Original Article

Clinical significance of preoperative carcinoembryonic antigen level in patients with clinical stage IA non-small cell lung cancer

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Background: The objective of this study was to assess the preoperative serum carcinoembryonic antigen (CEA) level in patients with clinical stage IA non-small cell lung cancer (NSCLC) and to evaluate its clinical significance.

Methods: Between January 2005 and December 2014, a total of 378 patients with clinical stage IA NSCLC underwent complete resection with systematic node dissection. The survival rate was estimated starting from the date of surgery to the date of either death or the last follow-up by the Kaplan-Meier method. Univariate analyses by log-rank tests were used to determine prognostic factors. Cox proportional hazards ratios were used to identify independent predictors of poor prognosis. Clinicopathological predictors of lymph node metastases were evaluated by logistic regression analyses.

Results: The 5-year survival rate of patients with an elevated preoperative serum CEA level was significantly lower than that of patients with a normal CEA level (75.5% *vs.* 87.7%; P=0.02). However, multivariate analysis did not show the preoperative serum CEA level to be an independent predictor of poor prognosis. Postoperative pathological factors, including lymphatic permeation, visceral pleural invasion, and lymph node metastases, tended to be positive in patients with an elevated preoperative serum CEA level. In addition, the CEA level was a statistically significant independent clinical predictor of lymph node metastases.

Conclusions: The preoperative serum CEA level was not an independent predictor of poor prognosis in patients with pathological stage IA NSCLC but was an important clinical predictor of tumor invasiveness and lymph node metastases in patients with clinical stage IA NSCLC. Therefore, measurement of the preoperative serum CEA level should be considered even for patients with early-stage NSCLC.

Keywords: Carcinoembryonic antigen (CEA); non-small cell lung cancer (NSCLC); stage IA; lymph-node metastasis

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide (1). More than 60% of patients with lung cancer present with stage IIIB/IV disease, and late diagnosis is common (2). The increased frequency of detecting stage IA non-small cell lung cancer (NSCLC) in Japan can be attributed to a nationwide mass screening system, and surgery for patients with early-stage small-sized NSCLC is being performed more often (3).

Tumor markers are non-invasive diagnostic tools for identifying malignant tumors and are commonly used

for cancer screening. Carcinoembryonic antigen (CEA) is an established tumor marker and has demonstrated its prognostic value in colorectal cancer (4). CEA is also overexpressed in approximately 35–60% of patients with NSCLC (5), and the clinical usefulness of the serum CEA level in lung cancer has recently been vigorously explored. Although it is well known that evaluation of the serum CEA level can be useful for monitoring responses to chemotherapy and predicting relapses in cases of advanced NSCLC (6-8), several questions remain unanswered regarding the significance of the preoperative CEA level in patients with early-stage small-sized NSCLC. Primarily, the significance of routine measurement of the preoperative serum CEA level for small-sized NSCLC is unknown. In addition, it is unclear whether the preoperative serum CEA level can be an independent prognostic factor in patients surgically treated for clinical stage I NSCLC. To address these issues, we reviewed a series of consecutive patients with clinical stage IA NSCLC who underwent complete resections in our hospital. The objective of this study was to assess the preoperative serum CEA level and evaluate its clinical significance in patients with clinical stage IA NSCLC.

Methods

Patients

A total of 431 patients clinically diagnosed as having stage IA NSCLC who underwent complete resection and lobectomy or a more extensive surgery with systematic node dissection between January 2005 and December 2014 at the Fujita Health University School of Medicine were identified from our departmental database. Of these, 378 consecutive patients met the inclusion criteria and were retrospectively reviewed. The inclusion criteria were the serum CEA level measured 1 month before surgery, absence of multiple malignancies in other organs, and absence of either preoperative chemotherapy or radiation therapy or both.

