ORIGINAL ARTICLE – THORACIC ONCOLOGY

Prognostic significance of neutrophil-to-lymphocyte ratio in locally advanced non-small cell lung cancer treated with trimodality therapy

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Running head: Prognostic impact of NLR in LA-NSCLC

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Synopsis

We evaluated the prognostic impact of postoperative NLR in LA-NSCLC patients treated with trimodality therapy. The high postoperative NLR value was not only an independent unfavorable prognostic factor, but also a promising indicator for the postoperative treatment.

Abstract

Purpose: Current evidence suggests that the neutrophil-to-lymphocyte ratio (NLR) is a prognostic factor in several types of cancer. In this study, we aimed to evaluate the prognostic impact of clinicopathological factors, including postoperative NLR, in patients with locally advanced non-small cell lung cancer (LA-NSCLC) who underwent surgery after chemoradiotherapy (CRT) with or without postoperative adjuvant chemotherapy.

Methods: The medical records of LA-NSCLC patients treated with trimodality therapy at our institution between June 1999 and May 2019 were reviewed. The association between several clinicopathological factors and overall survival (OS) was analyzed.

Results: A total of 168 patients were included in this study. Regarding the prognosis, 5-year OS rate was 68.1%, and 2-year recurrence-free survival rate was 66.1% in the entire population. In multivariate analysis, we identified that high postoperative NLR, not pretreatment or preoperative NLR, was one of the independent factors for unfavorable OS (NLR high vs. NLR low; hazard ratio = 2.45, 95% confidence interval: 1.53-3.94, $p < 0.001$). In addition, among patients with high postoperative NLR, patients who received postoperative adjuvant chemotherapy showed significantly better 5-year OS in comparison with those who did not ($p = 0.016$). On the other hand, postoperative adjuvant chemotherapy had no impact

on the prognosis in patients with low NLR (p = 0.19).

Conclusions: Our results suggest that the high postoperative NLR was not only an independent unfavorable prognostic factor in patients with LA-NSCLC who were treated with trimodality therapy, but also a promising indicator for the postoperative treatment in this population.

Introduction

Lung cancer remains the leading cause of cancer-related death worldwide.[1,2] Approximately 20 to 25% of patients with lung cancer present with locally advanced disease, and concurrent chemoradiotherapy (CRT) is the standard therapy for the patients with unresectable stage IIIA or IIIB non-small cell lung cancer (NSCLC).[3] In recent years, immune-checkpoint inhibitors (ICIs) have also been used as the standard of care for advanced NSCLC. The combination of chemotherapy with ICIs has demonstrated the clear superiority compared with chemotherapy alone.[4] Clinical trials are currently being conducted to demonstrate the efficacy of preoperative induction chemotherapy combined with ICI compared to chemotherapy alone (NCT03800134 and NCT03456063). In addition to these therapeutic strategies, surgical resection after the induction therapy is one of the possible options for locally advanced (LA)-NSCLC, and is mainly performed by experienced institutions. The rationale for induction treatment in patients with LA-NSCLC is to allow complete surgical resection by reducing the number of cancer cells in the primary tumor and metastatic local lymph nodes, and eradicating possible micrometastases.[5] In fact, cancer cells may still remain microscopically, even if the complete response seemed to be obtained radiographically after induction CRT. Thus, we consider that surgery after induction CRT is essential. Based on this idea, we have performed

trimodality therapy (CRT followed by surgery with or without postoperative adjuvant chemotherapy) for LA-NSCLC and reported the feasibility and favorable prognosis with moderate, but acceptable toxicities.[6-8] Recently, phase II study of a quadruple-modality therapy (induction chemoradiation followed by surgery with perioperative immunotherapy) for resectable stage discrete N2 IIIA-B NSCLC has been started in Japan (JapicCTI-195069).

