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Elevation of Neutrophil-to-Lymphocyte Ratio Is a Significant Poor Prognostic Factor in Completely Resected Centrally Located Lung Squamous Cell Carcinoma

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Abstract. *Background/Aim: The neutrophil-to-lymphocyte ratio (NLR) plays key roles in cancer growth. This study aimed to identify novel prognostic factors in patients who underwent complete resection of centrally located lung squamous cell carcinoma. Patients and Methods: We retrospectively investigated the clinical courses of 45 patients who underwent sleeve lobectomy or pneumonectomy for centrally located squamous cell carcinoma. Results: High NLR (p<0.001) and pathological T3/4 (p=0.008) were significant poor prognostic factors according to univariate analysis. Patients with pathological N2 had poor prognosis; however, there was no significant difference (p=0.095). Among these factors, only high NLR (p=0.003) was an independent poor prognostic factor according to multivariate analysis. Of the 23 patients with high NLR, 11 (49%) had recurrence, whereas in the 22 patients without high NLR, only two (9%) had recurrence. Conclusion: High NLR is an independent poor prognostic factor in centrally located lung squamous cell carcinoma. Our findings may guide the selection of optimal treatments for this subgroup of patients.*

Squamous cell carcinoma is a common histological subtype of centrally located lung cancer. Central location of lung squamous cell carcinoma is a significant indicator of poor outcome after complete tumor resection (1, 2). Tumor extension along the bronchus and pulmonary vessels is also an important prognostic factor (3). Systemic inflammatory responses play key roles in cancer development, growth, invasion, and metastasis (4). Inflammatory biomarkers, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been proposed as novel postoperative indicators of poor prognosis in primary lung cancer patients (5-7). We previously reported that high NLR was a postoperative poor prognostic factor in locally advanced non-small cell lung cancer (NSCLC) patients (8). NLR predicts response and prognosis in patients with lung cancer treated with immunotherapy (9). Moreover, it has been reported that increased pleural NLR could predict an early progression in stage IV NSCLC patients (10). However, a correlation between inflammatory biomarkers and surgical outcomes in patients with centrally located lung cancer has not been previously investigated. In this study, we aimed to identify novel prognostic factors in patients who had undergone complete resection of centrally located lung squamous cell carcinoma.

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Patients and Methods

We retrospectively investigated the clinical courses of 45 centrally located squamous cell carcinoma patients who underwent sleeve lobectomy or pneumonectomy at our institute from January 2017 to December 2020. Lung cancer cases that required pneumonectomy or sleeve lobectomy for metastatic hilar lymph node removal were excluded from the analyses. Right lower sleeve lobectomy was selected to avoid middle and lower bilobectomy. Patients who had undergone right lower sleeve lobectomy were excluded from the analyses. Before surgery, all patients gave informed consent for the use of their examination data in clinical studies. This study was approved by the local institutional ethical committee (Approval no. 4403, approval date: 3 October 2019).

Mediastinal lymph nodes with a short axis of >10 mm on computed tomography were diagnosed as clinically positive for metastasis. The criteria for surgical resection were absence of distant metastasis, no cancer cell-positive pleural or pericardial effusion, no N2 disease at two or more mediastinal levels, no bulky N2 disease, no N3 disease, and a predicted postoperative percent vital capacity of >40%. Patients with T4 lung cancer with N0 or N1 nodal extension and tumors that could be completely removed were considered candidates for surgery. Sleeve lobectomy was performed if anatomically appropriate. Bronchial stumps

were confirmed to be free of cancer cell infiltration through intraoperative pathological examination.

Induction chemoradiotherapy with platinum-based doublet and concurrent radiotherapy (40 Gy) was mainly recommended for patients with enlarged but completely removable N2 lymph node metastasis, but was not mandatory for all patients with N2 lymph node metastasis. Patients with pathological stage II and III lung cancer received adjuvant platinum-based doublet chemotherapy; while those with stage I lung cancer received oral tegafur adjuvant chemotherapy. We did not set criteria for omitting adjuvant treatment, and such treatments were initiated at the discretion of the physician in charge of each case.

