Pre- and Post-operative Serum Carcinoembryonic Antigen in Primary Lung Adenocarcinoma

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The clinical value of pre- and post-operative serum carcinoembryonic antigen (CEA) concentration (mean +/- SEM, ng/ml) in surgically treated primary lung cancer patients with adenocarcinoma (n=97) was studied. Preoperative CEA in pT2 patients (18.3 +/- 8.0) was higher than in pT1 (10.5 +/- 6.4, p<0.05) but was not different from pT3 patients (19.7 +/- 6.7). Preoperative CEA in pN1 patients (5.9 +/- 1.6) was lower than in pN2 (28.2 +/- 13.2, p<0.05) but not different from pN0 patients (8.8 +/- 3.8); p-stage II patients (8.2 +/- 4.7) had lower values than p-stage III patients (26.7 +/- 10.5, p<0.05), but not p-stage I patients (7.9 +/- 3.9). The CEA was not different between p-stages IA and IIA (3.5 +/- 0.6, 6.1 +/- 3.2) and IB and IIB (17.0 +/- 11.8, 11.7 +/- 7.8), but was different between IA and IB (p<0.05) and IIA and IIB (p<0.05). Preoperative CEA did not differ between patients who received complete (12.7 +/- 4.7) versus incomplete (9.5 +/- 6.0) resections, nor between patients who developed recurrence after surgery (21.9 +/- 10.4) versus those who were disease-free (30.9 +/- 21.7). CEA obtained 2 months after surgery in patients who recurred or metastasized after surgery (63.1 +/- 47.0) was higher than in disease-free patients (4.8 +/- 1.6, p<0.05). The post-/pre-operative CEA ratio in patients who recurred or metastasized after surgery (146.6 +/- 53.3%) was also higher than in disease-free patients (91.0 +/- 10.9%, p=0.05).

In conclusion, CEA reflected tumor size but not the tumor invasion nor hilar lymph node disease; patients with mediastinal lymph node involvement had higher CEA values. Preoperative CEA did not reflect the likelihood of complete resection nor postoperative metastasis, but post-operative CEA obtained 2 months after surgery did reflect postoperative metastasis. (Ann Thorac Cardiovasc Surg 2004; 10: 281–4)

Key words: CEA, tumor marker, adenocarcinoma, lung cancer

Introduction

Tumor markers have been used for diagnosis, screening, staging, and monitoring the effects of treatment.1,2) Carcinoembryonic antigen (CEA) is a widely-studied tumor marker.1,2) Although the initial interest in CEA was for colon cancer, subsequent studies have shown that serum CEA concentrations may be elevated in many other cancers. The objective of this study was to assess the frequency of elevated preoperative serum CEA concentrations in surgically treated patients with primary lung adenocarcinoma; to define the relationship between preoperative CEA and clinical and pathologic presenting features; and to evaluate the potential role of pre- and postoperative CEA.

Patients and Methods

Serum for measurement of CEA concentration was collected from surgically treated primary lung cancer patients with adenocarcinoma. Patients with other primary cancers were excluded from this study. Patients who had
distant or contralateral extra-lobar lung metastasis identified preoperatively were also excluded. Preoperative and postoperative samples, obtained 2 months after surgery, were taken from 97 patients over 7 years at Showa University Hospital. The pathologic tumor-node-metastasis (TNM) staging classification was based on the General Rule for Clinical and Pathological Record of Lung Cancer.\textsuperscript{3,4} Incomplete resection was defined as positive surgical margins. The serum CEA concentration of all blood samples was measured by an enzyme immunoassay sandwich method, the cutoff value of which was 5.0 ng/ml. Data are expressed as the mean +/- standard error of the mean. The CEA association with T factor, N factor, and stage was performed using analysis of variance. CEA associations with complete resectability and presence of postoperative metastasis were performed using the unpaired t-test. Survival was measured from the operation until death or last date of follow-up. Survival rates, including non-cancer-related deaths, were calculated by the Kaplan-Meier method and compared by log-rank test. A value of p<0.05 was considered significant.