Clinical information and pathological evaluations

Chest computed tomography (CT) was used to classify the stage of all patients, and tumor size was measured by chest CT prior to surgery. Regional lymph node metastasis was clinically defined when the shorter diameter was ≥1.0 cm. Additional diagnostic testing (brain magnetic resonance imaging and bone scintigraphy) was performed at the discretion of the individual physician according to the patient's symptoms and clinical findings. Positron emission tomography (PET) combined with CT was not used for the evaluation of lymph node metastasis in any of the patients enrolled in this study. No invasive modalities for mediastinal lymph node staging, such as mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration, were used preoperatively in any of these patients.

The histological type was determined according to the World Health Organization classification (9). Disease stages were based on the tumor, node, and metastasis (TNM) classification of the International Union against Cancer, 7th edition (10). Complete resection was defined as cancer-free surgical margins both grossly and histologically.

We examined patients at 3-month intervals for the first 2 years and at 6-month intervals thereafter on an outpatient basis. The follow-up evaluation included physical examination, chest radiography, and blood testing, including that of pertinent tumor markers. Further evaluations, including CT of the chest and abdomen, brain magnetic resonance imaging, and bone scintigraphy, were performed to detect any symptoms or signs of recurrence. Since 2010, PET-CT has also been performed when appropriate.

We reviewed the medical records of each patient for clinicopathological information, including age (dichotomized at the median age of 67 years), sex, smoking history (never- or ever-smoker), ratio of preoperative forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC; >70% or <70%), preoperative serum CEA level (cutoff at the normal upper limit of 5 ng/mL), tumor diameter measured by preoperative chest CT (T1a or T1b), side of tumor (right or left), distribution within the lobe (upper, middle, or lower), lymphatic permeation (present or absent), visceral pleural invasion (as defined in the TNM classification, 7th edition; present or absent), and lymph node metastasis (N0 or N1–3).

Statistical analysis

Differences in categorical outcomes were analyzed using the chi-square test. Continuous variables were compared using *t*-tests. Duration of survival was defined as the interval (in months) between the date of surgical resection and the date of either death or the last follow-up. For univariate analyses, all cumulative survival rates were estimated by the Kaplan-Meier method, and differences in variables were determined by the log-rank test. Multivariate analyses were performed using a Cox proportional hazards regression

model. The last actualization of survival data was performed in August 2015. Clinicopathological predictors of lymph node metastases or lymphatic permeation were evaluated by logistic regression analyses. All P values reported were two sided, and the significance level was set at a P value of <0.05. Analyses were performed using SPSS 11.0 statistical software (Dr. SPSS II for Windows, standard version 11.0, SPSS Inc., Chicago, IL, USA).

Data collection and analyses were approved, and the need to obtain informed consent from each patient was waived by the Institutional Review Board in August 2015.

Results

Clinicopathological prognostic factors for patients with clinical stage IA NSCLC (Table 1)

The 5-year overall survival rate of all 229 patients who underwent complete resection between January 2005 and December 2011 was 84.9%. The 5-year overall survival rate after surgery according to the clinicopathological features of the patients is listed in *Table 1*.

Univariate analysis (log-rank test) identified six significant predictors of poor prognosis: age, preoperative serum CEA level, histological type, lymphatic permeation, visceral pleural invasion, and N status (*Table 1*). The 5-year survival rate of patients with an elevated preoperative serum CEA level was 75.5%, which was significantly lower than that of patients with a normal preoperative serum CEA level (87.7%; P=0.02). The results of multivariate analysis using the Cox regression model indicated that age and N status remained statistically significant independent prognostic factors (*Table 1*).

Clinicopathological prognostic factors for patients with pathological stage IA NSCLC (Table 2)

The operative findings and pathological examination of surgical specimens revealed that 61 (26.6%) patients were reclassified as having pathological stage IB or higher and were upstaged. The 5-year overall survival rate of the remaining 168 patients diagnosed as having pathological stage IA was 91.4%. The 5-year overall survival rates of the 168 patients according to their clinicopathological features are listed in *Table 2*.

Univariate analysis (log-rank test) identified three significant poor prognostic factors: age, preoperative serum CEA level, and histological type. The results of multivariate analysis using the Cox regression model indicated that only age was a statistically significant independent prognostic factor (*Table 2*).