After discharge, all patients underwent follow-up chest radiographs and measurement of tumor markers every 2 to 4 months and computerized tomography scans after 6 months and every year thereafter.

Blood samples were obtained within a few days before surgery. Body height and weight were measured at the time of hospital admission. Comorbidities were defined as disorders being treated at the time of primary lung cancer diagnosis. Medians were used as cut-off points for age, NLR, and PLR. The cut-off for body mass index was calculated in accordance with World Health Organization guidelines (11). Overall survival was calculated using the Kaplan-Meier method and survival differences compared using the log-rank test. Independent risk factors associated with survival were calculated using a Cox proportional hazard model. A *p*-value of <0.05 indicated statistical significance. Statistical analyses were done using JMP 10 software (SAS Institute, Cary, NC, USA).

Results

Table I shows the characteristics of patients included in the study. Of the 45 patients, 10 had undergone pneumonectomy, and 35 sleeve lobectomy. Five patients had received preoperative treatments, and two of them had no residual cancer cells in resected specimens. Locoregional recurrence was observed in only one patient at the chest wall cut end. Results from univariate and multivariate analyses for predictors of poor prognosis are shown in Table II. Univariate analysis revealed that high NLR (p<0.001) and pathological T3/4 (p=0.008) were significant predictors of poor prognosis. Patients with pathological N2 had poor prognosis; however, there was no significant difference (p=0.095). Among these factors, only high NLR (p=0.003) was found to be a significant independent predictor of poor prognosis according to multivariate analysis.

Our analysis revealed 30- and 90-day mortality rates of 0% and no hospital deaths. The patients' median follow-up period was 35 months, during which 13 patients developed recurrent disease and 14 patients died. Compared with patients without a high NLR, those with high NLR had a significantly shorter overall survival (p<0.001, Figure 1A) and significantly shorter disease-free survival (p<0.001, Figure 1B).

Recurrence sites and patient numbers are shown in Figure 2. Some patients had more than two recurrence sites. Of the 23 patients with high NLR, 11 (49%) had disease recurrence during the study period; while of the 22 patients without a high NLR, only two (9%) had recurrence. Five patients had recurrence in the thoracic lymph node, which was outside the usual dissection area.

Table I. *Characteristics of patients in this study.*

		N=45
Age (years)		71 (42-83)
Sex	Male/Female	37/8
Smoking history	Yes/No	44/1
Comorbidities*	Cardiovascular disease	18
	Diabetes melitus	6
	Other organ malignant tumor	5
	Liver disease	5
	Cerebrovascular disease	5
Clinical T factor	1/2/3/4	6/17/12/10
Clinical N factor	0/1/2	11/28/6
Clinical Stage	I/II/III	6/17/22
Surgical procedure		
Right	Pneumonectomy	2
	Upper	10
	Middle and lower	2
	Upper and middle	1
Left	Pneumonectomy	8
	Upper	8
	Lower	6
	Lower and lingular segment	5
	Upper and segment 6	3
Patholgical T factor**	1/2/3/4	8/14/13/8
Patholgical N factor**	0/1/2	11/24/8
Pathological Stage**	I/II/III	6/20/17
Preoperative treatment		5 (11%)
Postoperative treatment		13 (29%)
Recurrence	Locoregional	1 (2%)
	Distant	12 (27%)

Value is median (range). *Some patients had more than two comorbidities. **A patient without residual tumor after preoperative treatment was excluded.

Discussion

In this study, we showed that high NLR and pathological T3/T4 were significant predictors of poor prognosis in patients who underwent complete resection of centrally located lung squamous cell carcinoma. Moreover, high NLR was an independent predictor of poor prognosis in this cohort. Patients with high NLR had significantly high rates of disease recurrence and extremely poor outcomes. These findings may guide the selection of optimal treatments for centrally located lung squamous cell carcinoma.