**Results**

Ninety-seven patients consisted of 67 men and 30 women with a mean age of 64 years (range 31 to 83 years). The mean maximum diameter of the tumors was 36 mm (range 2 to 98 mm). Tumors arose in the right upper lobe in 41 patients, right middle lobe in 2 patients, right lower lobe in 16 patients, left upper lobe in 26 patients, and left lower lobe in 12 patients. These were 44 well-differentiated, 27 moderately-differentiated, and 26 poorly or undifferentiated adenocarcinomas.

Preoperative CEA concentrations associated with T factor and N factor were analyzed as classified in Table 1. All 9 pT4 patients had intrapulmonary metastasis in the same lobe. The CEA in pT2 patients was significantly higher than the concentration in pT1 patients but the CEA did not differ between pT2 and pT3 patients. The CEA in pN2 patients was statistically higher than in pN1 patients but not different between pN1 and pN0 patients.

Preoperative CEA concentrations were 7.9+/-3.9 ng/ml in p-stage I patients (n=47), 8.2+/-4.7 ng/ml in p-stage II (n=15), 26.7+/-10.5 ng/ml in p-stage III (n=32), and 4.3+/-2.6 ng/ml in p-stage IV patients (n=3). All 3 p-stage IV patients had ipsilateral extralobar metastasis. The CEA in p-stage III patients was significantly higher than in p-stage I patients (p<0.05) and p-stage II patients (p<0.05) but was not different between p-stage I and p-stage II. Table 2 shows the distribution of detailed pathologic staging. For stage I and II patients, the preoperative CEA for p-stage IB patients was significantly higher than in p-stage IA patients. Additionally, the preoperative CEA in p-stage IIB was significantly higher than in p-stage IIA. However, the preoperative CEA was not statistically different between stages IA and IIA, and between stages IB and IIB. CEA concentrations in p-stage IIA and IIB patients were significantly higher than in p-stage IA, IB, IIA, and IIB.

The preoperative CEA was 12.7+/-4.7 ng/ml in patients who underwent complete resection (n=87) and 9.5+/-6.0 ng/ml in patients with incomplete resection (n=10), was not significantly different.

The preoperative CEA was 30.9+/-21.6 ng/ml in patients who did not recur and/or metastasize after surgery (n=65) and 21.9+/-10.4 ng/ml in patients with recurrence and/or metastasis (n=32), there was no difference between the groups.

Postoperative CEA values were obtained from 1 to 3 months (mean, 2.1 months) after surgery, the mean was 25.1+/-16.5 ng/ml. The postoperative follow-up time was 26 months (6 to 73 months) in patients in whom there
was no recurrence and/or metastasis after surgery \( (n=65) \) and 21 months (5 to 57 months) in whom there was recurrence and/or metastasis after surgery \( (n=32) \) (n.s.). The postoperative CEA values obtained from 1 to 3 months after surgery rose before clinical examinations or symptoms suggested metastasis. The postoperative CEA was 4.8±/–1.6 ng/ml in the former and 63.1±/–47.9 ng/ml in the latter group \( (p<0.05) \). The post-/pre-operative CEA ratio was 91.0±/–10.9% in patients in whom there was no recurrence and 146.6±/–53.3% in patients with recurrence \( (p=0.05) \).

Discussion

The role of CEA in lung cancer was first postulated in the 1970s;\(^5\) the preoperative serum CEA correlates with the stage of disease and prognosis. A consensus conference in 1980 recommended that a preoperative plasma CEA value be obtained in patients with bronchial carcinoma as an adjunct to clinical and pathologic staging methods.\(^6\) However, controversial positions have begun to emerge.\(^7,8\)

Our study showed that the preoperative CEA was higher in patients with pT2 than pT1. CEA correlated with the volume of the tumor but did not differ between patients with pT3 and pT2. CEA does not appear to reflect parietal pleural invasion. Patients with pT4 lung adenocarcinoma did not show higher CEA concentrations in our study. This may be due to the fact that all pT4 patients had an intralobar metastasis in the same lobe and pT4 in our patients did not have much volumes of tumor.

