Prognostic Significance of Tumour Marker Index Based on Preoperative CEA and CYFRA 21-1 in Non-small Cell Lung Cancer

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Abstract. *Background: Prognostic impact of tumour marker index (TMI) based on preoperative serum carcinoembryonic antigen (CEA) and CYFRA 21-1 in non-small cell lung cancer (NSCLC) was examined using patients with a follow-up period more than 5 years. Patients and Methods: Two hundred and ninety-three consecutive NSCLC patients were reviewed retrospectively, and any patients with follow-up periods less than 5 years were omitted. Results: The 5-year survival of the patients with normal and high serum CEA levels was 71.52% and 48.41%, respectively (p<0.0001). The 5-year survival of the patients with a high serum CYFRA 21-1 level was 39.66%, which was significantly poorer compared with that of the patients with a normal serum CYFRA 21-1 level (66.95%, p<0.0001). There was a 5-year-survival rate of 72.28% in patients with a TMI less than or equal to 1.0 compared to only 37.08% in patients with a TMI greater than 1.0 (p<0.0001). Both univariate and multivariate analyses indicated the independent prognostic impact of TMI. Conclusions: TMI may be useful for predicting the prognosis of NSCLC patients.*

In addition to TNM staging, the best predictor of outcome of non-small cell lung cancer (NSCLC), several previous reports have indicated that preoperative elevated serum carcinoembryonic antigen (CEA) and CYFRA 21-1 levels are associated with very poor survival rates following surgical resection in NSCLC (1-7). In contrast, other studies have found that an elevated preoperative CEA and/or CYFRA 21-1 level has no prognostic value (8-10). The majority of these authors performed their analyses with the calculated cumulative survival rate, which can occasionally be confounded by those patients with a short follow-up period.

These tumour markers might be more accurate and useful if used in combination rather individually, however, their evaluation when used in combination is often difficult. Previously, Muley *et al*. introduced an algorithm using serum CYFRA 21-1 and CEA levels (11, 12). A variable called tumour marker index (TMI) corresponding to the geometric mean of normalized CYFRA21-1 and CEA levels (marker value divided by diagnostic cut-off) was introduced. The TMI can evaluate not only the degree of marker elevation but also the combined use of two markers. Muley *et al*. reported the prognostic significance of TMI (11, 12). However another study failed to find any prognostic significance of TMI (10). One of the possible reasons for this discrepancy may be due to the differences in follow-up period.

In the present study, therefore, the prognostic impact of TMI based on serum CEA and CYFRA 21-1 level was retrospectively investigated for NSCLC patients with a follow-up period more than 5 years.

Patients and Methods

The present retrospective study was conducted from 1998 through 2004, and included 291 patients with NSCLC who had undergone complete resection which consisted of either a lobectomy or a pneumonectomy together with regional lymph node dissection. Patients also received intraoperative pleural lavage cytology (PLC) (13) and patients who did not receive PLC were excluded. Any patients with a follow-up period less than 5 years were excluded. There were 192 men and 99 women, with ages ranging from 26 to 90 years, with an average of 66 years. The overall follow-up periods ranged from 60.7 to 141.7 months. The baseline characteristics are summarized in Table I.

The clinical investigation section of the hospital measured serum CEA and CYFRA 21-1 levels, and the normal upper limit was 5.0 ng/ml and 2.4 ng/ml, respectively. Pathologic (p) TNM staging was recorded in all patients.

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Key Words: CEA, CYFRA 21-1, tumour marker index, non-small cell lung cancer, survival.

Table I. *Clinicopathologic characteristics*.

		No. of patients
Age (years)	≥65	177
	<65	114
Gender	Male	192
	Female	99
Histology	Adeocarcinoma	209
	Others	82
pStage	I	187
	II-III	104
pT	pT1	148
	pT2-4	143
pN	pN0	214
	pN1-2	77
PLC	Negative	263
	Positive	28
Serum CEA	Normal	165
	High	126
Serum CYFRA 21-1	Normal	233
	High	58

CEA: Carcinoembryonic antigen, PLC: pleural lavage cytology.

The TMI (11,12) was defined by taking the geometric mean of normalized values of serum CEA and CYFRA 21-1 levels, where normalization was performed by dividing individual marker values by corresponding diagnostic cut off points, *i.e.* 5.0 ng/ml for serum CEA and 2.4 ng/ml for serum CYFRA 21-1: √[(serum CEA level/5.0 ng/ml) × (serum CYFRA 21-1 level/2.4 ng/ml)].

Follow-up information, including cause of death, was ascertained through a review of clinic notes and direct or family contact.

Survival curves were obtained according to the Kaplan-Meier method. Comparison of survival curves was carried out using the log-rank test. Statistical calculations were conducted with JMP (SAS Institute Inc. Cary, NC, USA) and values of $p<0.05$ were accepted as significant.

