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Impact of nutritional status on long-term prognosis for patients with postoperative non small cell lung cancer

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Abstract

In lung cancer, postoperative prognosis can be generally predicted by the pathological stage, however, cancer recurrence has often been observed even in early stage patients. Therefore, accurate prediction is difficult. It has been suggested, as a reason, that this prediction does not consider host factors, i.e. immunological or nutritional status. In this prospective study, we evaluated the perioperative nutritional status as a host factor, and analyzed the relationship between the nutritional status and prognosis. Serum prealbumin levels were measured on preoperative and postoperative day 7 for forty patients with non small cell lung cancer who underwent lobectomy with lymph node dissection. We analyzed the correlation between serum prealbumin level and prognosis, and found that the prognosis of the group with a prealbumin level of more than 23 mg/dl during the preoperative period was statistically significantly better. Furthermore, the multivariate analysis revealed that a prealbumin level of more than 23 mg/dl during the preoperative period was an independent prognostic factor.

Key words: prealbumin, non-small cell lung cancer, prognostic factor

Main Text

1. Introduction

Lung cancer is one of the cancers with poor prognosis. The outcome of postoperative non small cell lung cancer (NSCLC) is difficult to predict precisely since relapse can occur even at early stages [1-3]. Although conventional prognostic prediction has been performed based on its pathological stage, host factors, such as immunological or nutritional state, have rarely been considered. Recently, several studies have reported a relationship between preoperative body mass index (BMI) and postoperative complication in thoracic surgery [4-6]. However, there have been few studies on the prediction of postoperative long term prognosis based on perioperative nutritional status [7-9]. We previously reported that low serum prealbumin level during the perioperative period was associated with early recurrence in postoperative NSCLC [10]. Here, we have conducted a prospective study regarding the relationship between perioperative prealbumin level and postoperative long term outcome, and analyzed the correlation between the perioperative nutritional status and patient prognosis.

2. Patients and Methods

Patients

This prospective study was performed with the approval of the Human Ethics Committee of Akita Red Cross Hospital. A total of 44 consecutive patients with NSCLC from October 2007 to September 2008 who underwent lobectomy with lymph node dissection by video assisted thoracic surgery (VATS) were enrolled in this study. Of the 44 patients, four were excluded because of incomplete follow up due to geographic relocation. The summary of the 40 patients is listed in Table 1. All patients had no preoperative therapy such as chemotherapy or radiotherapy. There were no severe postoperative complications or death.

Method

, The lung cancer stage of each patient was defined according to the TNM classification for lung cancer. Serum prealbumin level was measured preoperatively (five days before operation) and seven days after surgery by turbidimetric immunoassay (SRL, Tokyo, Japan). Postoperative adjuvant chemotherapy was administrated to 12 patients (30%). Patients with no adjuvant therapy were regularly followed-up every three months for the first two years. Periodic checkups were performed by computed tomography every six months. In this study, we defined high preoperative serum prealbumin level as 23 mg/dl ≦, and low as < 23. High postoperative serum prealbumin level was defined as 15mg/dl≦, and low as < 15, as described in a previous study, based on the ROC analysis about the existence or non-existence of the recurrence within postoperative 2 years [10]. The patients were divided into two groups and the association of perioperative serum prealbumin level with postoperative long term prognosis was analyzed.

Statistical analysis

Statistical analyses were performed using Stat-Mate III (ATMS, Tokyo, Japan). Differences between high and low preoperative prealbumin levels were compared by the χ^2 test. The probability of relapse free survival was calculated by the Kaplan-Meier method and compared using the generalized Wilcoxon test. Multivariate analysis was performed by a Cox proportional hazards model using the following variables: age, gender, pathological stage, histological type, preoperative and postoperative serum prealbumin level. These analyses yielded hazard ratios, their 95% confidence intervals, and *p* values. Values of $p < 0.05$ were considered to be significant.

3. Results

Clinical and histological features of the patients

Characteristics of the 40 patients with NSCLC are listed in Table 1. The pathological stage was significantly different between the two groups ($p = 0.02$). The group with high preoperative serum prealbumin level was dominated by early stage patients, while the low preoperative serum prealbumin level group included more advanced stages. There were more patients with high postoperative serum prealbumin level in the group with high preoperative prealbumin level compared to the group with low preoperative prealbumin level ($p = 0.02$).

