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Pathologic Correlation of Serum Carcinoembryonic Antigen and Cytokeratin 19 Fragment in Resected Nonsmall Cell Lung Cancer

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Background: This study focused on the association between preoperative serum carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (Cyfra 21-1) levels and pathologic parameters in patients with resected non-small-cell lung cancer (NSCLC). ***Materials and Methods:*** The records of 527 patients who underwent pulmonary resection of NSCLC were reviewed. The association between preoperative serum CEA and Cyfra 21-1 levels and variables that had p-values of less than 0.05 in a t-test or one-way analyses of variance was analyzed by multiple linear regression. ***Results:*** The mean serum CEA and Cyfra 21-1 levels prior to surgery were 6.8±23.1 mg/dL (range, 0.01 to 390.8 mg/dL) and 5.4±12.3 mg/dL (range, 0.65 to 140.2 mg/dL). The serum CEA levels were associated with tumor (T) and lymph node (N) stage and histology. The serum Cyfra 21-1 levels were associated with T stage, tumor size, and histology. Multiple linear regression indicated that serum CEA levels were associated with T (T3/4 vs. T1: β=8.463, p=0.010) and N stage (N2/3 vs. N0: β=9.208, $p<0.001$) and histology (adenocarcinoma vs. squamous cell: β=6.838, p=0.001), and serum Cyfra 21-1 levels were associated with tumor size (β=2.579, $p<0.001$) and histology (squamous cell vs. adenocarcinoma: β=4.420, p=0.020). ***Conclusion:*** Serum CEA level was correlated with T and N stage, and Cyfra 21-1 with tumor size. CEA and Cyfra 21-1 showed histologic correlation. CEA is mainly elevated in adenocarcinoma and Cyfra 21-1 in squamous cell carcinoma. These results might be helpful for predicting pathologic status in preoperative NSCLC.

Key words: 1. Carcinoma, non-small cell, lung
2. Neoplasm biology
3. Carcinoembryonic antigen (CEA)
4. Cytokeratin 19 fragment (Cyfra 21-1)

INTRODUCTION

Carcinoembryonic antigen (CEA) and cytokeratin 19 fragments (Cyfra 21-1) are the most commonly investigated tumor markers in non-small-cell lung cancer (NSCLC). They have been investigated for the purpose of early detection, prognosis stratification, treatment monitoring and selection, and recurrence monitoring. In NSCLC, adjuvant platinum-based chemotherapy is considered the standard treatment for stage II and III. A potential benefit of adjuvant chemotherapy for stage Ib has not yet been determined. Therefore, a current challenge in NSCLC is to identify patients that might benefit from adjuvant treatment [1,2]. Several studies have suggested that CEA and Cyfra 21-1 were independent

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prognostic factors and good tools for choosing candidates for adjuvant chemotherapy [3-10]. However, contrasting recommendations have also been reported [11-13]. We postulated that CEA and Cyfra 21-1, which seem to be associated with patient prognosis, might be related to pathologic factors. This study focused on the association between preoperative serum CEA and Cyfra 21-1 levels and pathologic parameters in relation to prognosis in patients with resected NSCLC.

MATERIALS AND METHODS

1) Patients

The records of 982 patients who underwent pulmonary resection of NSCLC between January 1999 and December 2006 were reviewed. Patients with pathologic stage I-IIIa were included in this study. Patients who received preoperative induction therapy and those with histology other than squamous cell, adenocarcinoma, and large cell lung cancer were excluded for the purpose of exact pathologic and histologic correlation. A final total of 527 patients were entered into the current retrospective study. The serum CEA level was measured from 1999 and Cyfra 21-1 was measured from 2004 at Severance Hospital.

The group contained 142 females and 385 males with a median age of 64.0 years (range, 36 to 82 years). The preoperative serum level was measured in 526 patients for CEA and 162 for Cyfra 21-1. Patient evaluation before surgery included medical history, physical examination, chest radiography, and blood tests. Computed tomography scans of the chest and upper abdomen, abdominal sonography, and bone scintigraphy were routinely performed. Cervical mediastinoscopy was performed in patients with suspected N2/3 disease. The extent of the primary lesion was carefully assessed, and systematic dissection of all hilar and mediastinal lymph nodes was performed in each case. All pathologic and clinical parameters were recorded in a prospective manner. Tumors were staged according to the International Staging System for Lung Cancer [14].

