Preoperative Serum Carcinoembryonic Antigen Level is a Prognostic Factor in Women With Early Non–Small-Cell Lung Cancer

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Background. **Carcinoembryonic antigen (CEA) is one of the markers evaluated in patients with non–small cell lung cancer (NSCLC). The significance of the preoperative serum CEA level in female patients with NSCLC is seldom discussed. In this study, we conducted a retrospective review to investigate the prognostic significance of the preoperative CEA level in female patients with stage I NSCLC.**

Methods. **In this study, we looked at 163 female patients with stage I NSCLC. Patient charts were reviewed to collect patient data, including the age of the patient, tumor location, tumor size, visceral pleural invasion, the stage of disease, and the preoperative serum CEA level. The cutoff value of serum CEA level was 6.0 ng/mL. The significance of preoperative CEA level in the prognosis of female patients with stage I NSCLC was evaluated.**

Results. **Among the 163 female patients with stage I NSCLC, 47 patients (28.8%) had abnormal preoperative serum CEA level (>6 ng/mL). Diagnosis of adenocarcinoma and bronchoalveolar carcinoma accounted for 83.4% of these 163 female patients. In-hospital mortality was encountered in 1 patient. Univariate analysis of survival in the other 162 female patients with stage I NSCLC showed that age, stage, tumor size, and preoperative CEA level were prognostic factors. Visceral pleural invasion had no impact on the prognosis of these patients. Multivariate analysis revealed that tumor size and preoperative CEA level were independent prognostic factors in female patients with stage I NSCLC.**

Conclusions. **Preoperative serum CEA level and tumor size are independent prognostic factors in female patients with stage I NSCLC. In contrast, visceral pleural invasion was not associated with the prognosis. Importantly, these results suggest that female patients with abnormally high preoperative CEA level and tumor size larger than 3 cm may need a thorough preoperative evaluation and careful postoperative follow-up to rule out occult metastasis of early NSCLC.**

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Lung cancer has become the leading cause of cancer death in many industrialized countries, including Taiwan. It claimed more than 7,000 lives in 2004 in Taiwan alone [1]. In recent years much attention has been focused on the rapidly increasing incidence of primary lung cancer in women. It is well known that cigarette smoking is the main risk factor for lung cancer. Indeed, a higher prevalence of smoking among women accounts for part of the increase in lung cancer incidence in women. Other risk factors for lung cancer in women include passive smoking, cooking oil vapors, and occupational exposure. In addition, several studies have shown that there are sex-associated differences in presentation, management, and prognosis of patients with non–small cell lung cancer (NSCLC) [2–4].

Patients with NSCLC were evaluated for markers including carcinoembryonic antigen (CEA). Although CEA is mainly associated with adenocarcinoma of the gastrointestinal tract, elevated levels of CEA have been reported in about 35% to 60% of patients with NSCLC, showing higher sensitivity in adenocarcinoma of lung and in advanced stages [5–10]. Sawabata and colleagues [11] have suggested that the serum CEA level might be a useful predictor of survival for patients with clinical stage I NSCLC, and that a persistently high CEA level after surgery is a particularly strong indicator of a very poor prognosis. Evaluation of serum CEA level is also useful for monitoring the response to postoperative chemotherapy and detecting whether there is cancer relapse [12]. The significance of the preoperative CEA serum level in female patients with lung cancer is still unclear.

In addition, visceral pleural invasion was adopted as a specific description in the TNM classification of the International Union Against Cancer (UICC) staging system in the mid-1970s and has remained unchanged [13].

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The new International System for staging lung cancer defined tumors with invasion of visceral pleura as T2. However, several authors have pointed out that visceral pleural invasion does not affect the outcome in stage I NSCLC. In this study, we conducted a retrospective review to investigate the prognostic significance of the preoperative CEA level and visceral pleural invasion on female patients with stage I NSCLC.

Patients and Methods

Taipei Veterans General Hospital Institutional Review Board approved this study (95-07-15A) and granted an exemption from informed consent on June 27, 2006.

From January 1995 to December 2002, among 336 consecutive female patients undergoing surgical treatment for NSCLC at Taipei Veterans General Hospital, pathologic diagnosis of stage I NSCLC was made in 163 female patients. Patients who had preoperative chemotherapy or radiotherapy were excluded in this study. The clinical data including the age of the patient, tumor location, tumor size, visceral pleural invasion, the stage of disease, and preoperative serum CEA level were collected by chart review. Patients either underwent radical mediastinal lymphadenectomy (the majority underwent this procedure) or mediastinal node sampling according to the surgeon's preference. In cases in which pleural effusion was present, a sample was collected and sent for cytologic examination. Patients with malignant pleural effusion were not included in the study.

