**Original
Article**

Pathological Status of Mediastinal Lymph Nodes after Preoperative Concurrent Chemoradiotherapy Determines Prognosis in Patients with Non-Small Cell Lung Cancer

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Objectives: The benefits of preoperative chemoradiotherapy for advanced nonsmall cell lung cancer (NSCLC) remain controversial. To evaluate prognostic indicators of clinical N2 NSCLC patients treated with concurrent chemotherapy followed by pulmonary resection, we performed a retrospective study.

Methods: We retrospectively investigated 52 patients with pathologically proven N2 NSCLC who underwent concurrent chemoradiotherapy before pulmonary resection. Each received 2 cycles of cisplatin-vinca alkaloid-based chemotherapy every 4 weeks. Radiotherapy, directed at the tumor and mediastinal nodes, was started on day 2 at a median dose of 44 Gy. A thoracotomy was performed 6 to 8 weeks after completion of chemoradiotherapy.

Results: The overall 5-year survival rate for the 52 patients was 38%. Complete pathological response by the tumor was found in 11 (21%). Down-staging of nodal stage occurred in 29 patients, (56%) and overall survival was better in those with lower pathological N status. The 5-year survival rate was 58% for pathological N0-N1 disease and 0% for N2 disease. While the response to induction therapy by the primary tumor was correlated with postoperative nodal stage, multivariate analysis revealed postoperative nodal stage as an independent prognostic factor.

Conclusion: Pathological status of mediastinal lymph nodes in response to preoperative concurrent chemoradiotherapy determined prognosis in our patients.

Keywords: nonsmall cell lung cancer, preoperative concurrent chemoradiotherapy, prognostic indicator

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Introduction

The most effective treatment for patients with locally advanced nonsmall cell lung cancer (NSCLC) remains controversial. The results of surgical resection alone for locally advanced NSCLC are poor; thus the treatment option of induction chemoradiotherapy has been investigated.^{1,2)} Although there is consensus about the indication for a multimodality approach in most patients with locally advanced disease, there is no clear agreement about which local therapy should be applied in a given situation.³⁾ Some reports have demonstrated that induction chemoradiotherapy followed by surgical resection

provides better progression-free survival but not overall survival.^{4,5)} The purpose of this multi-institutional study was to evaluate prognostic indicators of clinical N2 NSCLC patients treated with concurrent chemoradiotherapy followed by pulmonary resection.

Patients and Methods

We investigated 52 patients with surgical resectable clinical N2 NSCLC who underwent preoperative concurrent chemoradiotherapy before pulmonary resection between 1995 and 2008 at Osaka Prefectural Medical Center for Respiratory and Allergic Disease, Toneyama National Hospital, and Osaka University Hospital. An institutional review board approved this retrospective study and written informed consent for surgical intervention was obtained from each patient. Patients were assessed by a thoracic surgeon, radiation oncologist, and medical oncologist to establish that the cancer was potentially technically resectable. Preoperative pathological N2 disease was shown by mediastinoscopy (n = 35), perbronchial biopsy (n = 13), and thoracoscopy (n = 4) findings.

Patients received 2 cycles of chemotherapy every 4 weeks as follows: PV(M) regimen, cisplatin 80 mg/m² on day 1 and vindesine 3 mg/m² on days 1 and 8 with or without mitomycin 8 mg/m² on day 1 according to the protocol of Japan Clinical Oncology Group 9209 and 9806^{6,7)}; nPV regimen, cisplatin 80 mg/m² on day 1 and vinorelbine 20 mg/m² on days 1 and 8 every 4 weeks according to the protocol described by Naito et al.⁸⁾ Radiotherapy directed at the tumor and mediastinal nodes was started on day 2 concurrently in cycle 1 and the total radiation dose was 40 Gy in 20 fractions administered over 4 weeks. For poor responding patients (n = 10), an additional dose of 10 to 20 Gy was administered. Following induction chemoradiotherapy, each case was reevaluated to determine clinical response and indications for resection. A thoracotomy was performed in all patients 6 to 8 weeks after completion of chemoradiotherapy. The surgical procedures included a lobectomy or pneumonectomy with systemic node dissection.

A chi-square test was used to compare the results. Overall survival rates were estimated by the method of Kaplan and Meier, and compared with results of a log-rank test. All patient characteristics were tested multivariately against the primary outcome using a Cox-regression analysis based on the tested variable. All statistical analyses were performed using Statview version 5.0 for Windows (Abacus Concepts, Berkeley, CA). A p-value of

Table 1 Patient Characteristics (n = 52)

Characteristics	No. of patients
Gender	
Male	43
Female	9
Clinical stage	
IIIA	40
IIIB	12
Clinical T stage	
T1	5
T2	27
T3	8
T4	12
Clinical N stage	
N2	52
Histology	
Adenocarcinoma	34
Squamous cell carcinoma	15
Others	3
Type of mediastinal staging	
Mediastinoscopy	35
Perbronchial biopsy	13
Thoracoscopy	4

<0.05 was considered to be statistically significant.