Inflammation is an important feature of tumor microenvironment and associated with poor prognosis of various types of tumor.[9] Hematological inflammatory parameters such as neutrophil, lymphocyte, monocytes, and platelets can reflect the immune status and have important predictive value for the prognosis of tumors.[10,11] Neutrophil to lymphocyte ratio (NLR), a marker of systemic inflammation, is one of the indicators of systemic inflammation and has received considerable interest recently because it is simple and convenient.[12] Several studies have reported that pretreatment NLR value was correlated with the prognosis of various malignancies.[13-16] With regard to lung cancer, Jin and colleagues have reported that postoperative NLR and the changes in NLR during the treatments could predict the survival in patients undergoing complete resection of stage I NSCLC.[17] However, the prognostic impact of NLR in LA-NSCLC is still unclear. In this study, we retrospectively assessed the clinical course of LA-NSCLC patients who underwent surgical resection after CRT with or without

postoperative adjuvant chemotherapy, and evaluated the clinicopathological factors which had the impact on prognosis to identify the patients who might best benefit from trimodality therapy.

Methods

Patient selection and evaluation

This retrospective study was approved by Ethics Committee, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, Okayama, Japan (approval number: Eki1055) and written informed consent was waived. A total of 168 patients with LA-NSCLC who underwent surgery after CRT with or without adjuvant chemotherapy at Okayama University Hospital, Okayama, Japan between June 1999 and May 2019 were enrolled in this study. The International Association of the Study of Lung Cancer TNM staging system for NSCLC (eighth edition) was used to determine the disease stage and nodal location.[18] Even in the cases classified by the former edition, we re-classified them using the current edition. The clinical stage was determined using bronchoscopy, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging of the brain, and a radionuclide bone scan or 18F-fluorodeoxyglucose positron emission tomography-CT.

Trimodality therapy

While several chemotherapeutic regimens were applied, cisplatin (CDDP) and docetaxel (DOC) plus concurrent thoracic radiation with total dose of 40 or 46 Gy was generally used as the basic regimen for the preoperative CRT in our institution, as described previously.[7] S1-tegafur-oxonate combination was generally selected for the patients who were older than 75 years of age. After receiving a radiation dose of around 40 Gy, the patients were restaged according to the image analysis. The radiologic response was assessed using the Eastern Cooperative Oncology Group criteria and was classified as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Patients without unresectable lesions were scheduled to undergo surgery within 6 weeks of the completion of preoperative CRT. For poorly responding patients, an additional radiation dose of up to 14 or 20 Gy was administered to the boost volume. The detail of irradiated field for the thorax was previously described.[7,8] The surgical procedure was determined according to the disease extent, and included lobectomy, bilobectomy or pneumonectomy with complete ipsilateral mediastinal and subcarinal nodal dissection. Resection with reconstruction of the bronchus, chest wall, and/or major vessels was performed where necessary. Whereas the postoperative

treatment was left to the physician's discretion, adjuvant chemotherapy was administered in as many cases as possible if the medical condition was acceptable. The regimen was determined generally based on the pathological response to CRT, i.e., the same or similar regimen to preoperative chemotherapeutic regimen was selected in the case the effective response to preoperative CRT was observed.

Data collection

The data collected from all of the patient medical records included the following: age, sex, smoking history, histology, clinical stage, treatment course, pathological response to CRT and pretreatment, preoperative, and postoperative NLR. The pathological response to the preoperative CRT was classified into three categories, pathological complete response, pathological major response, and pathological minor response.[19] The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Postoperative NLR value was calculated based on the result of blood test within 1 month after discharge. We defined the difference between pretreatment and preoperative NLR as δ1-NLR, pretreatment and postoperative NLR as δ2-NLR, preoperative and postoperative NLR as δ3-NLR. All the patients were observed either until death or May 1, 2020.