Five patients had recurrence in thoracic lymph nodes, and four of them had pathological N2 lymph node metastasis. In patients with high NLR, cancer cells might spread into the lymph flow more progressively than expected before surgery. However, all lymph node recurrences were observed outside the usual dissection area. We speculate that cancer cells invade some lymph flows at a higher rate (12), because centrally located lung cancer is very close to mediastinal structures, and some cancer cells might spread easily through lymph flow pathways under the visceral and mediastinal pleura (13). Although no patient had

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

			Univariate analysis			Multivariate analysis		
		n	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age	≤71	28	1,00	0.44-4.01	0.692			
	>71	17	1,24					
Sex	Male	53	1,00	0.33-5.14	0.879			
	Female	15	0,90					
Comorbidities	Yes	23	1,00	0.69-6.48	0.209			
	No	22	0,50					
BMI	≤18.5	6	1,00	0.15-3.53	0.946			
	>18.5	39	0,95					
NLR	≤3.3	22	1,00	2.46-57.63	<0.001	1,00	1.85-47.47	0.003
	>3.3	23	8,98			7,17		
PLR	≤159	20	1,00	0.75-6.89	0.157			
	>159	25	2,13					
Surgical procedures	Pneumonectomy	10	1,00	0.21-2.38	0.686			
	Sleeve lobectomy	35	1,27					
Pathological N factor*	0/1	35	1,00	0.13-1.21	0.095	1,00	0.23-3.03	0.818
	2	8	2,71			1,16		
Pathological T factor*	1/2	22	1,00	1.46-15.99	0.008	1,00	0.79-11.56	0.108
	3/4	21	4,36			2,86		
Preoperative therapy	Yes	5	1,00	0.04-4.09	0.825			
	No	40	1,25					
Adjuvant chemotherapy	Yes	13	1,00	0.39-3.54	0.685			
	No	32	1,25					

HR: Hazard ratio; CI: confidence interval; BMI: body mass index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio. *A patient without residual tumor after preoperative treatment was excluded.