Blood samples for CEA measurement were obtained 2 weeks before pulmonary resection. Carcinoembryonic antigen levels were measured using an immunoradiometric assay (ELSA2-CEA) obtained from CIS Bio International (Gif-Sur-Yvette, Cedex, France). The cutoff value of serum CEA level was 6.0 ng/mL. The pathologic stage was determined using the new TNM system for lung cancer [13]. Zero time was defined as the date of pulmonary resection, and the terminal event was the death attributable to cancer. All other deaths resulting from other than cancer or unknown causes were treated as withdrawals in the cumulative survival analyses. Survival curves were calculated by the Kaplan–Meier method, and comparison was performed by log-rank test. Multivariate

Table 1. Demographic Data of Female Patients With Stage I Non–Small-Cell Lung Cancer (163 patients)

Variable	Range (Mean ± SD)	Number (%)
Age (y)	19–87 (61.2 ± 12.5)	
Follow up (mo)	1–129.7 (57.7 ± 28.9)	
Smoking habit		12 (7.4)
Symptoms		96 (58.9)
Cough		70 (42.9)
Chest pain		11 (6.7)
Hemoptysis		25 (15.3)
Preop CEA level >6 ng/mL		47 (28.8)
Number of removed lymph nodes	4–54 (18.4 ± 10.6)	
Tumor location		
Right upper lobe		57 (35.0)
Right middle lobe		17 (10.4)
Right lower lobe		37 (22.7)
Left upper lobe		32 (19.6)
Left lower lobe		20 (12.3)
Histopathology		
Adenocarcinoma		112 (68.7)
Bronchoalveolar carcinoma		24 (14.7)
Squamous cell carcinoma		13 (8.0)
Adenosquamous cell carcinoma		6 (3.7)
Large cell carcinoma		1 (0.6)
Others		7 (4.3)
Operation method		
Pneumonectomy		2 (1.2)
Bilobectomy		10 (6.1)
Lobectomy		142 (87.2)
Wedge resection		9 (5.5)
Complication		20 (12.3)
In-hospital mortality		1 (0.6)

CEA = carcinoembryonic antigen; Preop = preoperative; SD = standard deviation.

Table 2. Correlation Between Preoperative Carcinoembryonic Antigen Level and Clinical Variables in 163 Female Patients With Stage I Non–Small-Cell Lung Cancer

	Preoperative CEA Level		
Variable	Normal	Abnormal (>6 ng/mL)	*p* Value
Age			
≤65 y	68	27	
>65 y	47	20	0.843
Symptoms			
No	51	16	
Yes	65	31	0.243
Smoking habit			
No	107	44	
Yes	9	3	0.761
Histopathology			
Adenocarcinoma[a]	93	43	
Others	23	4	0.078
Pleural invasion			
No	69	27	
Yes	47	20	0.811
Tumor size			
≤3.0 cm	71	22	
>3.0 cm	45	25	0.093
Tumor stage by TNM			
T1	44	13	
T2	72	34	0.213

[a] Including bronchoalveolar carcinoma.

CEA = carcinoembryonic antigen.

analysis was performed using the Cox proportional hazard model. Probability values of less than 0.05 were considered significant.

Results

The demographic data of these 163 female patients with stage I NSCLC are shown in Table 1. The mean age at the time of pulmonary resection was 61.2 years. Only 12 female patients (7.4%) had a smoking history. Ninety-six patients had symptoms in the initial presentation (58.9%), including cough in 70 patients (42.9%), chest pain in 11 patients (6.7%), and hemoptysis in 25 patients (15.3%). Forty-seven patients (28.8%) had an abnormal preoperative serum CEA level (%>6 ng/mL). Diagnosis of adenocarcinoma and bronchoalveolar carcinoma accounted for 83.4% of 163 female patients with stage I NSCLC. The difference between preoperative CEA levels for the variables is shown in Table 2. There was no correlation between the preoperative CEA level and the clinical variables including age of the patient, symptom presentation, smoking habits, histopathology, pleural invasion, tumor size, and tumor stage in our female patients. In-hospital mortality was encountered in 1 patient.