Correlation between preoperative serum CEA level and clinicopathological factors (Table 3)

The relationship between the preoperative serum CEA level and clinicopathological factors of the patients is shown in *Table 3*. Among patients with non-adenocarcinoma, there were significantly more patients with an elevated preoperative serum CEA level than patients with adenocarcinoma (P<0.001). Lymphatic permeation, visceral pleural invasion, and lymph node metastases tended to be positive in patients with an elevated preoperative serum CEA level (P<0.001 for all).

Univariate and multivariate analyses of clinicopathological predictors of lymph node metastases

In patients with clinical stage IA NSCLC, N status remained a statistically significant independent prognostic factor in multivariate analysis. When we examined the potential clinicopathological predictors of lymph node metastases, univariate analyses revealed four significant clinical predictors: CEA level, tumor size, lymphatic permeation, and visceral pleural invasion (*Table 4*). The results of multivariate analysis indicated that the CEA level and lymphatic permeation were statistically significant independent clinical predictors of lymph node metastases (P=0.001 and P<0.001, respectively; *Table 4*).

Univariate and multivariate analyses of clinical predictors of lymphatic permeation

Because lymphatic permeation has been reported to be an independent risk factor for local failure other than lymph node metastases in patients with clinical N0 NSCLC undergoing limited surgical resection (11,12), we also examined possible clinical predictors of lymphatic permeation. Univariate analyses revealed five significant clinical predictors of lymphatic permeation: age, smoking status, FEV_1/FVC, CEA level, and tumor size (*Table 5*). The results of multivariate analysis indicated that CEA and tumor size were statistically significant independent clinical predictors of lymphatic permeation (P=0.013 and P<0.001, respectively; *Table 5*).

Table 1 Clinical characteristics and prognostic factors of patients with clinical stage IA NSCLC who underwent surgery

Characteristics	No. of patients [%]	5-year survival rate (%)	Univariate P value†	Multivariate analysis		
				HR	95% CI	P value
Total	229	84.9				
Age (years)						
<67	119 [52]	93.2	0.005*	1		
>67	110 [48]	76.5		2.591	1.043–6.434	0.04*
Sex						
Female	98 [43]	88.5	0.147	Not included in the multivariate model		
Male	131 [57]	82.0				
Smoking history						
Never-smoker	125 [55]	87.3	0.069	Not included in the multivariate model		
Ever-smoker	104 [45]	82.0				
CEA						
Within the normal range	174 [76]	87.7	0.02*	1		
Elevated	55 [24]	75.5		1.368	0.603–3.106	0.453
FEV_1%						
>70	123 [54]	86.2	0.387	Not included in the multivariate model		
<70	79 [35]	83.6				
Unknown	27					
Tumor laterality						
Right	130 [57]	87.6	0.131	Not included in the multivariate model		
Left	99 [43]	81.6				
Primary lobe						
Upper or middle lobe	160 [70]	83.4	0.387	Not included in the multivariate model		
Lower lobe	69 [30]	88.6				
Tumor size on chest CT (cm)						
<2.0	156 [68]	88.0	0.197	Not included in the multivariate model		
>2.0	73 [32]	78.3				
Histological type						
Adenocarcinoma	195 [85]	87.8	0.006*	1		
Non-adenocarcinoma	34 [15]	69.7		2.197	0.959–5.037	0.063
Lymphatic permeation						
Absent	158 [69]	90.9	0.007*	1		
Present	71 [31]	73.8		1.57	0.643–3.837	0.322
Visceral pleural invasion						
Absent	194 [85]	89.0	<0.001*	1		
Present	35 [15]	58.4		2.605	0.969–7.008	0.058
N status						
N0	207 [90]	86.8	0.022*	1		
N1–3	22 [10]	66.8		2.782	1.018–7.599	0.046*

Numbers in parentheses indicate percentages. *, significance level; †, log-rank test. HR, hazard ratio; CI, confidence interval; CEA, preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/mL; FEV_1%, forced expiratory volume percent in 1 s; CT, computed tomography; N, lymph node.