Table 1 Characteristics of the 40 patients with NSCLC.

	preoperative serum prealbumin level		
Variables	high	low	*p*
Number	28	12	
Age (years)	71.0±8.3	71.7±10.5	0.82
Gender			
Male	19	9	0.94
Female	9	3	
Pathological stage			
IA+IB	23	4	0.02
IIA+IIB	2	2	
IIIA+IIIB	3	6	
Histological type			
Adenocarcinoma	17	7	0.83
Squamous cell ca.	11	5	
Prealbumin (mg/dl)			
Preoperative	28.9±4.7	19.3±3.8	
POD7	18.8±4.8	14.9±3.8	0.02

Preoperative serum prealbumin level: high; ≧23 mg/dl, low; < 23 mg/dl, POD: postoperative days

Overall and relapse free survival analyses

The overall and relapse free 5-year survival curves by Kaplan-Meier method are shown in Fig. 1-3. Fig. 1 shows the overall and relapse free survival curves according to pathological stage. The overall survival rates were 74.1% for pStage IA+IB, 75% for pStage IIA+IIB, and 22.2% for pStage IIIA+IIIB ($p < 0.001$, pStage IA+IB vs. pStage IIIA+IIIB) (Fig. 1A). The relapse free survival rates were similar for pStage IA+IB and pStgae IIIA+IIIB (Fig. 1B). Based on the preoperative serum prealbumin level, the overall survival rates were 67.9% for the high preoperative serum prealbumin level group and 50% for the low preoperative serum prealbumin level group ($p = 0.15$) (Fig. 2A). Accordingly, the relapse free survival rates were 77.2% for the high preoperative serum prealbumin level group and 25% for the low preoperative serum prealbumin level group.

There was a statistically significant difference between the two groups ($p < 0.001$) (Fig. 2B). For the postoperative serum prealbumin level, the overall survival rates were 72.4% and 36.4% for the high and low postoperative serum prealbumin level groups, respectively ($p < 0.05$) (Fig. 3A), and the relapse free survival rates were 62.1% and 18.2% for the high and low postoperative serum prealbumin level groups, respectively ($p < 0.01$) (Fig. 3B).

Multivariate analysis

Table 2. Cox proportional hazards analysis to identify predictors of relapse free survival in 40 patients with NSCLC.

Factors	univariate	multivariate	
	p	Hazard ratio (95% CI)	*p*
Age (years)			
< 75 (n = 23) vs. ≧75 (n = 17)	0.40	0.80 (0.17-3.74)	0.78
Gender			
male (n = 28) vs. female (n = 12)	0.07	0.32 (0.06-1.71)	0.18
Pathological stage			
I (n = 27) vs. II-III (n = 13)	< 0.001	3.71 (1.12-12.3)	0.03
Histologic subtype			
Ad (n = 24) vs. SCC (n = 16)	0.18	0.80 (0.24-2.69)	0.72
Serum prealbumin level (mg/dl)			
Preoperative			
low (n = 12) vs. high (n = 28)	< 0.001	0.21 (0.06-0.69)	0.01
POD7			
low (n = 11) vs. high (n = 29)	< 0.01	0.90 (0.19-4.26)	0.90

CI: confidence interval, Ad: adenocarcinoma, SCC: squamous cell carcinoma,
POD: postoperative days

The results of multivariate analysis are shown in Table 2. The preoperative serum prealbumin level was identified as an independent prognostic factor for relapse free survival (hazard ratio, 0.21; 95% confidence interval, 0.06-0.69; $p = 0.01$). Another

independent prognostic factor identified was the pathologic stage (hazard ratio, 3.71; 95% confidence interval, 1.12-12.3; $p = 0.03$).