Results

The median patient age was 57 years old (range 32–73 years), and their clinicopathologic characteristics are shown in **Table 1**. The median radiation dose was 44 Gy (30–60 Gy), and data for preoperative treatments and surgical procedures are presented in **Table 2**. The overall cardiopulmonary morbidity, early mortality, and 90-day mortality rates were 38% (n = 20), 3.8% (n = 2), and 7.6% (n = 4), respectively. Postoperative cardiopulmonary morbidity rate was not associated with type of chemotherapy (CDDP + VDS vs. CDDP + VDS + MMC vs. CDDP + VNR; morbidity rate 47% vs. 45% vs. 22%; p = 0.38) or radiation dose (40 Gy ≥ vs. 40 Gy<; 46% vs 30%; p = 0.36), while it was greater in patients who underwent a pneumonectomy than in those who underwent a lobectomy (73% vs. 29%, p = 0.01).

Twenty-one patients were alive after a median follow-up period of 4.8 years, and the overall 5-year survival rate was 38% (**Fig. 1A**). Complete pathological response by the tumor was found in 11 patients (21%, see **Table 3A**), though there was no significant difference in survival rate according to tumor pathological response [Complete pathological response (CR-tumor) vs. Non-complete pathological response (NCR-tumor), p = 0.07, **Fig. 1B**].

Table 2 Preoperative treatment and surgical procedures, and results

Procedure/Result	No. of patients
Chemotherapy	
CDDP + VDS	31
CDDP + VDS+MMC	12
CDDP + VNR	9
Radiation dose	
40 Gy ≥	40
40 Gy <	12
Surgical procedure	
Lobectomy	43
Pneumonectomy	9
With combined resection	
Bronchoplasty	8
Rib	4
Pericardium	4
Major vessel	2
Diaphragma	2
Morbidity	
None	32
Pneumonia	7
(ARDS	2)
(Radiation pneumonitis	2)
Atelectasis	4
Empyema	4
(Broncho-fistula	2)
Chylothorax	2
Arrhythmia	5
Heart failure	2
Mortality	3
ARDS	2
Hemoptysis	1

CDDP: cisplatin; VDS: vindesine; MMC: mitomycin;
VNR: vinorelbine ARDS: adult respiratory distress syndrome

Pathological N0-1 status was found in 29 patients, (56%) and overall survival was better in those with a lower p-N status (Pathological N0-1 status vs. N2 status, $p = 0.005$, **Fig. 1C**), as the 5-year survival rate was 58% in patients with stage p-N0-1 disease and 0% in those with p-N2 disease. Overall survival did not differ according to the surgical procedure employed (lobectomy vs. pneumonectomy, $p = 0.74$).

Response to induction therapy by the primary tumor was correlated with postoperative nodal stage ($p = 0.01$, **Table 3B**). Only one patient with CR-tumor belonged to p-N2 group. The 5-year survival rate was 90% in patients with CR-tumor and p-N0-1 disease, 51% in those with NCR-tumor and p-N0-1 disease, and 0% in those with NCR-tumor and p-N2 disease. In univariate analysis, postoperative nodal stage was a prognostic factor (**Table 3C**). Two variables, including tumor response to

Patients at risk					
52	38	30	22	15	6

Patients at risk						
Complete	11	9	8	7	4	1
Non-complete	41	29	22	15	11	5

Patients at risk						
N0-1	29	21	19	14	12	6
N2	23	17	11	8	3	0

Fig. 1

A: Overall survival for all cases (n = 52).

B: Overall survival according to pathological response of the tumor.

C: Overall survival according to pathological nodal status after chemoradiotherapy.

