Introduction

Although sex differences in the presentation and prognosis of patients with non-small cell lung cancer (NSCLC) had been reported, much attention has focused recently on primary NSCLC in women because of a rapid increase in NSCLC mortality among women [1–8]. These studies demonstrated that many factors, including cigarette smoking, passive smoking, diet, occupation and indoor exposure, might influence the differences in lung cancer incidence between men and women [1–7]. At present, one of the most commonly used tumor markers is serum carcinoembryonic antigen (CEA). Several previous reports have indicated that preoperative elevated serum CEA levels are associated with more advanced disease and with very poor survival rates following surgical resection [8–12]. However, to our knowledge, there is only one study that mentioned the difference of the prognostic significance of CEA level between sexes [8].

Moreover, several studies have evaluated the usefulness of pleural lavage cytology (PLC) and have suggested that positive PLC findings may indicate a more aggressive tumor biology, a higher risk of recurrence, and a poorer survival rate [13–16]. Some researchers advocate adding PLC to the TNM staging system for NSCLC in order to stratify patients more accurately [13]. Both serum CEA level and PLC are inexpensive methods and routinely available. However, the prognostic significance of these factors in female patients was not known in detail. Therefore, a study focusing on the prognostic significance of CEA level and PLC findings were independent prog nostic factors for female patients with NSCLC.

Materials and Methods

The present retrospective study was conducted from 1997 through 2004, and included all female patients with NSCLC who had undergone complete resection, which consisted of either a lobectomy or a pneumonectomy together with regional lymph nodes dissection. Patients who had had preoperative chemotherapy or radiotherapy were excluded. A consecutive series of 122 women with NSCLC who underwent complete resection and PLC were included in this study. Patient ages ranged from 20 to 85 years, with an average of 66.44 years. The baseline characteristics are

Abstract

Background: The prognostic impact of serum carcinoembryonic antigen (CEA) levels and pleural lavage cytology (PLC) in female patients with non-small cell lung cancer (NSCLC) were examined.

Methods: A consecutive series of 122 women with NSCLC who underwent surgical resection and PLC were included in the study.

Results: The 5-year survival rate of patients with preoperative serum normal and elevated CEA levels was 86.79% and 58.46%, respectively (p = 0.0032). Positive PLC was present in 9/122 (7.38%) of patients. The 5-year survival rate of patients with positive PLC findings was 33.33%, which was significantly poor compared with that of patients with negative findings (83.16%, p = 0.0010). Multivariate analysis indicated that pN status, preoperative serum CEA levels and PLC findings were independent prognostic factors.

Conclusions: Preoperative serum CEA level and PLC findings were independent prognostic factors for female patients with NSCLC.
summarized in Table 1. The clinical investigation section of our hospital measured serum CEA levels using the two-site immunoenzymometric assay; the normal upper limit for this assay was 5.0 ng/mL.

All patients underwent thoracotomy and were examined with regard to PLC. Immediately following thoracotomy and prior to any further manipulation of the pulmonary parenchyma, the pleural cavity was carefully washed with 200 mL of physiologic saline solution. The fluid was irrigated over the visceral and parietal pleura. Special care was taken to prevent undue contamination of the lavage fluid with blood and to avoid contact with the pleural surface in order to collect only desquamated cells. The fluid was placed in a glass bottle containing heparin and centrifuged at 1500 rpm for 5 minutes. The sediment was stained using Giemsa and Papanicolaou methods. Cytologic results were divided into two categories: negative and positive. Papanicolaou classes I, II, and III were regarded as negative; classes IV and V were considered positive. Pathologic (p) TNM staging was recorded for all patients.

The follow-up information, including cause of death, was acquired through clinic follow-up 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 less than 0.05 were considered significant.

**Results**

As shown in Table 1, the majority of our patients had adenocarcinoma (105/122) and stage I (89/122) disease. Moreover, only 10 patients (8.2%) were current or former smokers.

As shown in Fig. 1, the 5-year survival of patients with normal and elevated preoperative serum CEA levels was 86.70% and 58.46%, respectively (p = 0.0032).

Positive PLC were present in 9/122 (7.38%) of patients. All patients with positive PLC findings were given a diagnosis of adenocarcinoma. Five-year survival of patients with positive PLC findings was 33.33%, which was significantly poor compared with that of patients with negative findings (83.16%, p = 0.0010, Fig. 2).

The results of univariate analysis are summarized in Table 2. The pN status, preoperative serum CEA level and positive PLC findings were related to patients’ prognosis, whereas age, histology, pT status and smoking habit were not. The results of multivariate analysis including all variables for which p < 0.05 on univariate analysis are summarized in Table 3. Of the variables that were included in the multivariate analysis, pN status, preoperative serum CEA level and positive PLC findings were independent prognostic determinants.

