

Elevation of the Neutrophil-to-Lymphocyte Ratio Is a Significant Postoperative Poor Prognostic Factor in Patients With Clinical T3-4 Centrally Located Primary Lung Cancer

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Abstract. *Background/Aim:* In centrally located non-small cell lung cancer (CLNSCLC) surgery, large tumors and extension to neighboring structures prevent the attainment of adequate surgical fields and make operations more difficult, and some patients have extremely poor outcomes. This study aimed to identify novel postoperative prognostic factors in patients with advanced CLNSCLC. *Patients and Methods:* CLNSCLC was defined as a tumor requiring pneumonectomy or sleeve lobectomy for complete removal. We retrospectively investigated the clinical courses of 35 patients with cT3-4 CLNSCLC. *Results:* This study included 21 patients with cT3 and 14 with cT4 lung cancer. Nine patients underwent pneumonectomy and 26 underwent sleeve lobectomy. Univariate analysis revealed that a high neutrophil-to-lymphocyte ratio (NLR, $p=0.005$) and carcinoembryonic antigen (CEA) positivity ($p=0.028$) were significant poor prognostic factors. Only high NLR ($p=0.020$) was a significant independent predictor in multivariate analysis. Nine of 16 patients with high NLR (56%) experienced disease recurrence, whereas 6 of 19 patients without high NLR (32%) had recurrent disease. *Conclusion:* High NLR and CEA positivity were significant poor prognostic factors in patients with cT3-4 CLNSCLC, and only high NLR was an independent predictor. Our findings may be helpful in selecting optimal treatments for advanced CLNSCLC.

In both lung squamous cell carcinoma and adenocarcinoma, a central tumor location is a poor prognostic factor (1, 2). Pneumonectomy or sleeve lobectomy is commonly required

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to achieve complete resection of centrally located non-small cell lung cancer (NSCLC). We previously reported that some patients who underwent complete resection of their advanced centrally located NSCLC had extremely poor outcomes (3, 4). In surgery for centrally located NSCLC, large tumors and extension to neighboring structures prevent the attainment of an adequate surgical field and make the operation more difficult. Identification of the prognostic factors is necessary for selecting optimal treatments for advanced centrally located NSCLC. This study aimed to identify novel postoperative prognostic factors in patients with advanced centrally located NSCLC.

Patients and Methods

Patients. Centrally located lung cancer was defined as a tumor requiring pneumonectomy or sleeve lobectomy for complete removal. Clinical and pathological staging were determined according to the 8th edition of the TMN Classification of Malignant Tumors (5). We retrospectively investigated the clinical courses of 35 patients with clinical T3-4 centrally located NSCLC who had surgical treatments at our institute from January 2011 to December 2020. Patients with NSCLC who required pneumonectomy or sleeve lobectomy to remove metastatic hilar lymph node were excluded from the analyses. Patients who underwent right lower sleeve lobectomy were also excluded from the analyses because right lower sleeve lobectomy was selected to avoid the middle and lower bilobectomy. Moreover, patients with clinical T3-4 NSCLC attributable to lung metastasis were also excluded. Before surgery, informed consent was obtained from all patients for the use of their examination data in clinical studies. This study was approved by the local institutional ethics committee of Osaka Metropolitan University (Approval no. 4403, approval date: October 3, 2019).

Methods of treatment. Mediastinal lymph nodes with a short axis of >10 mm on computed tomography were defined as

Table I. Characteristics of patients in this study.

		N=35	
Age (years)		70 (33-83)	
Sex	Male/Female	24/11	
Smoking history	Yes/No	34/1	
Comorbidities*	Cardiovascular disease	13	
	Diabetes melitus	7	
	Other organ malignant tumor	4	
	Liver disease	2	
	Cerebrovascular disease	2	
Clinical T factor	3/4	21/14	
Clinical N factor	0/1/2	7/22/6	
Clinical stage	II/III	2/33	
Surgical procedure	Right	Pneumonectomy	4
		Upper	7
		Middle and lower	3
		Upper and middle	1
	Left	Pneumonectomy	5
		Upper	4
		Lower	3
		Lower and lingular segment	5
		Upper and segment 6	2
Infiltrated structures**	Left atrium	4	
	Vagus nerve	3	
	Superior vena cava	2	
	Phrenic nerve	2	
	Esophageal wall	1	
Pathological T factor***	1/2/3/4	1/6/14/12	
Pathological N factor***	0/1/2	8/15/10	
Pathological Stage***	II/III	10/23	
Preoperative treatment		6 (17%)	
Postoperative treatment		13 (37%)	