Statistical analyses

All statistical analyses were performed using EZR version 1.41.1 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 4.0.0 (The R Foundation for Statistical Computing, Vienna, Austria).[20] To determine the optimal cutoff value for each NLR and δ-NLR, a receiver operating characteristic (ROC) curve was generated, and the cutoff value was defined as the point on the curve that was closest to the upper left corner of the plot. The overall survival (OS) and recurrence-free survival (RFS) rates were calculated from the starting date of preoperative CRT to the date of death or the last follow-up for OS and to the date of confirmed disease relapse for RFS. The survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. χ^2 tests were applied to compare the ratio between the two groups. Cox proportional hazard model was used for multivariate analysis. A value of $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

We reviewed the medical record of 168 patients with LA-NSCLC who underwent lung

resection after CRT with or without postoperative adjuvant chemotherapy. Patient characteristics are summarized in **Table 1**. With regard to the clinical stage (c-stage) before treatment, approximately 90% of the patients was diagnosed as having c-stage IIIA or higher. Three patients with c-stage IVA were included because reevaluation after CRT showed the improvement to operable status. The cN2 and cN3 statuses were pathologically confirmed in 59 of the 107 patients and 7 of the 12 patients, respectively, using either mediastinoscopy or endobronchial ultrasound before treatment initiation.

Trimodality intervention

Detailed information of trimodality therapy is shown in **Table 2**. Two courses of CDDP + DOC with 46 Gy radiation dose was the most common preoperative treatment and 142 patients (84.5%) completed preoperative CRT. On the other hand, CRT was not completed in 26 patients because of the severe toxicity or allergic reaction. With regard to the surgical procedures, 3 of 168 patients exhibited incomplete tumor resection with a microscopically positive surgical margin or pleural dissemination that was diagnosed pathologically after the surgery. Only severe postoperative complications including anastomotic complications and empyema were shown in **Table 2** and the morbidity and mortality of all complications were

shown in **Supplementary Table 1**. Pretreatment, preoperative, and postoperative NLR in each patient were calculated from the results of blood tests performed within the median of 6 days (range, 0 to 157) before CRT, median of 5 days (range, 0 to 34) before surgery, and median of 31 days (range, 10 to 221) after surgery, respectively. With regard to the adjuvant therapy, 77 patients (45.8%) underwent postoperative adjuvant chemotherapy. They included two of three patients with incomplete resection and 21 of 39 patients (53.8 %) with minor response to preoperative CRT.

ROC curve analyses

We performed ROC curve analyses to search appropriate cutoff values for each NLR. The cutoff value was 1.84 for pretreatment NLR, with an area under the curve (AUC) of 0.536. Pretreatment NLR had a sensitivity of 75.7% and a specificity of 37.2% for predicting OS. The best cutoff values for preoperative and postoperative NLR were 4.81 and 4.06, respectively, with AUCs of 0.544 (sensitivity: 17.6%, specificity: 93.6%) and 0.652 (sensitivity: 56.8%, specificity: 70.2%), respectively (Supplementary Figure 1). The AUCs for δ1-NLR, δ2-NLR, and δ3-NLR were 0.498, 0.614, and 0.609, respectively. The selected cutoff values for δ1-NLR, δ2-NLR, and δ3-NLR were -0.100, 2.40, and 2.21, respectively.

Survival analyses

The median follow-up period was 63 months (range, 5 to 252). Fifty-two patients died of NSCLC and 22 patients died of other causes. The disease relapse patterns were classified as locoregional sites (surgical margin, intrapulmonary, regional lymph node, and pleural cavity) and distant sites. Disease relapse was observed in 73 patients, with a locoregional relapse alone in 12 patients, a distant relapse alone in 45 patients, and both locoregional and distant relapse in 16 patients at the time of initial diagnosis of relapse. Five-year OS and 2-year RFS rates for the entire population were 68.1% and 66.1%, respectively (**Figure 1a**). To determine which patients were more likely to benefit from trimodality therapy, the association between clinicopathological factors and OS was examined using univariate analysis (**Table 3**). As expected, the 5-year OS rate in patients with major or CR to preoperative CRT was significantly better than that in patients with minor response (p = 0.0020), which was concordant with the previous studies.[21] The survival curves stratified by pathological response to CRT are shown in **Figure 1b**. On the other hand, there was no significant difference in OS between patients with clinical stage IIB and IIIA or higher and those with N2-N3 and N0-N1 (p = 0.84 and p = 0.91, respectively). It may suggest that induction CRT was more effective to the patients with