Table 3

A. Postoperative pathologic results		C. Univariate analysis of prognostic factors		
Characteristics	No. of patients	Variable	Hazard ratio (95% CI)	p value
Pathologic T stage		Tumor response		
T0*	11	Non-complete vs. complete	3.40 (0.81–14.3)	0.09
T1	16	p-N status		
T2	18	N2 vs N0-1	2.81 (1.29–6.11)	0.01
T3	6			
T4	1			
Pathologic N stage		D. Multivariate analysis of prognostic factors		
N0	25	Variable	Hazard ratio (95% CI)	p value
N1	4	Tumor response		
N2	23	Non-complete vs. complete	1.68 (0.44–6.35)	0.444
		p-N status		
		N2 vs N0-1	2.40 (1.04–5.57)	0.041

*T0, pathological complete response in primary tumor

B. Postoperative pathologic response in tumor and lymph nodes

Pathologic response in tumor	N status	
	p-N0-1	p-N2
Complete	10	1
Non-complete	19	22

*T0, pathological complete response; p = 0.01, chi-square test

CRT and postoperative nodal stage which were correlated with each other, were analyzed to determine the variables having an effect on survival in NSCLC patients (Table 3D). The analysis revealed that postoperative nodal stage was an independent prognostic factor.

Discussion

Cisplatin-vinca alkaloid-based chemotherapy combined with radiation was administered in the present cases, which has been reported to be the most popular and well-tolerated combination for NSCLC in Japan.^{6–8)} We previously used cisplatin and vindesine in the 1990s, and then changed vindesine to vinorelbine in the 2000s. Chemotherapy regimens with new agents, including paclitaxel, docetaxel, and gemcitabine, have recently been reported to be effective for advanced NSCLC.^{9,10)} These new agents combined with radiotherapy may also improve overall long-term survival by inducing an increased pathological response by the tumor to induction therapy in patients with local, advanced NSCLC.¹¹⁾

Similar to the German Lung Cancer Cooperative Group (GLCCG) trial,⁵⁾ we found that preoperative concurrent chemoradiotherapy increased pathological response and mediastinal down-staging, while multivariate

analysis showed that pathological N status was an independent predictor of survival. These results suggest that new methods for achieving better control of mediastinal lymph node involvement are needed to improve the overall outcome for patients with locally advanced NSCLC. Along that line, we believe that it is important to accurately select patients in whom preoperative N2 or N3 disease will be controlled by induction chemoradiotherapy for improvement of long-term survival with trimodality therapy. Since N2 disease after chemoradiotherapy has a negative prognostic significance, nodal status should be assessed after induction chemoradiotherapy using computed tomography (CT) and ¹⁸F-fluorodeoxy glucose-positron emission tomography (FDG-PET) examinations. When apparent N2 disease is confirmed even after induction chemoradiation, it may be best to avoid a pulmonary resection and treat the patient with definitive chemoradiotherapy. In addition, aggressive staging with EBUS-TBNA as well as a re-mediastinoscopy can be performed, in addition to conventional examinations to exclude such patients from surgical resection.^{12–14)} On the other hand, response to induction therapy by the primary tumor was shown to be correlated with postoperative down-staging of mediastinal nodes in the present study; thus it is necessary to evaluate using CT or FDG-PET to monitor

treatment response by the primary tumor after induction chemoradiotherapy and predict down-staging of mediastinal nodes. The value of FDG-PET for the primary tumor and its response to therapy should be evaluated in a future study.

The most commonly used dose for induction therapy ranges from 40 to 45 Gy.^{2,8)} Sonett et al. reported that high dose radiation promotes a high pathologically complete response rate and pulmonary resection may be performed safely after CRT including greater than 59 Gy radiotherapy.¹¹⁾ In our series, 6 patients received 60 Gy radiotherapy as CRT and each safely underwent pulmonary resection.

The type of surgery is also a determinant of morbidity and mortality. Albain and colleagues recently reported significantly higher mortality rates with a pneumonectomy (26%) as compared to a lobectomy (1%); thus no survival difference was found between the surgical and non-surgical arms in their study,¹⁵⁾ because the increased mortality in patients who required a pneumonectomy after induction chemoradiotherapy adversely affected the overall survival of the surgical group. However, some reports have shown that induction chemoradiotherapy does not increase the risk of morbidity and mortality after a pneumonectomy in properly selected patients.^{3,15)} In the present study, there was no significant difference for 90-day mortality and overall survival between patients who underwent a pneumonectomy and those who received a lobectomy, whereas cardiopulmonary morbidity and early mortality rates were greater in patients with a pneumonectomy than those with a lobectomy. Notably, a right pneumonectomy after chemoradiotherapy has been reported to be associated with relatively increased risk and should be performed only in selected patients.¹⁶⁾

Our study has some potential limitations, as it was an observational study performed at 3 different centers and not a randomized trial. Therefore, multicenter prospective randomized trials in Japan are needed for accurate investigation of the effects and risks of trimodality treatment in patients with NSCLC.

Conclusion

Pathological response by mediastinal lymph nodes to preoperative concurrent chemoradiotherapy determined the prognosis in our patients with N2 NSCLC.

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