4. Discussion

In this prospective study, we demonstrated that the preoperative serum prealbumin level was a useful predictive factor for the long term prognosis for postoperative NSCLC. In the preoperative evaluation, the staging by computed tomography was generally conducted for predicting the postoperative outcome. However, we often experience an early recurrence of the cancer in patients even if they are in the early stage, i.e. pathological stage IA. A tumoral factor, CEA, is used as a tumor marker and has been useful in addition to this image evaluation. Poor prognosis has been reported for patients with high preoperative CEA even if it has been evaluated by computed tomography to be in the early stage [1, 11-18]. Recently, it has also been reported that the postoperative prognosis for EGFR mutation positive patients is better than that of negative patients in lung adenocarcinoma [19-21]. However, these studies were focused on tumor factors without consideration of host factors. For host factors, there have been some recent reports on the prediction of postoperative complications by BMI [6-8]. According to these reports, it was demonstrated that the risk of postoperative complication in obese patients were less than that of underweight patients. While BMI evaluation was easy to use, the evaluation timing during the postoperative period sometimes posed a problem. Therefore, in a one point measurement, it is unclear if the measured point was done during a stable weight period or during a progressive weight loss. Furthermore, some measurements were difficult due to limited duration for preoperative preparation. Therefore, the accuracy is inferior as the degree of physical consumption due to neoplasm is not reflected. Prealbumin measurement used in our study enables multiple evaluations due to its short half-life of 1-2 days. Prealbumin was measured both preoperatively and postoperatively, where we discovered that preoperative prealbumin level was more useful than the postoperative level in prognostic prediction. While patients with low postoperative prealbumin level had significantly poor prognosis in univariate analysis, it was not an independent prognostic factor in multivariate analysis. The influence of variable surgical stress was considered as a possible confounding factor. There were some reports suggesting that that C-reactive protein (CRP) as an inflammatory marker was a useful preoperative prognostic factor [22-24]. However, the cut-off value or measuring method was different in each study and a standard should be established in future [25].

It is very important to consider the operative indication for poor preoperative nutritional status. VATS is useful to minimize surgical stress [26, 27]. In

addition, perioperative rehabilitation is critical since it can evaluate the risk factor that is not revealed from preoperative data, which is measured only at rest [28]. Furthermore, preoperative nutritional assessment is thought to be necessary for planning therapy with curability and safety as priority considerations [29]. Preoperative immunonutrition has been recently reported to be useful [30], however, it was a small-scale study requiring further future investigation. We also conducted a prospective study based on the preoperative immunonutrition for NSCLC patients (manuscript in preparation). There are few lung cancer patients where oral intake is hindered and there has been little interest in nutrition. However, our study suggests that nutritional assessment is essential for predicting prognosis. Therefore, it is expected that research will progress in the field of immunonutrition effects.

In conclusion, we demonstrated that the preoperative serum prealbumin level is an independent long-term prognostic factor.

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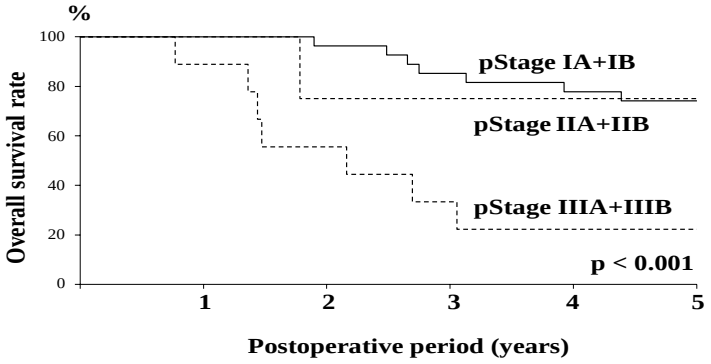
Figure legends