advanced stage, that is, it was more beneficial to the patients with stage IIIA or higher than those with stage IIB. Of note, the 5-year OS in patients with preoperative NLR ≥ 4.81 was significantly worse than that in patients with postoperative NLR < 4.81 (p = 0.026) and the 5-year OS in patients with postoperative NLR ≥ 4.06 was significantly worse than that in patients with postoperative NLR < 4.06 (p < 0.001) (Figure 1c). The 5-year OS in patients with δ2-NLR ≥ 2.40 was significantly worse than that in patients with δ2-NLR < 2.40 (p = 0.0038) and the 5-year OS in patients with δ3-NLR ≥ 2.21 was significantly worse than that in patients with δ3-NLR < 2.21 (p = 0.0073). In addition, the 5-year OS rate in patients who underwent postoperative adjuvant chemotherapy was significantly better than that in patients who did not undergo postoperative adjuvant chemotherapy (*p* = 0.0053). We subsequently performed multivariate analysis to determine the factors significant for OS. As indicated in **Table 4**, pathological response to preoperative CRT, postoperative NLR, and postoperative adjuvant chemotherapy were significantly associated with OS (*p* < 0.001, *p* < 0.001, and *p* = 0.0010, respectively) indicating that these were independent prognostic factors for patients with LA-NSCLC treated by trimodality therapy. These results prompted us to focus on the significance of postoperative NLR and its relationship with postoperative adjuvant chemotherapy

Significance of postoperative NLR

To gain insights into the clinical implications of postoperative NLR, we classified the patients in this cohort into two groups based on the postoperative NLR cutoff value of 4.06, and analyzed the relationship between postoperative NLR and clinicopathologic factors using χ^2 test. As a result, clinicopathologic factors, including age, sex, smoking history, histological subtypes, clinical stage, nodal status, emphysematous change, completion of CRT, tumor location, surgical procedure, operation time, blood loss and postoperative complications, were not significantly associated with postoperative NLR, indicating that those factors had no impact on postoperative NLR (**Supplementary Table 2**). We next examined the relationship between postoperative adjuvant chemotherapy and postoperative NLR. Five-year OS stratified by postoperative NLR was compared between the groups of patients who either did or did not undergo postoperative adjuvant chemotherapy using log-rank test. The results revealed that in the group of patients who did not undergo postoperative adjuvant chemotherapy, patients with postoperative NLR ≥ 4.06 showed a significantly shorter 5-year OS, compared to those with postoperative NLR < 4.06 (p = 0.0023) (**Table 5)**. On the other hand, in the group of patients who underwent postoperative adjuvant chemotherapy, there was no significant relationship between postoperative NLR and 5-year OS (p = 0.13). Furthermore, in the group

of postoperative NLR ≥ 4.06, the 5-year OS in patients who underwent postoperative adjuvant chemotherapy was significantly better than that in patients who did not undergo postoperative adjuvant chemotherapy (p = 0.016). In addition, in the group of patients with postoperative NLR < 4.06, there was no significant relationship between postoperative adjuvant chemotherapy and 5-year OS (p = 0.19). The survival curves stratified by the level of postoperative NLR and the status of postoperative adjuvant chemotherapy are shown in **Figure 2**. Subsequently, we investigated the role of postoperative adjuvant chemotherapy in survival (**Supplementary Table 3)**. The regimens of postoperative adjuvant chemotherapy were as follows: CDDP + DOC (n = 52), CDDP + pemetrexed (PEM) (n = 4), CDDP + S-1 (n = 3), CDDP + irinotecan (n = 3), CDDP + VNR (n = 2), CDDP + gemcitabine (GEM) (n = 1), CBDCA + PTX (n = 4), CBCDA + DOC (n = 1), CBCDA + PEM (n =1), CBCDA + GEM (n = 1), single agent of S-1 (n =1), tegafur/uracil (n = 1), VNR (n = 1), gefitinib (n = 1), pembrolizumab (n =1). Two courses of CDDP + DOC was the most common postoperative adjuvant chemotherapy regimen and 52 patients (76.5%) completed this treatment. On the other hand, postoperative adjuvant chemotherapy was not completed in 16 patients because of either severe toxicity or allergic reaction (n = 7), pneumonia (n = 4), patient refusal (n = 2), onset of enteritis (n = 1), cancer recurrence (n = 1), and patient death (n = 1). We then classified the

