognostic significance of computed tomography in resected N2 lung cancer. Ann Thorac Surg 1992; 54:533-7.
5. DeCamp MM, Rice TW, Adelstein DJ, et al. Value of accelerated multimodality therapy in stage IIIA and IIIB non-small cell lung cancer. J Thorac Cardiovasc Surg 2003;126:17-27.
6. Bueno R, Richards WG, Swanson SJ, et al. Nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. Ann Thorac Surg 2000;70:1826-31.
7. Shields TW. The significance of ipsilateral mediastinal lymph node metastasis (N2 disease) in non-small cell carcinoma of the lung. J Thorac Cardiovasc Surg 1990;99:48-53.
8. Niizeki H, Morikawa T, Okushiba S, et al. The role of computed tomography in mediastinal lymph node staging in non-small cell lung cancer. Turk Resp J 2003;4:108-12.
9. Lewis JW Jr, Pearlberg JL, Beute GH, et al. Can computed tomography of the chest stage lung cancer? - yes and no. Ann Thorac Surg 1990;49:591-6.
10. Faling LJ, Pugatch RD, Jung-Legg Y. Computed tomography scanning of the mediastinum in the staging bronchogenic carcinoma. Am Rev Respir Dis 1981;124:690-5.
11. Watanabe Y, Shimizu J, Oda M, et al. Aggressive surgical intervention in N2 non-small cell cancer of the lung. Ann Thorac Surg 1991;51:253-61.
12. Buccheri G, Ferrigno D. Identifying patients at risk of early postoperative recurrence of lung cancer: a new use of the old CEA test. Ann Thorac Surg 2003;75:973-80.
13. Okada M, Nishio W, Sakamoto T, et al. Prognostic significance of perioperative serum carcinoembryonic antigen in non-small cell lung cancer: analysis of 1,000 consecutive resections for clinical stage I disease. Ann Thorac Surg 2004;78:216-21.
14. Regnard JF, Magdeleinat P, Azoulay D, et al. Results of resection for bronchogenic carcinoma with mediastinal lymph node metastases in selected patients. Eur J Cardiothorac Surg 1991;5:583-7.
15. Vansteenkiste JF, de Leyn PR, Deneffe GJ, et al. Survival and prognostic factors in resected N2 non-small cell lung cancer: A study of 140 cases. Ann Thorac Surg 1997;63:1441-50.
16. Goldstraw P, Mannam G, Kaplan D, et al. Surgical management of non-small cell lung cancer with ipsilateral mediastinal node metastasis (N2 disease). J Thorac Cardiovasc Surg 1994;107:19-28.
17. Sebastian-Quetglas F, Molins L, Baldo X, et al. Clinical value of video-assisted thoracoscopy for preoperative staging of non-small cell lung cancer. A prospective study of 105 patients. Lung Cancer 2003;42:297-301.