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Preoperative lymphocyte count is an independent prognostic factor in node-negative non-small cell lung cancer

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ABSTRACT

A number of prognostic factors have been reported in non-small cell lung cancer (NSCLC). Although lymph node metastasis is the most poorly predictive value in completely resected NSCLC, a significant number of patients have a fatal recurrence even in node-negative curative NSCLC. Recently inflammatory response has been shown as a predictive value in NSCLC. Neutrophils and lymphocytes play an important role in cancer immune response. In this study, we retrospectively examined the impact of preoperative peripheral neutrophil and lymphocyte counts on survival, and investigated the relationships of these factors to clinicopathological factors in node-negative NSCLC. A total 237 patients were evaluated. When the cut-off value of neutrophil count was 4500 mm^{-3} with a maximum log-rank statistical value, overall 5-year survival rates were 79.7% for the low-neutrophil-count group and 69.5% for the high-neutrophil-count group ($P = 0.04$). When the cut-off value of lymphocyte count was 1900 mm^{-3} with a maximum log-rank statistical value, overall survival rates were 67.9% for the low-lymphocyte group and 87.7% for the high-lymphocyte group ($P < 0.001$). High-neutrophil-counts were associated with tumor size ($P = 0.002$) and pleural invasion ($P < 0.001$). Low-lymphocyte-counts were correlated with vascular invasion ($P = 0.018$) and recurrence of NSCLC ($P = 0.01$). Multivariate analysis showed that the lymphocyte count was an independent prognostic factor (hazard ratio: 3.842; 95% confidence interval: 1.827–8.078; $P < 0.001$), but the neutrophil count was not ($P = 0.185$). We conclude that a peripheral lymphocyte count, which is associated with vascular invasion, is an independent prognostic factor in node-negative NCSLC.

1. Introduction

Non-small cell lung cancer (NSCLC) is one of the most common causes of cancer-related death. A number of prognostic factors have been proposed for patients with NSCLC, such as age, sex, performance status, tumor size, pleural invasion, lymphatic invasion, vascular invasion, lymph node metastasis, and distant metastasis [1–4]. Although lymph node metastasis is recognized as the worst prognostic factor in completely resected NSCLC [2,3], a significant number of patients have systemic recurrence even in node-negative curative NSCLC. Recently, the systemic inflammatory response has also been shown to have predictive value [5–7]. The neutrophil–lymphocyte ratio have been found to be an important indicator of adverse prognosis in colorectal cancer [8,9], gastric cancer [10,11], and NSCLC [12,13]. In addition, neutrophils have been implicated in the promotion of aerogenous metastasis in patients with bronchioalveolar carcinoma [14], and lymphocytes recognized as playing a fundamental role in cell-mediated immunologic destruction of host cancer cells [15]. The purpose of the present study, therefore, was to examine the impact of preoperative peripheral neutrophil and lymphocyte counts on survival and to investigate the relationships of the neutrophil and lymphocyte counts to clinicopathological factors in node-negative NSCLC.

2. Materials and methods

2.1. Patients

We conducted a retrospective analysis of patients diagnosed with NSCLC who underwent surgery at the Tsukuba University Hospital between January 2000 and December 2009. Data from 455 patients were obtained from the hospital's database. Two hundred eighteen patients were excluded owing to positive lymph node metastasis ($n = 94$), unmeasured differential leukocyte count ($n = 59$), incomplete radical surgery ($n = 42$), preoperative treatment ($n = 18$), suspicion of granulocyte-colony stimulating

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Table 1
Clinicopathological characteristics of patients.

	Total $n=237$
Age (mean ± SD), years	66.9 ± 10.1
Sex (male/female)	147/89
ECOG performance status (0/1/2)	173/15/1
Smoking index (mean ± SD)	733 ± 776
Resected side (right/left)	137/100
Surgical procedure(Pneumonectomy/Lob/Seg/Wedge)	1/189/24/23
Histological type (Ad/Sq/Large/others)	159/53/12/13
Pathological staging (I/II/III)	204/32/1
Tumor status (T1/T2/T3/T4)	136/80/20/1
Tumor size (mean ± SD), mm	26.8 ± 17.2
Pleural invasion (positive/negative)	59/178
Vascular invasion (positive/negative)	78/157
Lymphatic invasion (positive/negative)	58/177
Leukocyte counts (mean ± SD), mm^{-3}	6300 ± 1800
Neutrophil counts (mean ± SD), mm^{-3}	3700 ± 1400
Lymphocyte counts (mean ± SD), mm^{-3}	1900 ± 710
Albumin (mean ± SD), g/dL	4.0 ± 0.4
C-reactive protein (mean ± SD), mg/dL	0.45 ± 1.63
Postoperative adjuvant chemotherapy	13
Recurrences of NSCLC	29
Cause of death (lung cancer/others/unknown)	21/20/2

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; Lob, lobectomy or bilobectomy; Seg, segmentectomy; Wedge, wedge resection; Ad, adenocarcinoma; Sq, squamous cell carcinoma; Large, large cell carcinoma.

factor-producing tumor with leukocytosis ($n=3$), and autoimmune disease ($n=2$). Thus, 237 patients were included in this study. No patients had infection, such as pneumonia. A peripheral venous blood sample was collected from each patient within a month before surgery. A Blood test was performed using fully automated blood cell counting system and confirmed by laboratory technicians. Histological classification was carried out according to the WHO guidelines [16]. The tumors were staged according to the TNM classification of malignant tumors [17]. Vascular invasion was detected using elastica van Gieson staining and lymphatic invasion was determined using D2-40 staining.