patients who underwent postoperative adjuvant chemotherapy into two groups based on the postoperative NLR cutoff value of 4.06, and compared the clinical characteristics using χ^2 test to examine the potential bias between high- and low-NLR in patients who underwent postoperative adjuvant chemotherapy. As a result, no significant difference in clinicopathologic factors including age, sex, histological subtypes, pathological response to CRT, completion of adjuvant chemotherapy and residual tumor, were observed between two groups. In the high-NLR group of patients who underwent postoperative adjuvant chemotherapy, 5-year OS rate was 85.2% in patients who completed postoperative adjuvant chemotherapy, and 30.0% in those who did not (p = 0.0095) (**Supplementary Figure 2**). Taken together, these results indicated that only the patients with postoperative NLR ≥ 4.06 had benefited of postoperative adjuvant chemotherapy. Furthermore, it suggests the possibility that postoperative NLR value can be one of the useful indicators of the decision for postoperative adjuvant chemotherapy.

Discussion

A systemic inflammatory response leads to angiogenesis, inhibition of apoptosis, and DNA damage.[22] Various markers of systemic inflammatory response such as cytokines, C-reactive protein (CRP), Glasgow prognostic score, NLR and platelet to lymphocyte ratio (PLR)

have prognostic roles in various common solid tumors, and the value of a systemic inflammatory response has been extensively examined in NSCLC.[23,24] Although we focused on NLR in this study, we need to consider other systemic inflammatory markers as a future task. Regarding the relationship between NLR and CRT, Ishikawa and colleagues have reported that it was demonstrated that an elevated post-CRT NLR tended to be correlated with poor pathological response of CRT in rectal cancer.[25] In that study, the post-CRT NLR was higher than the pre-CRT NLR, but there was no difference in total WBC, indicating a decrease in lymphocytes. Since lymphocytes, especially T cells play a central role in anti-tumor immunity, the decrease of NLR after CRT might reflect the overall ability of the host to protect cancer.

In this study, we reviewed the clinical course of 168 patients with LA-NSCLC who underwent surgery after CRT with or without postoperative adjuvant chemotherapy, and identified that the significant factors for the better survival were the effective pathological response to preoperative CRT, postoperative adjuvant chemotherapy, and low postoperative NLR. We also analyzed the sample set of 156 patients treated with CDDP and DOC only, and another set of 142 patients who received the entire treatment cycles. As a result of these analyses, the prognosis was also significantly lower in the group with high postoperative NLR (data not shown). In addition, our results suggested that the patients with high postoperative

NLR may benefit from postoperative adjuvant chemotherapy. The selection of appropriate therapeutic modalities is the key for the multidisciplinary treatment of LA-NSCLC, and postoperative NLR value might serve as not only a promising prognostic factor but also a novel indicator for the decision regarding the administration of postoperative adjuvant chemotherapy. Further investigations such as an optimal cutoff value of NLR are needed.