The value of a tumor marker depends on its ability to be released from the tumor into serum where it can be assayed. This study showed that the preoperative serum CEA concentration was higher in patients with mediastinal lymph node (LN) disease than in patients with hilar LN involvement. This may be related to tissue CEA leaking into blood via lymphatic vessels.

Gropp et al. reported that the prognostic value of serum CEA is greatly influenced by the presence or absence of metastases and that the patients with lung cancer limited to one hemithorax have a lower incidence of an elevated CEA than patients with distant metastases.\(^9\) In our study, M1 patients did not show higher CEA concentrations than M0 patients, all M1 patients had an ipsilateral extra-lobar metastasis, and patients with distant metastasis were not included in this study.

There are five possible applications for tumor markers: screening, diagnostic tools, prognostic indicators, monitoring disease progress, and detecting relapse. In 1980, the National Institute of Health stated that preoperative plasma CEA concentrations correlated with clinical stage of disease.\(^6\) Patients with preoperative CEA concentrations at the lower end of the abnormal range have better survival rates than those whose concentrations are over 10 ng/ml.\(^6\) Still, the correlation between increasing plasma CEA concentrations and progressive cancer is not perfect, and a normal CEA value cannot be taken as evidence of localized disease.\(^6\) In 1997, the American Thoracic Society and European Respiratory Society published guidelines stating that routine measurement of this tumor marker in staging or evaluation of disease progression is not recommended.\(^8\) There is no evidence that a CEA-producing lung adenocarcinoma has more malignant potential than a non-CEA-producing lung adenocarcinoma.\(^10\) However, the patients in our study had resectable lung cancer, i.e., relatively early-stage disease, and this may have influenced our results.

Though preoperative CEA did not reflect complete resectability or the likelihood of postoperative metastasis, early postoperative CEA values reflect postoperative metastasis in our study. Additionally, the post-/pre-operative CEA ratio may reflect this possibility, although it did not reach statistical significance. Gail et al. and Buccheri et al. demonstrated that persistently elevated postoperative CEA concentrations indicate residual dis-

<table>
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<td>IV</td>
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Table 2. Carcinoembryonic antigen (CEA) concentration (mean ±/– standard error of the mean, ng/ml) associated with clinicopathologic staging

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ease, poor prognosis, and increased risk of recurrence.\textsuperscript{11,12)} In our opinion, combined with our previous study examining squamous cell carcinoma antigen,\textsuperscript{13)} serum tumor markers obtained soon after surgery may reflect postoperative metastasis, recurrence, or prognosis, while preoperative markers may not reflect these. The main usefulness of postoperative CEA sampling is the prediction of ultimate surgical failure in patients apparently cured by tumor resection.

Buccheri and Ferrigno have shown the utility of obtaining preoperative CEA in any potentially operable patient with non-small cell lung cancer; this allows the identification of a significant proportion of patients who are at high risk of developing early relapse.\textsuperscript{14)} However, as many authors have shown, the aim of preoperative tumor markers is often that the elevated marker is selected as a “monitor” during the postoperative course. Yet, preoperative tumor markers may not predict postoperative prognosis or the biologic aggressiveness of the disease.

In conclusion, CEA reflected tumor size (T1 vs. T2) but not tumor invasion (T2 vs. T3). Though CEA did not reflect hilar LN metastasis (N0 vs. N1), patients with mediastinal LN metastasis had higher CEA concentrations. Preoperative CEA did not reflect complete resection nor predict postoperative metastasis, but postoperative CEA concentration did reflect postoperative metastasis, despite the fact that our follow-up period after surgery was relatively short.

References