Values represent median (range). *Some patients have more than two comorbidities. **Some patients have more than two infiltrated structures. ***A patient without residual tumor after preoperative treatment was excluded.

clinically positive for metastasis. Positron emission tomography/computed tomography (PET/CT) was not mandatory during this study period. Twenty-eight patients underwent PET/CT before surgery. The criteria for surgery were the absence of distant metastasis, cancer cell-positive pleural or pericardial effusion, N2 metastasis at two or more mediastinal stations, bulky N2 metastasis, and N3 metastasis and a predicted postoperative percent vital capacity of >40%. Patients with completely removable T4 lung cancer with N0-1 metastasis were considered candidates for surgery. If anatomically appropriate, sleeve lobectomy was selected to avoid pneumonectomy. Bronchial stumps were confirmed to be free of cancer cell infiltration by intraoperative pathological examination.

Patients with tumors involving neighboring organs or those with enlarged but completely removable N2 lymph node metastasis were recommended to receive induction

chemoradiotherapy with platinum-based doublet and concurrent radiotherapy (40 Gy), but this was not mandatory for all patients with N2 metastasis. Patients with pathological stage II-III NSCLC were recommended to receive adjuvant platinum-based doublet chemotherapy, whereas those with stage I NSCLC were recommended to receive oral tegafur adjuvant chemotherapy. Such treatments were introduced at the discretion of the physician in charge of each patient.

Sample collection and follow-up. Body height and weight were measured on admission. Blood samples were obtained within a few days before surgery. Disorders being treated at the time of lung cancer diagnosis were defined as comorbidities. After discharge, all patients underwent follow-up chest radiography and tumor markers measurement every 2-4 months and CT after 6 months and every year thereafter.

Statistical analysis. Median values were used as cutoffs for age, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). The cutoff for body mass index was calculated according to World Health Organization guidelines (6). The cutoffs for tumor markers were calculated in accordance with institutional cutoffs and previous reports (7, 8). Overall survival (OS) was calculated by the Kaplan-Meier method, and survival differences were compared using the log-rank test. Independent risk factors associated with survival were calculated using the Cox proportional hazard model. $p < 0.05$ indicated statistical significance. Statistical analyses were performed using JMP 10 software (SAS Institute, Cary, NC, USA).

Results

Table I presents the characteristics of the patients in the study. This study included 21 patients with clinical T3 and 14 patients with clinical T4 lung cancer. And 10 patients with clinical T4 lung cancer had tumors which were suspected to infiltrate into neighboring structures. Of the 35 analyzed patients, 9 and 26 underwent pneumonectomy and sleeve lobectomy, respectively. Six patients received preoperative treatment, and two of them had no residual cancer cells in the resected specimens. Thirteen patients received postoperative treatment. The results of univariate and multivariate analyses for predictors of poor prognosis are presented in Table II. Univariate analysis revealed that high NLR ($p=0.005$) and carcinoembryonic antigen (CEA) positivity ($p=0.028$) were significant predictors of poor prognosis. In these factors, only high NLR ($p=0.020$) was a significant independent predictor of poor prognosis in multivariate analysis.