The institutional review board (IRB) of the Yonsei University College of Medicine approved this retrospective study. The need for subsequent individual consent of patients whose records were evaluated was waived because individuals were not identified in this study.

2) CEA and Cyfra21-1 measurement

Blood samples were obtained by peripheral venous puncture on admission to the unit prior to any staging or resection. Serum CEA or Cyfra 21-1 levels were measured as part of routine clinical examination. CEA was assessed by UniCel DxI 800 Immunoassay (Beckman Coulter, Brea, CA, USA), and Cyfra 21-1 by Elecsys 2010 system (Boehringer Mannheim, Mannheim, Germany) according to the manufacturer's instructions. Serum levels <5.0 ng/mL were defined as normal for CEA and <3.3 ng/mL for Cyfra21-1.

3) Statistical analysis

Statistical analysis was performed using SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA). The mean serum CEA and Cyfra21-1 levels for each variable were compared using a t-test or one-way analyses of variance (ANOVA). The association between serum CEA and Cyfra 21-1 levels was examined for variables that had p-values of less than 0.05 in a t-test or one-way ANOVA using multiple linear regression analysis. The tumor size and Cyfra 21-1 level were analyzed as continuous variables in multiple linear regression analysis. A p-value of less than 0.05 was considered significant.

RESULTS

1) Pathologic correlation with CEA and Cyfra21-1

The mean serum CEA and Cyfra 21-1 levels prior to surgery were 6.8±23.1 mg/dL (range, 0.01 to 390.8 mg/dL) and 5.4±12.3 mg/dL (range, 0.65 to 140.2 mg/dL). The serum CEA and Cyfra 21-1 levels were broken down according to clinicopathologic parameters in Tables 1 and 2.

Serum CEA levels were associated with tumor (T) stage (T1 vs. T2 vs. T3/4, p=0.032) and N stage (N0 vs. N1 vs. N2/3, $p<0.001$) and histology (adenocarcinoma vs. squamous cell vs. large cell, p=0.032) but not with sex, age, smoking status, or tumor size. T and N stage and histology were analyzed by multivariate analysis to further assess their association with preoperative serum CEA levels. Multiple linear regression analysis indicated that T (T3/4 vs. T1: β=8.463, p=0.010) and N stage (N2/3 vs. N0: β=9.208, $p<0.001$) and

Table 1. Mean (standard deviation) CEA serum levels by clinicopathologic parameters and multiple linear regression analysis

Variable		Number	CEA serum levels (ng/mL)	p-value	β	p-value
Sex	Male	385	6.9±25.7	0.885		
	Female	141	6.6±13.5			
Age	<64	262	5.8±25.0	0.316		
	≥64	264	7.8±20.9			
Smoking	Yes	239	8.3±30.9	0.186		
	No	287	5.6±13.3			
T stage	T1	137	4.2±9.9	0.032	Reference	
	T2	306	6.4±16.2		2.705	0.257
	T3/4	83	12.5±47.2		8.463	0.010
N stage	N0	337	4.2±7.1	<0.001	Reference	
	N1	74	6.6±18.9		3.337	0.259
	N2/3	115	14.4±44.7		9.208	<0.001
Tumor size	<3	231	5.3±12.8	0.196		
	≥3	289	7.9±28.8			
Histology	Adenocarcinoma	257	9.5±31.7	0.032	Reference	
	Squamous	235	4.1±8.4		-6.838	0.001
	Large cell	33	5.1±8.4		-4.565	0.275

Values are presented as mean±standard deviation. Adjusted R square=0.047, β indicates regression coefficient in multiple linear regression.
CEA, carcinoembryonic antigen; T, tumor; N, lymph node.

Table 2. Mean (standard deviation) Cyfra 21-1 serum by clinicopathologic parameters and multiple linear regression analysis

Variable		Number	Cyfraserum levels (ng/mL)	p-value	β	p-value
Sex	Male	111	6.3±14.3	0.166		
	Female	51	3.4±6.1			
Age	<64	73	4.9±16.6	0.635		
	≥64	89	5.8±7.3			
Smoking	Yes	84	6.8±16.0	0.129		
	No	73	3.9±6.1			
T stage	T1	56	2.3±1.4	0.010	Reference	
	T2	86	5.9±7.8		-4.371	0.055
	T3/4	20	11.8±31.6		0.335	0.915
N stage	N0	110	6.0±14.8	0.638		
	N1	26	4.5±3.5			
	N2/3	26	3.8±3.1			
Tumor size	<3	78	2.5±1.9	0.002	2.579	<0.001
	≥3	82	8.3±16.8			
Histology	Squamous	66	9.3±18.5	0.003	Reference	
	Adenocarcinoma	84	2.5±2.3		-4.420	0.020
	Large cell	12	4.4±3.2		-3.336	0.332