Table 2 Clinical characteristics and prognostic factors of patients with pathological stage IA NSCLC who underwent surgery

Characteristics	No. of patients (%)	5-year survival rate (%)	Univariate P value†	Multivariate analysis		
				HR	95% CI	P value
Total	168	91.4				
Age (years)						
<67	91 [54]	98.7	0.009*	1		
>67	77 [46]	83.6		5.469	1.187–25.195	0.029*
Sex						
Female	76 [45]	91.9	0.387	Not included in the multivariate model		
Male	92 [55]	90.5				
Smoking history						
Never-smoker	96 [57]	92.7	0.076	Not included in the multivariate model		
Ever-smoker	72 [43]	89.6				
CEA						
Within the normal range	140 [83]	92.6	0.019*	1		
Elevated	28 [17]	85.8		3.113	0.939–10.319	0.063
FEV_1%						
>70	96 [57]	93.3	0.826	Not included in the multivariate model		
<70	50 [29]	91.8				
Unknown	22					
Tumor laterality						
Right	92 [55]	93.5	0.075	Not included in the multivariate model		
Left	76 [45]	89.1				
Primary lobe						
Upper or middle lobe	113 [67]	92.2	0.838	Not included in the multivariate model		
Lower lobe	55 [33]	85.8				
Tumor size on chest CT (cm)						
<2.0	123 [73]	91.9	0.757	Not included in the multivariate model		
>2.0	45 [27]	89.6				
Histological type						
Adenocarcinoma	147 [88]	93.6	0.049*	1		
Non-adenocarcinoma	21 [12]	78.7		2.097	0.599–7.346	0.247
Lymphatic permeation						
Absent	134 [80]	93.2	0.148	Not included in the multivariate model		
Present	34 [20]	84.9				

Numbers in parentheses indicate percentages. *, significance level; †, log-rank test. HR, hazard ratio; CI, confidence interval; CEA, preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/mL; FEV_1%, forced expiratory volume percent in 1 s; CT, computed tomography.

Table 3 Correlation between preoperative serum CEA level and clinicopathological factors

Characteristics	Number of patients [%]	CEA		P value
		Within the normal range	Elevated	
Total	378	278	100	
Age (years)				
Mean ± SD	378	66.1±9.8	68.5±8.7	0.023*
Sex				
Female	157 [42]	125 [80]	32 [20]	0.025*
Male	221 [58]	153 [69]	68 [31]	
Smoking history				
Never-smoker	195 [52]	157 [81]	38 [19]	0.002*
Ever-smoker	183 [48]	121 [66]	62 [34]	
FEV_1%				
Mean ± SD	346	71.9 ±11.3	71.9±11.3	0.097
Unknown	32			
Tumor size on chest CT (cm)				
<2.0	253 [67]	190 [75]	63 [25]	0.386
>2.0	125 [33]	88 [70]	37 [30]	
Tumor laterality				
Right	217 [57]	154 [71]	63 [29]	0.197
Left	161 [43]	124 [77]	37 [23]	
Primary lobe				
Upper or middle lobe	265 [70]	195 [74]	70 [26]	0.978
Lower lobe	113 [30]	83 [73]	30 [27]	
Histological type				
Adenocarcinoma	345 [91]	263 [76]	81 [24]	<0.001*
Non-adenocarcinoma	34 [9]	15 [44]	19 [56]	
Lymphatic permeation				
Absent	248 [66]	197 [79]	51 [21]	<0.001*
Present	130 [34]	81 [62]	49 [38]	
Visceral pleural invasion				
Absent	315 [83]	244 [77]	71 [23]	<0.001*
Present	63 [17]	54 [60]	36 [40]	
N status				
N0	344 [91]	263 [76]	81 [24]	<0.001*
N1–3	34 [9]	15 [44]	19 [56]	

Numbers in parentheses indicate percentages. *, significance level. SD, standard deviation; CEA, preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/mL; FEV_1%, forced expiratory volume % in 1 s; CT, computed tomography; N, lymph node.