The 30- and 90-day mortality rates were 0%, and no patients died in the hospital. The median follow-up period was 31 months, during which time 15 patients developed

Table II. Univariate and multivariate analyses of poor prognostic factors.

		n	Univariate analysis			Multivariate analysis		
			HR	95% CI	p-Value	HR	95% CI	p-Value
Age	≤70	19	1,00	0.45-4.51	0,592			
	>70	16	1,36					
Sex	Male	24	1,00	0.44-5.01	0,610			
	Female	11	0,74					
Comorbidities	Yes	18	1,00	0.69-8.17	0,188			
	No	17	0,46					
BMI	≤18.5	6	1,00	0.18-4.39	0,861			
	>18.5	29	0,87					
NLR	≤3.3	19	1,00	1.66-24.59	0,005	1,00	1.23-19.28	0,020
	>3.3	16	5,47					
PLR	≤181	17	1,00	0.63-6.48	0,254			
	>181	18	1,92					
CEA (ng/ml)	≤5.0	25	1,00	0.01-0.85	0,028	1,00	0.01-1.47	0,147
	>5.0	10	5,98					
CYFRA (ng/ml)	≤2.0	11	1,00	0.52-7.73	0,391			
	>2.0	24	1,72					
Surgical procedures	Pneumonectomy	9	1,00	0.13-1.95	0,407			
	Sleeve lobectomy	26	0,59					
Pathological N factor*	0/1	23	1,00	0.57-6.07	0,275			
	2	10	1,93					
Pathological T factor*	1-3	21	1,00	0.58-5.64	0,292			
	4	12	1,83					
Adjuvant chemotherapy	Yes	13	1,00	0.16-1.88	0,399			
	No	22	1,64					

*A patient without residual tumor after preoperative treatment was excluded. HR, Hazard ratio; CI, confidence interval; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CYFRA, cytokeratin 19 fragment.

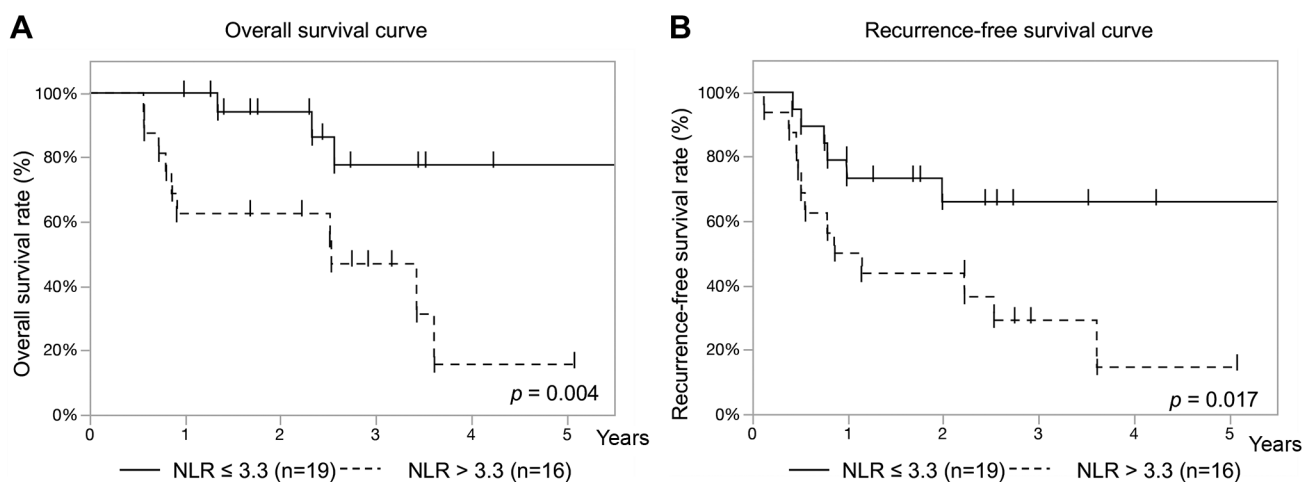


Figure 1. Overall survival (A) and disease-free survival curves (B) according to neutrophil-to-lymphocyte ratio (NLR) score.

recurrent disease and 13 patients died. Compared with the patients without high NLR, those with high NLR had significantly shorter OS ($p=0.004$, Figure 1A) and recurrence-free survival ($p=0.017$, Figure 1B).