Results

As shown in Figure 1A, the 5-year survival of the patients with normal and high serum CEA levels was 71.52% and 48.41%, respectively ($p<0.0001$). The 5-year survival of the patients with a high serum CYFRA 21-1 level was 39.66%, which was significantly poorer compared with that of the patients with a normal serum CYFRA 21-1 level (66.95%, $p<0.0001$, Figure 1B).

When both tumour marker levels are within normal upper limits, the TMI cannot be greater than 1.0. Therefore, in the present study, the discriminatory value of TMI was set as 1.0. Using this discriminatory value, the patients were subdivided into two groups: TMI less than or equal to1.0 and TMI greater than 1.0. There were 202 patients with TMI less than or equal to 1.0, and 89 patients with TMI greater than 1.0. The survival curve based on TMI is shown in Figure 2. There was a 5-year-survival rate of 72.28% in patients with a TMI less than or equal to 1.0 compared to only 37.08% in patients with a TMI greater than 1.0 ($p<0.0001$). Both univariate and multivariate analyses indicated an independent prognostic impact of TMI.

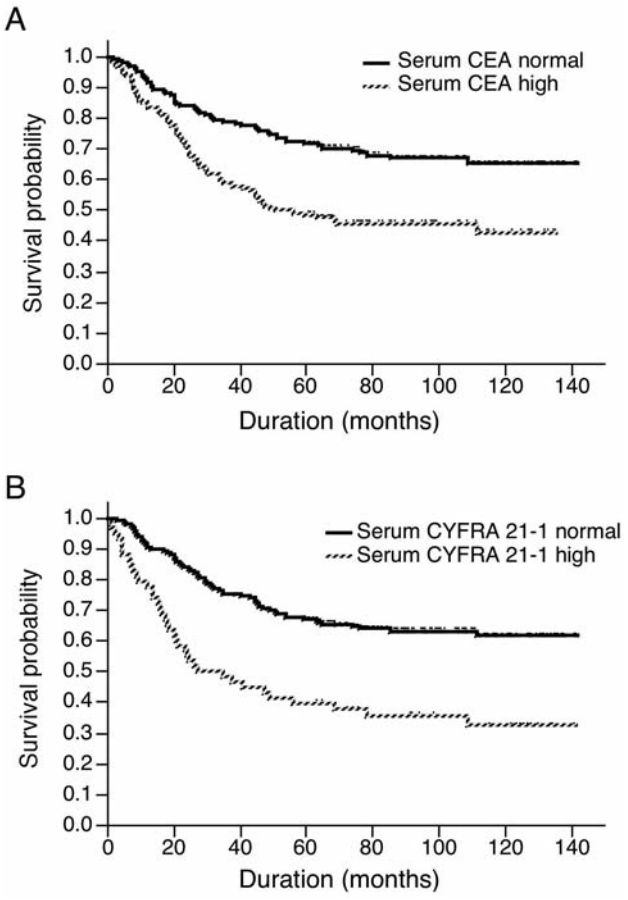

Figure 1. *Survival of patients based on serum CEA level (A) and CYFRA 21-1 (B).*

The results of univariate analysis are summarized in Table II. When serum CEA and CYFRA 21-1 level were analyzed separately, both were related to patient prognosis. However, the TMI had a higher risk ratio and was statistically more significant. The gender, histology, pT srarus, pN status, positive PLC findings and TMI were related to patient prognosis, whereas patient age was not.

The results of multivariate analysis including all variables for which $p<0.05$ on univariate analysis are summarized in Table III. Of the variables that were included in the multivariate analysis, histology, pT srarus, pN status, positive PLC findings and TMI were independent prognostic determinants.

Discussion

The prognostic significance of preoperative serum CEA and CYFRA 21-1 was investigated using a follow-up period of more than 5 years and an actual number of survivors.

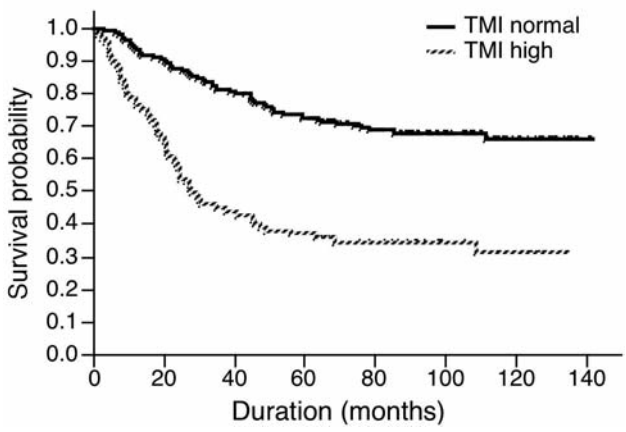

Figure 2. *Survival of patients based on tumour marker index.*

Table II. *Univariate analysis.*

Risk Factors	Risk ratio	95% CI	*p* Value
Age	1.082319	0.9025-1.3064	0.3971
Gender	1.400643	1.1450-1.7398	0.0008
Histology	1.582791	1.3200-1.8917	<0.0001
pT	1.714736	1.4242-2.0817	<0.0001
pN	1.964127	1.6394-2.3488	<0.0001
PLC	1.871704	1.4719-2.3304	<0.0001
CEA	1.432133	1.1990-1.7151	0.0001
CYFRA 21-1	1.568951	1.2883-1.8930	<0.0001
TMI	1.760532	1.4722-2.1035	<0.0001