Table 4 Univariate and multivariate analyses of clinicopathological predictors of lymph node metastases

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
<67	1			Not included in the multivariate model		
>67	1.497	0.732–3.058	0.269			
Sex						
Female	1			Not included in the multivariate model		
Male	1.658	0.818–3.367	0.16			
Smoking history						
Never-smoker	1			Not included in the multivariate model		
Ever-smoker	1.209	0.595–2.457	0.6			
CEA						
Within the normal range	1			1		
Elevated	4.113	1.999–8.461	<0.001*	3.019	1.386–6.578	0.005*
FEV_1%						
>70	1			Not included in the multivariate model		
<70	1.464	0.698–3.068	0.683			
Unknown						
Tumor size on chest CT (cm)						
<2.0	1			1		
>2.0	2.844	1.392–5.811	0.004*	1.937	0.894–4.195	0.094
Tumor laterality						
Right	1			Not included in the multivariate model		
Left	1.161	0.521–2.179	0.938			
Primary lobe						
Upper or middle lobe	1			Not included in the multivariate model		
Lower lobe	1.429	0.626–3.256	0.397			
Histological type						
Adenocarcinoma	1			Not included in the multivariate model		
Non-adenocarcinoma	1.397	0.473–4.132	0.546			
Lymphatic permeation						
Absent	1			1		
Present	11.072	4.450–27.550	<0.001*	8.417	3.252–21.785	<0.001*
Visceral pleural invasion						
Absent	1			1		
Present	2.288	1.034–5.059	0.041*	1.799	0.427–2.494	0.143

Numbers in parentheses indicate percentages. *, significance level. HR, hazard ratio; CI, confidence interval; CEA, preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/mL; FEV_1%, forced expiratory volume percent in 1 s; CT, computed tomography.

Table 5 Univariate and multivariate analyses of clinical predictors of lymphatic permeation

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
<67	1			Not included in the multivariate model		
>67	1.244	0.813–1.904	0.314			
Sex						
Female	1			1		
Male	1.636	1.053–2.543	0.029*	1.276	0.668–2.439	0.46
Smoking history						
Never-smoker	1			1		
Ever-smoker	1.946	1.265–2.995	0.002*	1.762	0.953–3.258	0.071
CEA						
Within the normal range	1			1		
Elevated	2.337	1.461–3.738	<0.001*	1.935	1.152–3.251	0.013*
FEV_1%						
>70	1			1		
<70	1.988	1.264–3.125	0.003*	1.661	0.995–2.770	0.052
Unknown						
Tumor size on chest CT (cm)						
<2.0	1			1		
>2.0	2.413	1.545–3.770	<0.001*	2.603	1.601–4.231	<0.001*
Tumor laterality						
Right	1			Not included in the multivariate model		
Left	0.936	0.778–1.996	0.764			
Primary lobe						
Upper or middle lobe	1			Not included in the multivariate model		
Lower lobe	1.245	0.626–3.256	0.361			
Histological type						
Adenocarcinoma	1			1		
Non-adenocarcinoma	1.995	1.132–3.514	0.017*	1.626	0.820–3.225	0.164

Numbers in parentheses indicate percentages. *, significance level. HR, hazard ratio; CI, confidence interval; CEA, preoperative serum carcinoembryonic antigen level, normal upper limit at 5 ng/mL; FEV_1%, forced expiratory volume percent in 1 s; CT, computed tomography.

Discussion

CEA was first identified in 1965 in human colon cancer tissue extracts (13). CEA is a cell surface-anchored molecule involved in cell adhesion and is an oncofetal antigen that is normally present only during fetal development; however, the serum CEA level is known to be elevated by several malignant tumors, including NSCLC (14). Elevated serum CEA levels have been reported in approximately 35–60% of patients with NSCLC, and these CEA levels correlate with the cancer stage (5,15). Although several authors have reported that evaluating the serum CEA level is useful for monitoring responses to chemotherapy and predicting relapses in cases of advanced NSCLC (6-8), the significance of evaluating the serum CEA level in patients with early-stage small-sized NSCLC has remained unclear. In this study, we evaluated the clinical significance of the serum

CEA level in patients with clinical stage IA NSCLC.