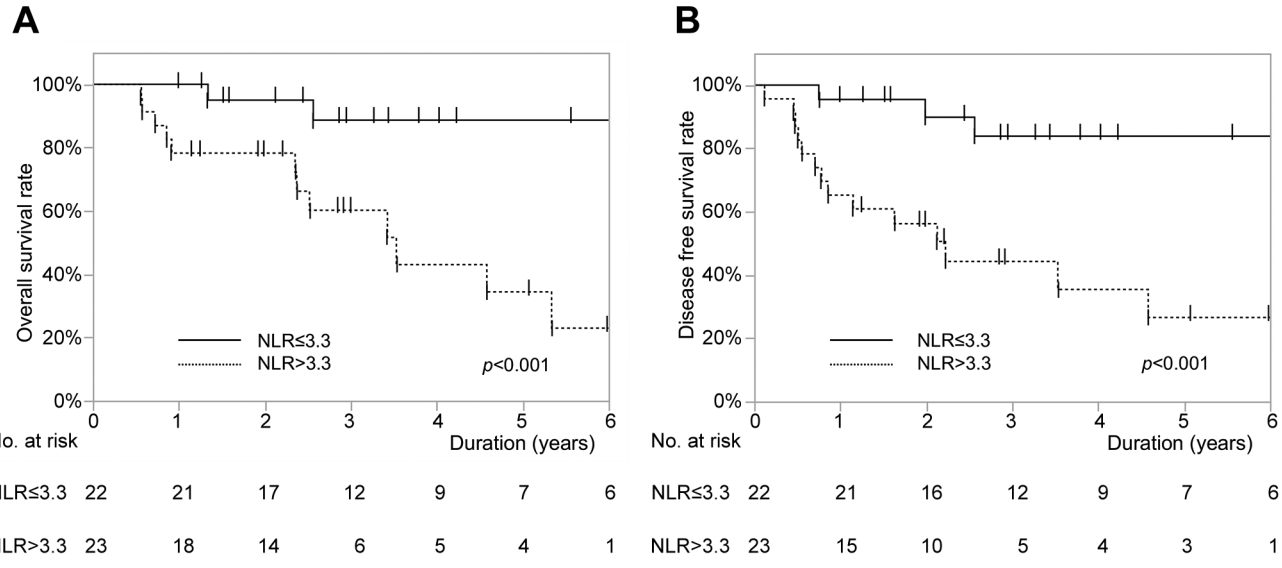

Figure 1. *Overall survival (A) and disease-free survival curves (B) according to neutrophil-to-lymphocyte ratio (NLR) score.*

cancer cell-positive pleural or pericardial effusion at the time of operation, three had pleural dissemination and one had carcinomatous pericarditis during the follow-up period. Recurrence in the pleura or pericardium may be due to remnant cancer cells in the mediastinal pleura or pericardium that could not be noticed during the operation.

Circulating tumor cells (CTCs) are cancer cells that escape from the primary lesion or from metastatic foci and enter the