2.2. Statistical analysis

Univariate analysis was performed using the Kaplan–Meier method, and statistical significances between survival curves were assessed by the log-rank test. Overall survival was determined from the date of surgery to the date of death or last follow-up. In selecting the optimal cutoff value for determining the effect of the neutrophil and lymphocyte count on overall survival, a running log-rank test was performed at intervals of 100 mm^{-3} between the 5th percentile and the 95th percentile of neutrophil and lymphocyte counts. The cutoff value was defined when the log-rank statistical value was maximum [18]. To examine the association with clinicopathological factors, the chi-square test (or Fisher's exact test when appropriate) was used for categorical variables, and the *t* test for continuous variables. To assess the independent predictive value of survival of different variables, multivariate analysis was performed using the Cox proportional hazards model. The result was considered to be significant when the *P* value was less than 0.05. Statistical analyses were performed using PASW Statistics 18 (SPSS, Chicago, IL, USA).

3. Results

3.1. Patients' characteristics

The clinicopathological characteristics of the patients are shown in Table 1. There were 147 men and 89 women. The patients' age at the time of operation ranged from 29 to 89 years (mean age, 66.9 years). The mean follow-up was 43 months (range, 1–118 months). Thirteen patients were performed postoperative adjuvant chemotherapy and 29 patients had recurrences of lung cancer. The overall 5-year survival rate of all 237 patients was 77.7%.

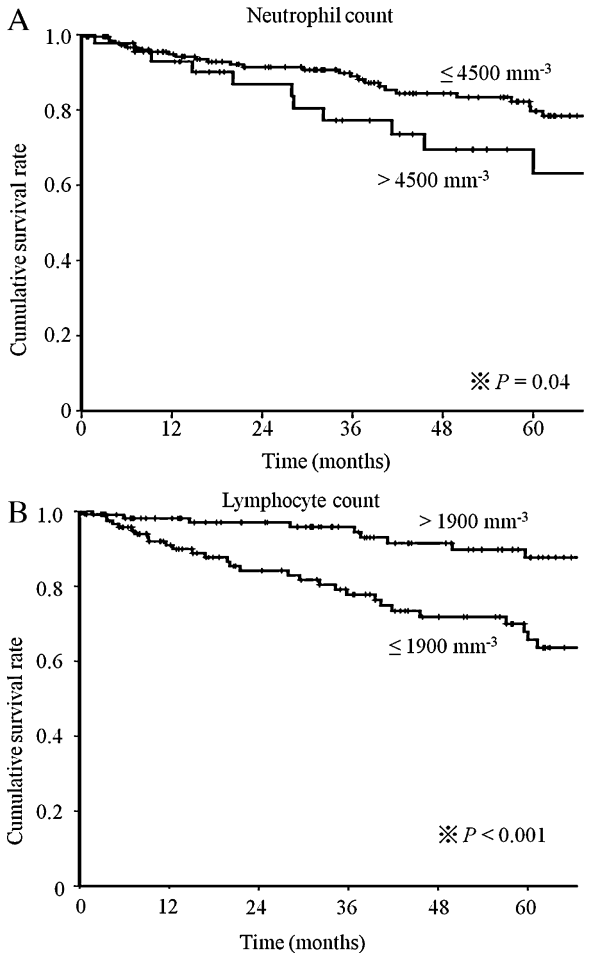

Fig. 1. (A) Overall survival curves at the optimal cutoff value of the neutrophil counts (4500 mm^{-3}). The overall 5-year survival rates were 79.7% for the low-neutrophil-count group (neutrophil count ≤4500 mm^{-3}; $n=191$), which was significantly higher than 69.5% for the high-neutrophil-count group (neutrophil count >4500 mm^{-3}; $n=46$). (B) Overall survival curves at the optimal cutoff value of the lymphocyte counts (1900 mm^{-3}). The overall 5-year survival rates were 67.9% for the low-lymphocyte-count group (lymphocyte count ≤1900 mm^{-3}; $n=110$), which was significantly lower than 87.7% for the high-lymphocyte-count group (lymphocyte count >1900 mm^{-3}; $n=127$).

3.2. Optimal cutoff values for neutrophil and lymphocyte counts

As for the neutrophil count, the maximum log-rank statistical value was 4.210 ($P=0.04$) when the cutoff value was 4500 mm^{-3}. Kaplan–Meier survival curves according to the optimal cutoff value are shown in Fig. 1A. The overall 5-year survival rates were 79.7% for the low-neutrophil-count group (neutrophil count ≤4500 mm^{-3}; $n=191$) and 69.5% for the high-neutrophil-count group (neutrophil count >4500 mm^{-3}; $n=46$). As for the lymphocyte count, the maximum log-rank statistical value was 13.19 ($P<0.001$) when the cutoff value was 1900 mm^{-3}. Kaplan–Meier survival curves according to the optimal cutoff value are shown in Fig. 1B. The overall 5-year survival rates were 67.9% for the low-lymphocyte-count group (lymphocyte count ≤1900 mm^{-3}; $n=110$) and 87.7% for the high-lymphocyte-count group (lymphocyte count >1900 mm^{-3}; $n=127$).