CI: confidence interval, CEA: carcinoembryonic antigen, PLC: pleural lavage cytology, TMI: tumour marker index.

Table III. *Multivariate analysis.*

Risk Factors	Risk ratio	95% CI	*p* Value
Gender	1.185223	0.9602-1.4832	0.1155
Histology	1.389134	1.1489-1.6753	0.0008
pT	1.254074	1.0234-1.5465	0.0289
pN	1.665629	1.3794-2.0078	<0.0001
PLC	1.494384	1.1648-1.8813	0.0021
TMI	1.427576	1.1838-1.7204	0.0002

CI: confidence interval, CEA: carcinoembryonic antigen, PLC: pleural lavage cytology, TMI: tumour marker index.

However, elevated serum these markers are not always due to the malignant potential of the tumour. Alexander *et al*. (14) reported a correlation between smoking and serum CEA levels. Serum CYFRA21-1 level was also reported to be higher in patients who were heavy smokers (15). Moreover, the CYFRA21-1 level is reportedly higher in patients with benign lung disorders such as pneumonia and pulmonary fibrosis (15). Therefore there is a possibility that elevated preoperative serum CEA and/or CYFRA 21-1 levels in some patient groups are primarily attributable to other factors such as smoking status. Furthermore, the results of serum CEA and CYFRA 21-1 levels were also not consistent. Among 165 patients with normal serum CEA levels, 21 patients had high serum CYFRA 21-1 levels. In contrast, 89 patients had a high serum CEA but a normal CYFRA 21-1 level. The reason for these discrepancies might be the difference in the extraction mechanisms used to determine serum CEA and CYFRA 21-1 levels. To evaluate these markers more accurately, the combined use of serum CEA and CYFRA 21-1 levels, therefore, may prove a useful prognostic determinant because both serum CEA and CYFRA 21-1 level are useful prognostic factors. However it is sometimes difficult to evaluate patients with one positive marker. From this point of view, in the present study, the TMI introduced by Muley *et al*. (11, 12), which can evaluate two markers collectively, was selected. These results showed the prognostic significance of TMI based on serum CEA and CYFRA 21-1. Muley *et al*. also reported that elevated levels of TMI have a strong negative prognostic impact on survival in operated early stage of NSCLC (11, 12). In contrast, Blankenburg *et al*. showed that TMI was not associated with a worse outcome (10). One of the reasons for the discrepancy may be due to differences in follow-up duration of patient populations. Due to the heterogeneity of follow-up duration between studies, different results among the previous studies might therefore be expected. In this current study, therefore, NSCLC patients diagnosed after 2005 were omitted, and the follow-up period of all patients was more than 5 years in all cases. Using a follow-up period of more then 5 years and an actual number of survivors, the results from the current study show the prognostic significance of TMI.

TMI can evaluate the degree of marker elevation. In the present study, the discriminatory value of TMI was set as 1.0. Using this discriminatory value, it was possible to differentiate clearly between two prognostic groups. However, it is possible that other useful discriminatory values exist and they should be investigated in future studies. Muley *et al*. introduced the TMI based on serum CEA and CYFRA 21-1 levels, and they found two discriminatory values at 0.48 and 0.83 (11). However, they did not describe the method used to find these discriminatory values.

The measurement of serum CEA and CYFRA 21-1 levels is inexpensive and routinely available. Despite current advanced diagnostic procedures for preoperative staging, the present results show a role for the use of the TMI based on serum CEA and CYFRA 21-1 levels as an adjunct to conventional staging for NSCLC patients. From these results, it can be hypothesized that adjuvant chemotherapies may be useful for patients with high TMI. The subgroup of patients

with high TMI could represent a reasonable study population for an adjuvant therapy trial. Further prospective studies in this area are warranted.

In conclusion, TMI based on serum CEA and CYFRA 21-1 levels appears to be an independent prognostic determinant in patients with NSCLC. When planning postoperative adjuvant therapies, the Authors believe that the TMI based on serum CEA and CYFRA 21-1 levels should be considered. Unfortunately, there is no evidence that adjuvant therapy would be useful in patients with a TMI greater than 1.0, but this may be a question for future studies.

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