Figure 2 presents the recurrence sites and numbers from patients. Some patients had more than two recurrence sites. Of the 16 patients with high NLRs, nine (56%) exhibited disease recurrence during the study period, compared with

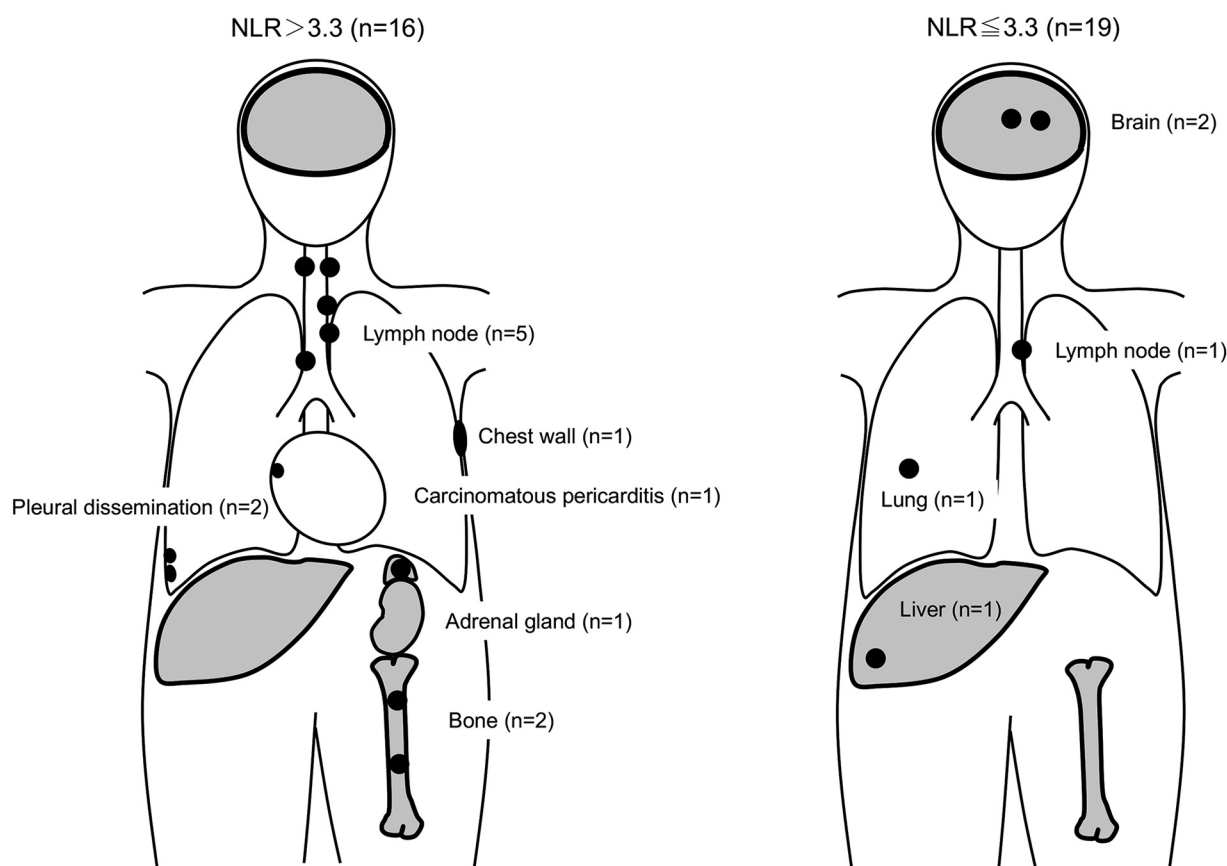


Figure 2. Details of recurrence sites according to neutrophil-to-lymphocyte ratio (NLR) score.

six patients (32%) without high NLRs. Lymph node recurrence was observed outside the usual dissection area in all patients.

Table III presents the correlations between patients' characteristics and NLR. C-reactive protein levels were higher in patients with high NLRs, albeit without significance.

Discussion

We identified high NLR and CEA positivity as significant poor prognostic factors after complete resection in patients with clinical T3 or T4 centrally located NSCLC. Of these factors, only high NLR was an independent poor prognostic factor. Distant metastases were commonly observed in patients with high NLR, and their prognoses were significantly poor.

Systemic inflammatory biomarkers, such as NLR, PLR and systemic immune-inflammation Index, have been reported to be strong predictors of prognosis in patients with primary lung cancer (9-11). Significant impacts of NLR on prognosis have also been reported in both completely resected and advanced lung cancer patients (12-14). NLR

Table III. Comparison of characteristics according to the NLR level.