Whereas postoperative NLR value is associated with the prognosis of LA-NSCLC patients treated with trimodality therapy, there was no significant association shown between the prognosis and pretreatment or preoperative NLR. It is known that the ratio of neutrophil is temporally increased in response to surgical stress.[26] However, postoperative NLR in this study was evaluated after patient discharge (median 31 days after surgery). It is less likely that surgical stress had some impact on the postoperative NLR, because the literature has shown that inflammation due to the surgical wound healing process ceases 1 month after the operation.[27] Indeed, no significant relationship between surgery-related factors (surgical procedure, the amount of blood loss, and operation time) and postoperative NLR was observed in our cohort. The question remains, why did only postoperative NLR correlate with prognosis? Several studies have reported a positive correlation between tumor progression and NLR levels, suggesting that NLR may be a marker of tumor burden.[28,29] In addition, Jin and

colleagues have also reported that patients with high postoperative NLR value had a shorter OS and disease-free survival even in the cases with stage I NSCLC.[17] These previous studies provided one possible explanation, namely that NLR may reflect the postoperative latent residual tumor. In the case that the tumor volume significantly decreases by the treatment including surgery, care should be taken to not only pre-treatment NLR but also post-treatment NLR.

Considering that the recurrence was frequently observed in LA-NSCLC patients treated with trimodality therapy,[30] the additional adjuvant therapy should be taken into account to improve the clinical outcome. Even the complete response by the pathological evaluation only means that the induction CRT was effective in the primary lesion, that is, it is difficult to evaluate if the micrometastasis exists somewhere in the body. Therefore, it is meaningful to give postoperative adjuvant chemotherapy, even in the cases with the complete response pathologically. However, patients after intensive treatment sometimes cannot afford to undergo postoperative adjuvant chemotherapy due to considerable toxicity; therefore, there is a need to establish a novel indicator for selecting patients who should undergo postoperative adjuvant chemotherapy. Our results indicated that whereas patients with high postoperative NLR who received postoperative adjuvant chemotherapy had a better prognosis in comparison with

those who did not, there was no significant association between postoperative adjuvant chemotherapy and prognosis in patients with low postoperative NLR. However, it does not mean that patients with low postoperative NLR values are refractory to postoperative adjuvant chemotherapy, but that the prognosis was considered to be originally better. On the other hand, patients with high postoperative NLR had a poor prognosis, thus postoperative adjuvant chemotherapy improved the prognosis. Furthermore, a completion of adjuvant therapy achieved better long-term survival than those who did not complete the adjuvant therapy. As described above, there is the possibility that NLR positively correlates with tumor burden; thus, postoperative adjuvant chemotherapy might contribute to the elimination of microscopic residual tumor in patients with high postoperative NLR. To further investigate the potential of NLR as a postoperative prognostic marker, future studies on the time course changes in NLR, including the response to postoperative adjuvant chemotherapy, are mandatory.

Our study had several limitations. First, this was a retrospective study based on a database of the modest sample size from a single institution. In addition, there should have been changes in the management of patients during approximately 20 years. Second, the timing of measuring NLR varied among the cases. These factors might have introduced potential biases in our results.

In conclusion, we identified that the high postoperative NLR value was not only an unfavorable prognostic factor in LA-NSCLC patients treated with trimodality therapy, but also a promising indicator of the decision for postoperative adjuvant chemotherapy. Although further investigation is needed to clarify the significance of NLR in the treatment of LA-NSCLC, postoperative NLR may be useful in deciding on the optimal future treatment options.

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Figure legends

Fig. 1a. Overall survival (OS) and recurrence-free survival (RFS) in the entire population.

Fig. 1b. Overall survival (OS) stratified by the pathological response to the preoperative chemoradiotherapy.

Fig. 1c. Overall survival (OS) stratified by the postoperative neutrophil-to-lymphocyte ratio (NLR).

Fig. 2. Overall survival (OS) stratified by the level of postoperative neutrophil-to-lymphocyte ratio (NLR) and the presence or absence of postoperative adjuvant chemotherapy.

Supplementary Figure legends

Supplementary Fig. 1. ROC curves to determine the cutoff value for pretreatment, preoperative and postoperative NLR.

Supplementary Fig. 2. Overall survival (OS) stratified by the completion of postoperative adjuvant chemotherapy in the high postoperative NLR (≥ 4.06) group of patients who underwent postoperative adjuvant chemotherapy.