Values are presented as mean±standard deviation. Adjusted R square=0.233, β indicates regression coefficient. Tumor size was analyzed as a continuous variable in multiple linear regression.
Cyfra 21-1, cytokeratin 19 fragment; T, tumor; N, lymph node.

histology (adenocarcinoma vs. squamous cell: β=6.838, p=0.001) were correlated with preoperative CEA levels (Table 1).

Serum Cyfra 21-1 levels were associated with T stage (T1 vs. T2 vs. T3/4, p=0.010), tumor size (＜3 vs. ≥3, p ＜0.002), and histology (adenocarcinoma vs. squamous cell vs. large cell, p=0.003). These factors were analyzed by multivariate analysis to further assess their association with preoperative serum Cyfra 21-1 levels. Multiple linear regression analysis indicated that tumor size (β=2.579, p＜0.001) and histology (squamous cell vs. adenocarcinoma: β=4.420, p=0.020) were correlated with preoperative Cyfra 21-1 levels (Table 2).

DISCUSSION

The serum CEA level was correlated with T and N stage. Cyfra 21-1 was correlated with tumor size. CEA and Cyfra 21-1 also showed histologic correlation. CEA was mainly elevated in adenocarcinoma and Cyfra 21-1 in squamous cell carcinoma.

Tumor markers such as CEA and Cyfra 21-1 have been studied for the purpose of early cancer detection, prognostic stratification, and monitoring of the treatment response and cancer recurrence, although the use of these markers for lung cancer detection or monitoring is not currently recommended or encouraged [15]. The guidelines of the National Comprehensive Cancer Network on NSCLC do not include preoperative CEA or Cyfra 21-1 in pretreatment evaluation [16].

Adjuvant chemotherapy might be considered the standard treatment in stage II and III lung cancer with the evidence that it improves patient survival. The greatest benefit was seen in stage II patients. In stage Ib patients, the benefit is still questionable. Stratifying patients who will benefit from adjuvant treatment for stage Ib is the current issue. The possible roles of CEA and Cyfra 21-1 in NSCLC are expected to stratify the prognosis. Several studies have reported that patients with elevated preoperative serum levels of CEA and Cyfra 21-1 had a shorter overall survival compared to those with normal marker concentrations [3-10]. Even more tumor marker index (the square root of Cyfra 21-1 concentration/3.3 ng/mL×CEA concentration/5.0 ng/mL) based on Cyfra 21-1 and CEA was suggested as a prognostic factor in NSCLC [10]. However, other studies have found that elevated preoperative serum levels of CEA and Cyfra 21-1 were completely lacking in prognostic value [11-13].

According to our data, elevated CEA and Cyfra 21-1 levels both showed poor prognosis. However, in multivariate analysis, neither had any significance. Only well-known prognostic factors such as T and N stage and tumor size were significant (data not shown). Based on these findings, we believed that serum levels of CEA and Cyfra 21-1 might be closely correlated with pathologic parameters, which could explain the poor prognosis of elevated CEA and Cyfra 21-1. We found that the serum CEA level was correlated with the T and N stage and Cyfra 21-1 with tumor size. Although it is generally accepted that serum CEA and Cyfra 21-1 levels are associated with more advanced stage [6,17-20], some studies have suggested that these levels are not always related to TNM stage and their prognostic significance might be due to different mechanisms; accordingly CEA and Cyfra 21-1 were independent prognostic factors and could be used to stratify prognosis [21-23]. However, the present results disprove their suggestion.

CONCLUSION

In summary, our results indicate that preoperative serum levels of CEA and Cyfra 21-1 seem to be associated with pathologic parameters. The serum CEA level was correlated with T and N stage. Cyfra 21-1 was correlated with tumor size. CEA and Cyfra 21-1 showed histologic correlation. CEA was mainly elevated in adenocarcinoma and Cyfra 21-1 in squamous cell carcinoma. These findings might be helpful in predicting pathologic status in preoperative NSCLC but could not provide additional information to predict patient prognosis and develop a treatment plan.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was

reported.

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