Table 3. Comparison of Survival for Female Patients With Stage I Non–Small-Cell Lung Cancer (162 patients)

Variable	Number (%)	5-Year Survival (%)	*p* Value
Age (y)			
≤65	95 (58.6)	69.2	
>65	67 (41.4)	55.8	0.049
Symptoms presentation			
No	67 (41.4)	61.7	
Yes	95 (58.6)	71.9	0.536
Smoking habit			
Yes	12 (7.4)	74.1	
No	150 (92.6)	67.3	0.411
Preop FEV_1 (L)			
≤1.5	56 (34.6)	61.0	
>1.5	106 (65.4)	72.3	0.125
Pathologic stage			
IA	56 (34.6)	80.6	
IB	106 (65.4)	61.0	0.009
Tumor size (cm)			
≤3	92 (56.8)	77.7	
>3	70 (43.2)	54.5	0.001
Visceral pleural invasion			
Nil	95 (58.6)	71.1	
Yes	67 (41.4)	62.8	0.248
Number of removed lymph nodes			
<15	61 (37.7)	64.4	
≥15	101 (63.3)	70.0	0.633
Preop CEA level (ng/mL)			
≤6	115 (71.0)	71.4	
>6	47 (29.0)	58.3	0.027
Histopathology (including BAC)			
Adenocarcinoma	135 (83.3)	70.3	
Others	27 (16.7)	54.8	0.297
Operation approach			
Lobectomy	142 (87.7)	69.3	
Others	20 (12.3)	56.1	0.777

BAC = bronchioalveolar carcinoma; CEA = carcinoembryonic antigen; FEV_1 = forced expiratory volume in 1 second; Preop = preoperative.

Univariate analysis of survival in the other 162 female patients with stage I NSCLC showed that age of the patient, stage of the tumor, tumor size, and the preoperative CEA level were prognostic factors. Visceral pleural invasion had no impact on the prognosis of female patients with stage I NSCLC (Table 3). The survival curves are shown in Figure 1. In multivariate analysis, when the variables such as pleural invasion, age, histopathology, tumor size, and preoperative CEA level were entered into the multivariate equation, only tumor size and preoperative CEA level were significantly associated with the prognosis (Table 4).

Comment

The possible role of CEA in NSCLC was first postulated in the 1970s [14]. In a consensus development conference held in 1980 concerning the role of CEA as a marker in the management of cancer, recommendations were made stating that a preoperative plasma CEA value (1) should be obtained in patients having either colorectal or bronchial carcinomas and (2) should be used as an adjunct to clinical and pathologic staging methods [12].

On the contrary, the American Thoracic Society and the European Respiratory Society jointly published their clinical guidelines for pretreatment evaluation of NSCLC in 1997 and stated: ". . . Unfortunately, none [ie, no serum tumor marker] appears sufficiently sensitive and has a high enough specificity to add to our ability to reliably detect occult disease or influence disease management. The routine measurement of any of these substances in the screening, staging, or evaluation of disease progression is not recommended" [15]. Similarly, the 2006 guidelines of the National Comprehensive Cancer Network of NSCLC do not include preoperative CEA as a pretreatment evaluation [16].

The significance of serum CEA levels had also been discussed in several studies. In the report by Icard and colleagues [17], 152 patients with lung cancer and a CEA level greater than 10 ng/mL were enrolled in a study to investigate the prognostic significance of preoperative CEA level. The authors found a critical unfavorable CEA level of prognostic significance of 30 ng/mL. The increase of preoperative CEA levels was associated with the severity of disease [17]. Recently, Okada and coauthors [18] reported their experience with 1,000 consecutive resections for stage I lung cancer and concluded that perioperative measurement of serum CEA concentrations yields information valuable for detecting patients at high risk of poor survival. However, the difference of the