Several studies have reported that the preoperative CEA level is an independent prognostic factor in patients surgically treated for clinical stage I NSCLC (16,17). However, the preoperative CEA level was not determined to be an independent prognostic factor in patients with clinical stage I NSCLC by multivariate analysis in the present study. However, we demonstrated that an elevated preoperative serum CEA level correlated with tumor invasiveness factors, including lymphatic permeation and visceral pleural invasion (*Table 3*), and was a significant independent clinical predictor of lymph node metastases (*Table 4*).

Considering the originating features of CEA, cancer metastasis may be enhanced by an increased serum CEA level, with CEA functioning as an adhesion molecule and a chemoattractant (18). Accumulated evidence strongly suggests that CEA activates Kupffer cells and stimulates interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, thereby promoting adhesion of tumor cells to the endothelium (19). Adhesion molecules that induce invasion can also facilitate the migratory process, resulting in the propagation of cancer metastasis (18). The present study supports these molecular and experimental findings by providing evidence of the increased potential for lymph node metastases in patients with clinical stage IA NSCLC having an abnormal CEA level.

Lymph node metastasis is a poor prognostic factor for patients with NSCLC. Nodal staging based on CT imaging reportedly showed a sensitivity ranging from 50% to 80% and a specificity ranging from 60% to 90% in studies published during the last decade (20,21). In the present study, the preoperative CEA level and lymphatic permeation were significant independent clinical predictors of lymph node metastases. Because we can identify the presence of lymphatic permeation only from resected lung specimens, we cannot consider the preoperative CEA level for predicting lymph node metastases. Therefore, the preoperative serum CEA level is only a clinical predictor of lymph node metastases, which requires the consideration of performing endobronchial ultrasound or PET with ^{18}F-fluorodeoxyglucose to assess the hilar or mediastinal lymph nodes in patients undergoing non-surgical management, such as stereotactic body radiation therapy and minimally invasive percutaneous ablative therapies, and in patients with an elevated serum CEA level having small tumors and lymph nodes that are negative on CT investigation.

Sublobar resection, such as segmentectomy and wedge resection, may benefit patients with NSCLC and comorbid diseases or decreased pulmonary function as well as older patients with a limited life expectancy (22,23). However, a higher local or regional recurrence rate after limited surgical resection has often been observed despite the pathological confirmation of a negative surgical margin. This finding was likely attributable to the tumor involvement of intratumoral vessels, even for pathological N0 disease, with the spread of tumor cells into lymphatic vessels outside the primary tumor leading to local recurrence (24). Koike *et al.* (25) also previously reported that lymphatic permeation was the only independent predictor of both poor prognosis and recurrence in patients with clinical T1aN0M0 NSCLC undergoing intentional segmentectomy. To successfully select patients for limited resection, simple clinical predictors of lymphatic permeation are required because presence of lymphatic permeation can be definitively identified only in resected lung specimens at present. In this study, the preoperative CEA level was a significant independent clinical predictor of lymphatic permeation. Therefore, limited surgical resection should be carefully indicated for patients with an elevated preoperative serum CEA level.

This was a retrospective study, and the analyses performed had several limitations. In particular, some patients originally had an elevated serum CEA level because of various factors, including smoking, and evaluation of the serum CEA level in these patients could not precisely reflect the effects of such factors. Despite these limitations, we have clearly shown the utility of assessing the preoperative serum CEA level in patients with early-stage NSCLC. Although routine measurement of the preoperative serum CEA level for small-sized NSCLC is not widely performed, it is a useful test that may assist in predicting outcomes of patients with clinical stage IA NSCLC.

Conclusions

The preoperative serum CEA level was not an independent predictor of poor prognosis in patients with pathological stage IA NSCLC. However, preoperative measurement of the serum CEA level for patients with early-stage NSCLC is useful because it is an important predictor of tumor invasiveness and lymph node metastases in patients with clinical stage IA NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The research was approved by the Internal Review Board of the institution.

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