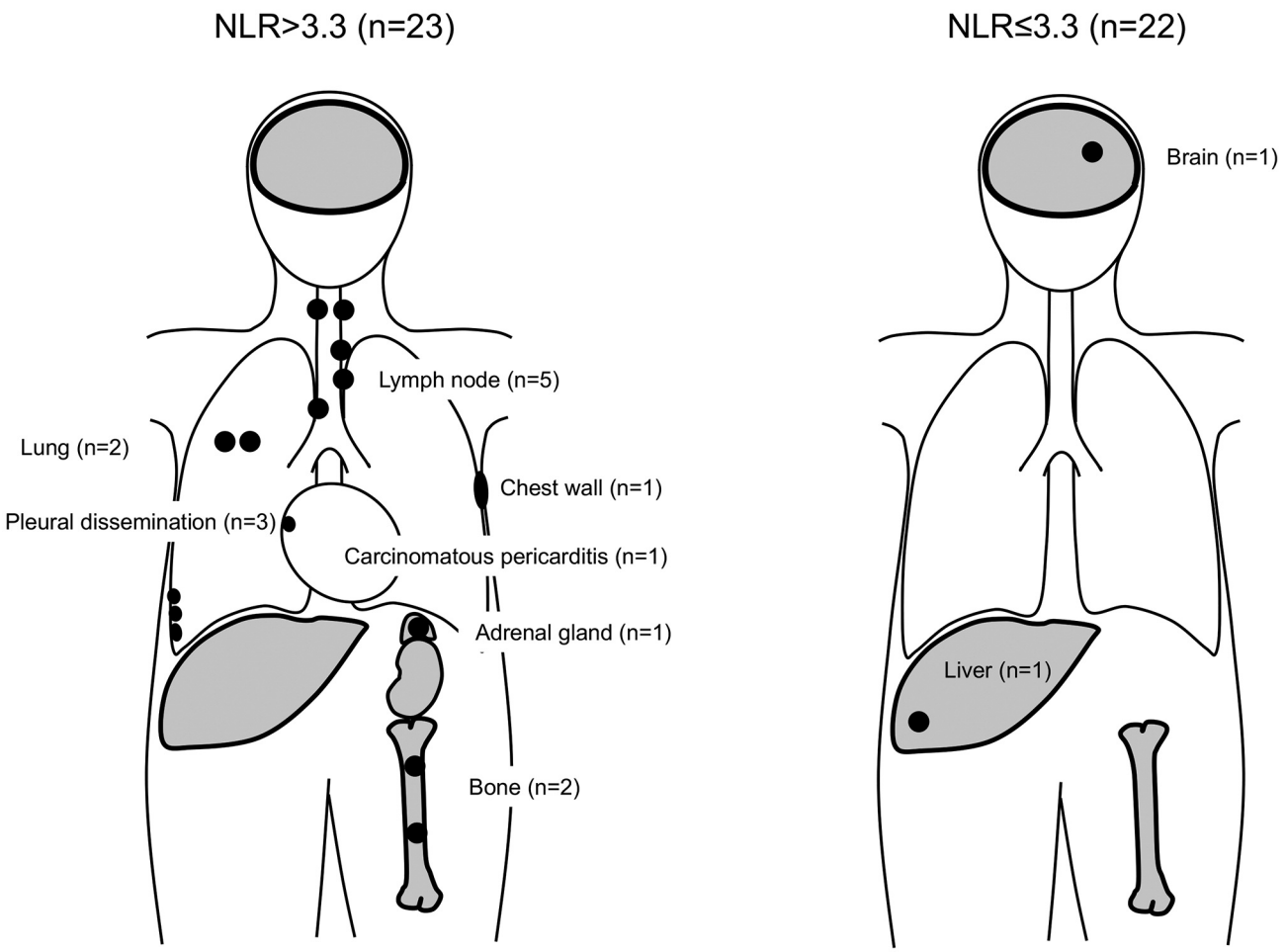

Figure 2. *Details on recurrence sites according to neutrophil-to-lymphocyte ratio (NLR) score.*

bloodstream, denoting a switch from localized to systemic disease (14). In patients with resectable gastric cancer, a significant correlation was observed between CTC counts and NLR score (15). In this study, we found that half of the patients with high NLR had disease recurrence during the study period and experienced extremely poor outcomes. In these patients, recurrences were commonly observed in distant organs, and no patient had hilar local recurrence. The presence of CTCs may contribute to poor prognosis in patients with high NLR.

An indication of surgery and the lymph node dissection area should be determined carefully in patients with centrally located lung squamous cell carcinoma, especially those with high NLR. Although the NLR score was identified as an important indicator for providing adjuvant chemotherapy, we suggest that the way to improve prognosis after complete resection of centrally located lung cancer is to control the remaining cancer cells, which may spread through lymph or vessel flow pathways aggressively. However, conventional platinum doublet chemotherapy did not have an acceptable beneficial effect on prognosis in our patient population.

Lung squamous cell carcinoma remains largely excluded from targeted therapies. It is reported that adding cetuximab to chemotherapy when both epidermal growth factor receptor fluorescence in situ hybridization and immunohistochemistry are positive in stage IV squamous cell lung cancer patients significantly improves overall survival (16). Several large phase III trials of adjuvant immunotherapy or immunochemotherapy in patients with resected non-small cell carcinoma stage IB to IIIA have revealed beneficial effects on the prognosis of patients positive for programmed death-ligand 1 (17). Additional analyses are ongoing. Thus, novel beneficial adjuvant therapies for locally advanced squamous cell carcinoma are needed.

This study has several limitations. First, it was a small retrospective study. However, data from more patients are emerging and further analyses are underway. Second, surgical procedures and ancillary treatments were selected at the discretion of the physician in charge of each case. Hence,

selection criteria for surgical procedures and perioperative therapy should be established. Third, the molecular mechanisms underlying malignant behaviour in patients with high NLR were not investigated. Thus, molecular targets for anticancer treatment should be established in patients with high NLR.

In conclusion, we have identified high NLR as an independent predictor of poor prognosis in patients who underwent complete resection of centrally located lung squamous cell carcinoma. An indication of surgery and lymph node dissection area should be determined carefully in patients with centrally located lung squamous cell carcinoma, especially those with high NLR.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Takuma Tsukioka designed this study, analyzed the data, prepared the figures and wrote the original draft. Hiroaki Komatsu, Hidetoshi Inoue, Ryuichi Ito and Satoshi Suzuki collected the clinical data. Nobuhiro Izumi and Noritoshi Nishiyama critically reviewed the manuscript. All Authors read and approved the final manuscript.

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