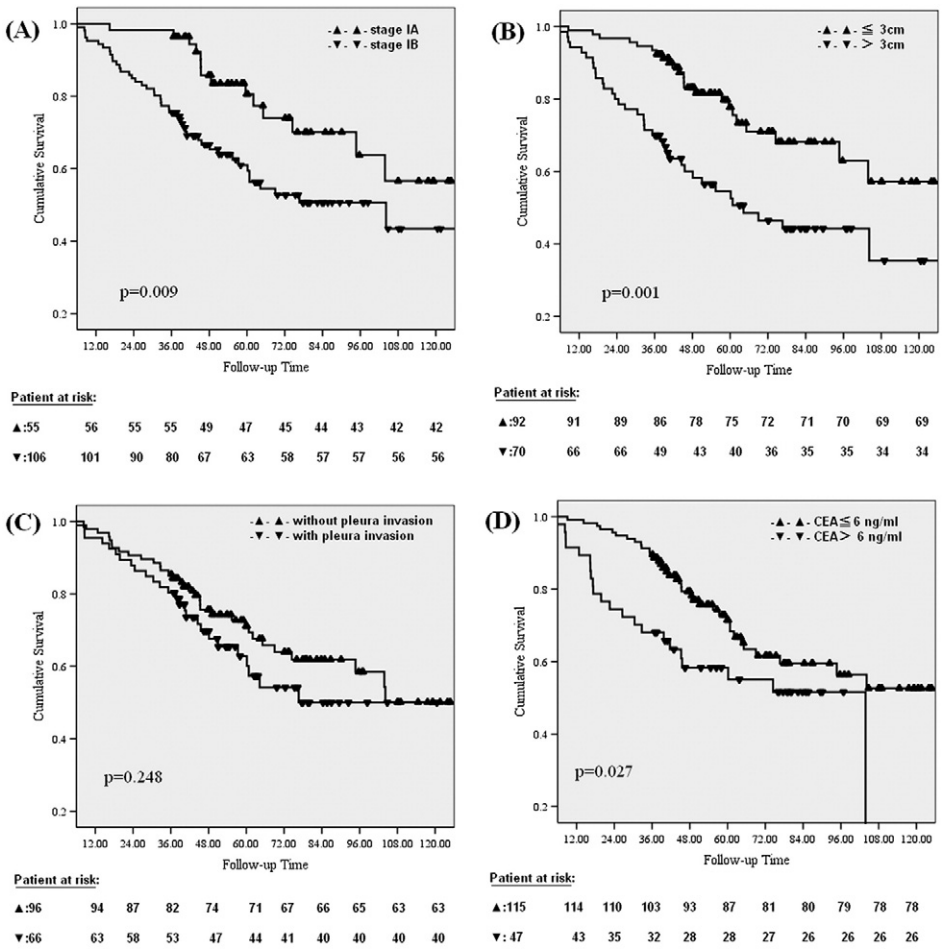

Fig 1. Survival curves of female patients with stage I non–small cell lung cancer, compared by stage, p = 0.009 (A); tumor size, p = 0.001 (B); visceral pleural invasion, p = 0.248 (C); and preoperative carcinoembryonic antigen (CEA) level, p = 0.027 (D).

prognostic significance of CEA level between sexes was not mentioned in these studies. Elevated levels of serum CEA have been observed in patients with nonmalignant disease such as chronic bronchitis, emphysema, or colitis [19, 20].

Cigarette smoking and aging are also associated with increased serum CEA level [21, 22]. Cigarette smoking is a major risk of lung cancer, and only approximately 3% of lung cancers occur in nonsmokers in the Western world [23]. In contrast, in Taiwan, the majority of women with lung cancer are nonsmokers [24]. In our study, only 7.6% of female patients with stage I lung cancer had smoking history in our study. In addition, up to 83.4% of our patients had adenocarcinoma or bronchioalveolar carcinoma.

This study investigated the relationship between serum CEA levels and early NSCLC in female patients with stage I disease. Patients with more advanced stages of NSCLC were ruled out for the purposes of this study to minimize factors such as cigarette smoking and prognosis stratification across early and advanced stages of tumor. The results showed that preoperative CEA level is a prognostic factor in female patients with stage I NSCLC.

We did not look at the significance of CEA level in nonsmoking men as most of the male patients in our

Table 4. Multivariate Analysis of Prognostic Factors in Female Patients With Stage I Non–Small-Cell Lung Cancer

Variable	Coefficient ± SE	Odds Ratio	95% CI	*p* Value
No. of tumors with VPI	0.150 ± 0.274	1.162	0.679–1.987	0.585
Adenocarcinoma	0.313 ± 0.345	1.368	0.696–2.690	0.363
Age >65 y	0.512 ± 0.264	1.669	0.994–2.801	0.053
Preop CEA level (>6 ng/mL)	0.581 ± 0.278	1.787	1.037–3.080	0.037
Tumor size (>3 cm)	0.792 ± 0.277	2.208	1.282–3.803	0.004

CEA = carcinoembryonic antigen; CI = confidence interval; Preop = preoperative; SE = standard error; VPI = visceral pleural invasion.

series had a smoking history. It is still unknown whether the CEA level is also a prognostic factor in male patients with squamous cell carcinoma. The possible absence of the correlation between CEA level and the prognosis of patients with squamous cell carcinoma could be related to the fact that squamous cell carcinoma is more often related to smoking history than adenocarcinoma.