**Discussion**

In the present series, the majority of our patients had never smoked. There might be striking differences in smoking habits between men and women [1–8]. Such a difference in smoking habits possibly resulted in a different clinical presentation, histology, and treatment. In other words, lung tumor etiology may vary between men and women.
progress via different pathways in men and women, depending on the metabolisms of tobacco-related carcinogens. In addition to smoking-related carcinogens, there could be other differences in molecular abnormalities and hormonal status between men and women [2]. Although several previous studies investigated female lung cancer patients, the majority of these studies focused on the sex differences of patients. The significance of routinely available factors, such as serum CEA level and PLC, in female patients with NSCLC is still unclear.

CEA is a serum tumor marker that is one of the most commonly used to date for lung cancer patients. Several reports, including our previous study, had indicated that elevated preoperative serum CEA levels are associated with more advanced disease and with a very poor survival after surgical resection [8–12]. However, to our knowledge, there is only one study on the prognostic significance of CEA that focused on female patients [8]. In our results, preoperative serum CEA levels were an independent prognostic factor in female patients with NSCLC. Cigarette smoking is associated with an increased serum CEA level [17,18]. However, the majority of our patients had never smoked and the influences of smoking might be smaller in the present series. In our study, 7.38% (9/122) of female patients had a positive PLC. Previous studies have reported the rate of positive PLC findings to be 4.5% to 38.6% [13–16], a wide range attributable to differences in patient stages or to the use of different techniques for collecting the samples or different diagnostic standards for evaluating them. Most previous studies do conclude that patients with a positive PLC have a poor survival rate because a small amount of malignant pleural effusion or a few minute pleural dissemination nodules are probably overlooked at thoracotomy [13–16]. In our results, a positive PLC finding was also an independent prognostic factor in female patients with NSCLC. Positive PLC findings could suggest more aggressive biological behavior of the tumor. How the tumor cells enter the pleural cavity is still unknown. It has been suggested that positive PLC results from cell exfoliation from the primary tumor or cell diapedesis through the lymphatics, or both [13–16]. Another cause may be the exfoliation of malignant cells from metastatic mediastinal lymph nodes.

With regard to the histology, an elevated preoperative serum CEA level is reported to be an independent prognostic factor for NSCLC patients with adenocarcinoma but not squamous cell carcinoma [11]. It has also been reported that the serum CEA level in adenocarcinoma is significantly higher than that in squamous cell carcinoma [10–12]. Moreover, the positive ratio of PLC was reported to be much higher in adenocarcinoma than in squamous cell carcinoma [15]. Therefore, if the number of patients with squamous cell carcinoma is high in a study population, then the prognostic power of serum CEA levels and PLC might be reduced.

### Conclusion

In conclusion, the preoperative serum CEA level and PLC findings were independent prognostic factors for female patients with NSCLC. At present, perioperative measurement of serum CEA and PLC is not commonly performed during staging or the resection of tumors in patients with NSCLC. Both serum CEA level and PLC are inexpensive methods and routinely available. We do recommend routine measurement of serum CEA or PLC in female patients with NSCLC. A further prospective multicenter study with a representative number and controlled, standardized procedure is needed to add the measurement of serum CEA levels and PLC to the staging system.

### Conflict of interest

None declared.

### References


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**Table 2** Univariate analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Favorable</th>
<th>Unfavorable</th>
<th>Risk ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 65</td>
<td>≥ 65</td>
<td>0.941</td>
<td>0.647–1.369</td>
<td>0.7491</td>
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<tr>
<td>Smoking</td>
<td>adenocarcinoma</td>
<td>others</td>
<td>1.153</td>
<td>1.668–1.798</td>
<td>0.5752</td>
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<tr>
<td>pf status</td>
<td>never</td>
<td>current/former</td>
<td>1.535</td>
<td>0.831–2.478</td>
<td>0.1534</td>
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<tr>
<td>pn status</td>
<td>pf1</td>
<td>pf2 – 4</td>
<td>1.378</td>
<td>0.947–2.005</td>
<td>0.0928</td>
</tr>
<tr>
<td>Serum CEA</td>
<td>normal</td>
<td>elevated</td>
<td>1.705</td>
<td>1.167–2.476</td>
<td>0.0066</td>
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<tr>
<td>PLC</td>
<td>negative</td>
<td>positive</td>
<td>2.069</td>
<td>1.289–3.135</td>
<td>0.0041</td>
</tr>
</tbody>
</table>

CI: confidence interval, CEA: carcinoembryonic antigen, PLC: pleural lavage cytology

**Table 3** Multivariate analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Favorable</th>
<th>Unfavorable</th>
<th>Risk ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN status</td>
<td>pN0</td>
<td>pN1 – 2</td>
<td>1.661</td>
<td>1.109–2.467</td>
<td>0.0147</td>
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<tr>
<td>Serum CEA</td>
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<td>1.636</td>
<td>1.099–2.419</td>
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<td>PLC</td>
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<td>positive</td>
<td>1.812</td>
<td>1.115–2.788</td>
<td>0.0184</td>
</tr>
</tbody>
</table>

CI: confidence interval, CEA: carcinoembryonic antigen, PLC: pleural lavage cytology


Stevens DP, Mackay IR, Cullen KJ. Increased carcinoembryonic antigen in heavy cigarette smokers. Lancet 1973; 7840: 1238 – 1239