Table 1. Characteristics of the patients with LA-NSCLC treated by trimodality therapy (n = 168)

Characteristics	Results
Age (years)	
Median (range)	61 (31-79)
Sex	
Male	130 (77.4%)
Female	38 (22.6%)
Smoking history (Pack-years)	
< 30	54 (32.1%)
≥ 30	114 (67.9%)
Histological subtypes	
Adenocarcinoma	95 (56.5%)
Squamous cell carcinoma	58 (34.5%)
Others	15 (9.0%)
Emphysematous change	
Yes	67 (39.9%)
No	101 (60.1%)
c-Stage	
IIB	18 (10.7%)
T3N0 / T2N1	12 / 6
IIIA	88 (52.4%)
T4N0 / T3 or T4N1 / T1 or T2N2	12 / 18 / 58
IIIB	53 (31.5%)
T3 or T4N2 / T1 or T2N3	47 / 6
IIIC	6 (3.6%)
T3 or T4N3	6
IVA	3 (1.8%)
T2N2M1a / T3N1M1b / T4N2M1b	1 / 1 / 1
Lymph node status	
N0 / N1 / N2 / N3	24 / 25 / 107 / 12
Main tumor location	
Right	92 (54.8%)
Left	76 (45.2%)

LA-NSCLC; locally advanced non-small-cell lung cancer

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Table 2. Characteristics of trimodality therapy (n = 168)

Variables	Results
Chemotherapy	
CDDP + DOC	156 (92.8%)
CBDCA + PTX	4 (2.4%)
S-1	4 (2.4%)
CDDP + Others	3 (1.8%)
CDGP + 5FU	1 (0.6%)
Dose of radiation therapy	
< 40Gy	3 (1.8%)
40Gy	8 (4.8%)
46Gy	142 (84.5%)
> 46Gy	15 (8.9%)
CRT response	
CR/PR/SD/PD	2 (1.2%) / 128 (76.2%) / 36 (21.4%) / 2 (1.2%)
CRT completion	
Yes/No	142 (84.5%) / 26 (15.5 %)
Days to operation from completion of CRT, median (range)	41 (14–349)
Type of pulmonary resection	
Lobectomy/ Bilobectomy/ Pneumonectomy	143 (85.1 %) / 17 (10.1 %) / 8 (4.8 %)
Severe postoperative complication[a]	
Yes/No	12 (7.1%) / 156 (92.9%)
Postoperative hospitalization days (Median, range)	20 (8-635)
Residual tumor	
R0/R1	165 (98.2%) / 3 (1.8%)
Pathological response of induction CRT	
Minor response	39 (23.2%)
Major response	68 (40.5%)
Complete response	61 (36.3%)
NLR (pretreatment)	
Median (range)	2.41 (0.692-11.5)
NLR (preoperative)	
Median (range)	2.24 (0.526-45.5)

NLR (postoperative)	
Median (range)	3.68 (0.226-83.0)
δ1-NLR	
Median (range)	-0.0451(-9.05-41.9)
δ2-NLR	
Median (range)	1.22 (-9.59-75.0)
δ3-NLR	
Median (range)	1.18 (-31.5-76.9)
Adjuvant chemotherapy	
Yes/No	77 (45.8%) / 91 (54.2 %)

a; Anastomotic complications and empyema

CDDP; cisplatin, DOC; docetaxel, CBDCA; carboplatin, PTX; paclitaxel,

S-1; tegafur/gimeracil/oteracil, CDGP; nedaplatin, 5FU; fluorouracil

CRT; chemoradiotherapy, NLR; neutrophil-to-lymphocyte ratio

Table 3. Univariate analysis (Logrank test) for overall survival (n = 168)