Fig. 1

A. Kaplan-Meier analysis of overall survival according to the pathological stage in NSCLC patients



B. Kaplan-Meier analysis of relapse free survival according to the pathological stage in NSCLC patients

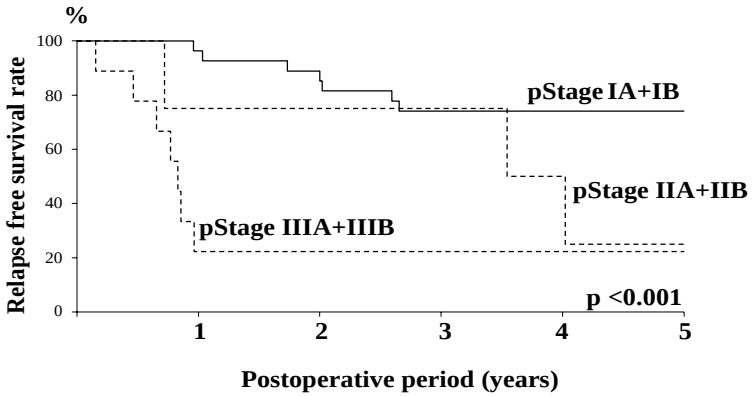
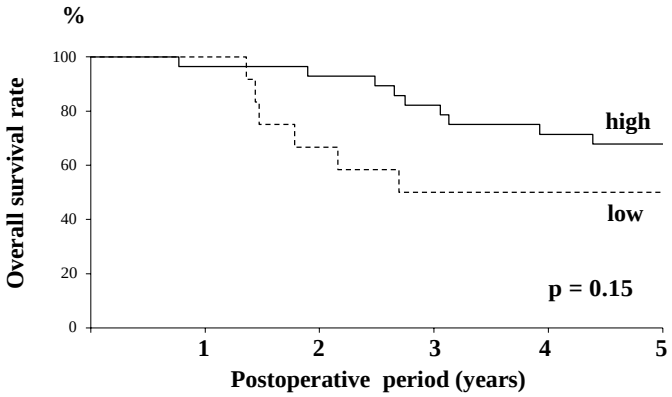


Fig. 2

A. Kaplan-Meier analysis of overall survival according to the preoperative serum prealbumin level in NSCLC patients: high; prealbumin ≧23mg/dl, low; prealbumin < 23 mg/dl.



B. Kaplan-Meier analysis of relapse free survival according to the preoperative serum prealbumin level in NSCLC patients: high; prealbumin ≧23mg/dl, low; prealbumin < 23 mg/dl.

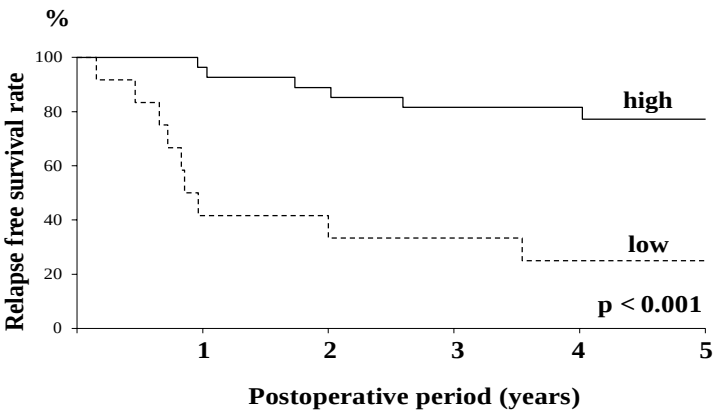
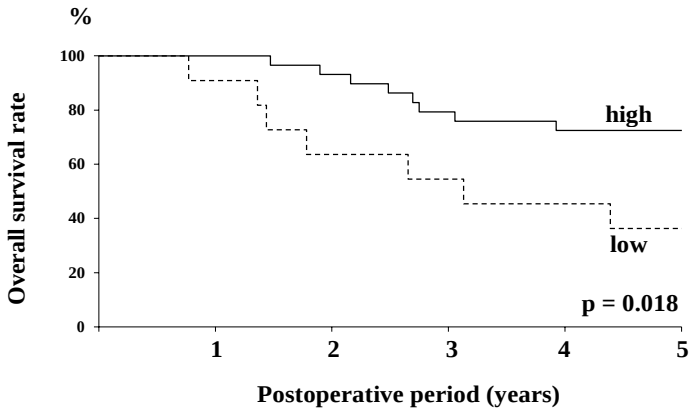


Fig. 3

A. Kaplan-Meier analysis of overall survival according to the postoperative serum prealbumin level in NSCLC patients: high; prealbumin ≧15mg/dl, low; prealbumin < 15 mg/dl.



B. Kaplan-Meier analysis of relapse free survival according to the postoperative serum prealbumin level in NSCLC patients: high; prealbumin ≧15mg/dl, low; prealbumin < 15 mg/dl.