	NLR		p-Value
	≤3.3 (n=19)	>3.3 (n=16)	
Age	69 (33-75)	70 (53-83)	0.253
Sex (Male/Female)	12/7	12/4	0.450
Comorbidities	9 (47%)	9 (56%)	0.600
BMI	22.5 (15.8-34.4)	21.6 (16.2-29.8)	0.408
CRP (mg/dl)	0.65 (0.05-14.03)	2.11 (0.05-34.00)	0.055
Albumin (g/dl)	3.7 (2.6-4.5)	3.7 (2.2-4.4)	0.403
SUV*	15.6 (7.3-33.1)	16.3 (5.1-33.8)	0.982
Tumor size (mm)**	56 (31-80)	65 (30-120)	0.385

Values represent median (range). NLR, Neutrophil-to-lymphocyte ratio; BMI, body mass index; CRP, C-reactive protein; SUV, standardized uptake value. *Twenty-eight patients had positron emission tomography/computed tomography before surgery. **A patient without residual tumor after preoperative treatment was excluded.

was also reported to strongly correlate with the treatment response of immunotherapy in lung cancer patients (15, 16). This is the first report of the correlation between

postoperative prognosis and inflammatory biomarkers in patients with large sized centrally located NSCLC. In this study population, no patient characteristics were associated with the levels of NLR. Elevated NLR indicates the presence of tumor-associated inflammation, neutrophil-mediated tumor progression, and suppression of the anti-tumor immune response of lymphocytes (17-19). Because of their large size and central location of the tumors, the tumor-associated local inflammatory condition might easily reflect the systemic inflammatory response.

Recurrence is frequently observed in patients with high NLR, and distant organ metastases are common. Takahashi *et al.* (20) demonstrated that the rate of distant metastasis after complete resection was significantly higher in the high NLR compared to the low NLR group, among patients with stage I NSCLC. The role of tumor-associated neutrophils (TANs) in cancer development has recently attracted considerable attention. TANs express an N1 phenotype with anticancer efficacy and an N2 phenotype with cancer-promoting activity (21). The N1 phenotype exerts anticancer efficacy *via* the direct destruction of cancer cells and interactions with other constituents of the immune system. Conversely, the N2 phenotype can play an important role as a constituent of tumor-promoting inflammation by accelerating angiogenesis, immunosuppression and extracellular matrix remodeling (22). Transforming growth factor (TGF)- β 1 accelerates the polarization of TANs to the N2 phenotype, whereas inhibition of TGF- β 1 results in a shift toward the N1 phenotype (21). However, there was no significant difference in cancer cell TGF- β 1 expression according to the tumor location (peripheral or central) or histological subtypes in patients with NSCLC (23). Unfortunately, we cannot explain the mechanisms by which NLR strongly influences prognosis in advanced centrally located lung cancer. Understanding the molecular mechanisms of the malignant behavior in advanced centrally located NSCLC may lead to development of novel therapies for this subgroup of patients.

This study had certain limitations. First, this was a small retrospective study. Accumulation of data from more patients and further analyses are currently ongoing. Second, treatments were selected at the discretion of the physician in charge of each patient. Selection criteria for surgical procedures should be established in future studies. Finally, preoperative examination has not yet been standardized. A standard preoperative examination schedule, including PET/CT, should be established.

Conclusion

We found that high NLR and CEA positivity were significant poor prognostic factors in patients with clinical T3 or T4 centrally located NSCLC. Of these factors, only high NLR

was an independent poor prognostic factor. Distant metastases were commonly observed in patients with high NLR, and their prognosis was significantly poor. Our findings may be helpful in selecting optimal treatments for patients with advanced centrally located NSCLC.

Conflicts of Interest

All Authors have no conflicts of interest to declare.

Authors' Contributions

Takuma Tsukioka designed this study, analyzed the data, prepared the figures and wrote the original draft. Nobuhiro Izumi and Noritoshi Nishiyama oversaw the study and revised the article. All Authors reviewed the article.

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