Variables	n	5-year OS	95% CI	*p* value
Age (years)				0.170
< 62	84	74.3%	62.9-82.6	
≥ 62	84	61.8%	49.7-71.8	
Sex				0.68
Male	130	69.6%	60.5-77.0	
Female	38	63.0%	43.9-77.2	
Smoking history (Pack-years)				0.85
< 30	54	67.0%	51.7-78.4	
≥ 30	114	68.7%	58.8-76.7	
Histological subtypes				0.83
Adenocarcinoma	95	71.0%	59.8-79.6	
Squamous cell carcinoma	58	64.4%	50.3-75.4	
Others	15	63.5%	33.1-83.0	
c-Stage				0.84
IIB	18	76.9%	49.4-90.7	
IIIA or higher	150	67.0%	58.4-74.3	
Nodal status				0.91
N0 / N1	49	74.3%	59.0-84.5	
N2 / N3	119	65.6%	55.6-73.8	
Emphysematous change				0.78
Yes	67	72.0%	58.7-81.7	
No	101	66.0%	55.4-74.6	
Completion of CRT				0.46
Yes	142	67.5%	58.5-74.9	
No	26	71.3%	48.9-85.2	
Pathological response to CRT				0.0020
Minor	39	45.3%	28.8-60.4	
Complete / Major	129	75.8%	67.0-82.6	
Pretreatment NLR				0.092
< 1.84	54	76.2%	61.7-85.7	
≥ 1.84	114	64.1%	53.9-72.6	

Preoperative NLR				0.026
< 4.81	149	68.9%	60.3-76.1	
≥ 4.81	19	61.2%	35.3-79.4	
Postoperative NLR				< 0.001
< 4.06	99	74.5%	63.9-82.5	
≥ 4.06	69	59.0%	46.0-69.8	
δ1-NLR				0.36
< -0.100	81	64.1%	51.7-74.1	
≥ -0.100	87	71.5%	60.2-80.1	
δ2-NLR				0.0038
< 2.40	126	73.7%	64.4-80.8	
≥ 2.40	42	51.2%	34.4-65.6	
δ3-NLR				0.0073
< 2.21	123	73.5%	64.0-80.8	
≥ 2.21	45	53.7%	37.7-67.2	
Adjuvant chemotherapy				0.0053
Yes	77	76.0%	63.7-84.6	
No	91	61.5%	50.3-71.0	

OS; overall survival, CI; confidence interval,

CRT; chemoradiotherapy, NLR; neutrophil-to-lymphocyte ratio

δ1-NLR; difference between pretreatment and preoperative NLR,

δ2-NLR; difference between pretreatment and postoperative NLR,

δ3-NLR; difference between preoperative and postoperative NLR

Table 4. Multivariate analysis (Cox proportional hazard regression model) for overall survival

Variables	Hazard ratio	95% CI	*p* value
c-Stage	0.662	0.262-1.67	0.38
Nodal status	1.05	0.532-2.09	0.94
Completion of CRT	1.12	0.628-2.00	0.70
Pathological response to CRT	0.355	0.208-0.607	< 0.001
High preoperative NLR	1.13	0.563-2.26	0.73500
High postoperative NLR	2.36	1.53-3.94	< 0.001
Adjuvant chemotherapy	0.429	0.261-0.713	< 0.001

CI; confidence interval

Table 5. The association between postoperative NLR and adjuvant chemotherapy

Variables	n	5-year OS	95% CI	*p* value
Log-rank test for OS among patients without adjuvant chemotherapy (n = 91)				
Postoperative NLR				0.0023
< 4.06	50	72.1%	56.7-82.8	
≥ 4.06	41	49.0%	32.6-63.5	
Log-rank test for OS among patients with adjuvant chemotherapy (n = 77)				
Postoperative NLR				0.13
< 4.06	49	77.1%	60.4-87.5	
≥ 4.06	28	73.7%	52.5-86.5	
Log-rank test for OS among patients with postoperative NLR ≥ 4.06 (n = 69)				
Adjuvant chemotherapy				0.016
Yes	28	73.7%	52.5-86.5	
No	41	49.0%	32.6-63.5	
Log-rank test for OS among patients with postoperative NLR < 4.06 (n = 99)				
Adjuvant chemotherapy				0.19
Yes	49	77.1%	60.4-87.5	
No	50	72.1%	56.7-82.8	

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