Our findings suggest that even when the patients with an abnormally elevated preoperative serum CEA level had complete resection for pathologically confirmed stage I NSCLC, the prognosis was worse than the patients with normal preoperative serum CEA level. This may have been related to the tumor burden or failure to eradicate all pulmonary disease even though curative resection was apparently performed. Several studies have shown that a preoperative CEA level higher than 50 ng/mL always indicates a higher frequency of metastasis even after surgical resection [17, 18, 25]. In addition, Icard and colleagues [17] reported that patients with preoperative CEA level greater than 50 ng/mL died within 2 years. In our study, 7 female patients with a preoperative CEA level greater than 50 ng/mL had a limited median survival of 16.6 months. Only 1 patient was still alive 56.4 months after operation.

Although the T2 classification includes tumors of any size with invasion of the visceral pleura, several studies have failed to establish visceral pleura invasion as a significant prognostic factor for NSCLC [26–28]. Whether the extent of visceral pleural invasion by tumor affects the outcome is unknown. The Japan Lung Cancer Society classifies the visceral pleural invasion as follows: p0, tumor with no pleural involvement beyond its elastic layer; p1, tumor that extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface; p2, tumor that is exposed on the pleural surface but does not involve adjacent anatomic structures; and p3, tumor that involves adjacent anatomic structure [29]. The Society classifies a p2 tumor of any size as T2 and a p1 tumor of 3 cm or less as T1.

In contrast, the UICC TNM system classification describes only tumors with visceral pleural invasion as T2. In our study, we followed the definition of the UICC TNM system for staging NSCLC and found that visceral pleural invasion was not a prognostic factor in female patients with stage I NSCLC. In patients with T1 size tumors, survival between the patients without visceral pleural and the patients with visceral pleural invasion (stage T2) was not significantly different. The result was the same in patients with T2 size tumors.

In conclusion, preoperative CEA serum level and tumor size are independent prognostic factors in female patients with stage I NSCLC. Visceral pleural invasion was not associated with the prognosis. Importantly, these results suggest that female patients with abnormally elevated preoperative CEA level or tumor size larger than 3 cm may need a thorough preoperative evaluation and careful postoperative follow-up to rule out occult metastasis of early NSCLC.

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INVITED COMMENTARY

The authors [1] examined the role of serum carcinoembryonic antigen (CEA) level as a prognostic factor in patients with nonsmall cell lung cancer (NSCLC). Small studies have examined this serum marker; however CEA has not yet reached the level of evidence necessary for incorporation into consensus conference guidelines for staging or prognosis. Still, studies from Japan [2, 3] and the current study from Taiwan, have suggested that increased levels of CEA may be associated with poorer prognosis.

In this article, the authors describe a population of nonsmoking Taiwanese women (92.4% without a history of cigarette smoking) with predominantly adenocarcinoma and bronchoalveolar carcinoma (83.4%). Lobectomy was performed in 87% of these individuals. Elevated preoperative CEA levels (>6.0 ng/mL) and larger tumor size were associated with poorer prognosis. Are these findings related to histology, ethnicity, or other genetic alterations that may predispose to adenocarcinoma in nonsmoking women? The answer to these and other questions will require a larger analysis of prospectively collected serum, tissue, and clinical data.

However, until completion of these analyses, patients with an adenocarcinoma of the lung, particularly in women nonsmokers, may be considered for serum CEA level determination. Patients with CEA ≥6 ng/mL may represent a population with poorer survival mandating closer follow-up and consideration for multimodality or other targeted therapies [4]. Although adjuvant chemotherapy is not a current recommendation for stage I NSCLC, the ability to predict those stage I patients with poor prognosis would be helpful. Early-stage, poor-prognosis patients could be selected for specific therapies for subsequent survival benefit compared with current models of observation alone.

The poorer survival with increased preoperative CEA in nonsmoking Asian women must be considered in relationship to women (and men) of various ethnicities and smoking status. These small retrospective independent studies, may provide models for subsequent evaluation of CEA and other serum markers for staging, prognosis, and therapy for patients with early stage NSCLC.

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