# Combined Evaluation of Postoperative Serum Levels of Carcinoembryonic Antigen Less than or Equal to 2.5 ng/ml and Absence of Vascular Invasion may Predict no Recurrence of Stage I Adenocarcinoma Lung Cancer

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**Study Objectives:** It has been reported that high levels of serum carcinoembryonic antigen (CEA) after surgery, or the presence of vascular invasion or both, are strong indicators of postoperative recurrence in patients with non-small cell lung cancer. The purpose of this study is to evaluate which kind of patients with p-stage I adenocarcinoma need adjuvant chemotherapy, using those predictors.

**Patients and Methods:** We studied 136 patients with curatively resected p-stage I adenocarcinoma during the 7-year period of January 1, 2000 to December 31, 2006. Receiver operating characteristics curves were constructed using postoperative CEA levels measured 2 months after surgery. Clinical variables were examined as possible predictors of disease recurrence by multivariate analysis using the Cox proportional-hazards model.

**Results:** The median time of follow-up after surgery was 28.3 months. Fifteen (11%) of 136 patients had postoperative recurrence (7 p-stage IA cases and 8 p-stage IB cases). The presence of vascular invasion (hazard ratio: 10.229, 95% confidence intervals: 2.811–37.223, $p = 0.0004$) and high postoperative CEA levels (hazard ratio: 1.650, 95% confidence intervals: 1.196–2.275, $p = 0.0023$) increased the risk of recurrence. There was no recurrence in patients who had both postoperative CEA levels less than or equal to 2.5 ng/ml and no vascular invasion.

**Conclusion:** Combined evaluation of postoperative CEA levels and vascular invasion makes it possible to predict disease recurrence in the curatively resected p-stage I adenocarcinoma patients.

**Key Words:** Adjuvant chemotherapy, Cox proportional-hazards model, Predictors for postoperative recurrence, Receiver operating characteristics (ROC) curve, Uracil/tegafur (UFT).

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According to the 2007 American College of Chest Physicians guidelines for diagnosis and management for lung cancer, for both stage IA and IB non-small cell lung cancer (NSCLC) patients who had the curative resection, adjuvant chemotherapy has not been recommended for routine use.[1] In Japan, oral uracil/tegafur (UFT) therapy is performed as adjuvant chemotherapy in pathologic (p-) stage IB adenocarcinoma patients because it has been reported that a 5-year survival rate is 85% in the UFT group compared with 74% in the control group ($p = 0.005$)[2] and meta-analysis has showed that UFT therapy reduced the risk of postoperative death (hazard ratio 0.74, 95% confidence intervals [CI] 0.61–0.88, $p = 0.001$).[3] As there is as yet no way to predict beforehand who has recurred in p-stage IB patients, UFT therapy seems indicated for both the patients in whom the disease would not recur even if they had not received UFT, and the patients in whom the disease would recurred even if they had received UFT. In addition, Tsuchiya et al.[4] reported that 5-year overall survival rate in p-stage IA NSCLC patients with pathologically vascular invasion nearly overlapped that of p-stage IB NSCLC patients and improved significantly by postoperative UFT therapy. It is therefore very important to accordingly determine who needs adjuvant chemotherapy in p-stage IA cases as well as those in whom this therapy can be avoided in p-stage IB cases. It is now necessary to find additional predictors for postoperative recurrence of p-stage I NSCLC accompanied with vascular invasion.

Although there are no recommendations for the routine measurement of any tumor markers in the screening, staging, or evaluation of disease progression,[5] many recent studies have shown that high preoperative levels of carcinoembryonic antigen (CEA) in early stage adenocarcinoma of the lung are related to poor prognosis after surgery.[6–10] However, it is also well known that serum CEA levels increase in heavy smokers and decrease after they gave up smoking.[11–13] These results indicate that the postoperative serum CEA levels may be a more useful prognostic predictor in lung cancer patients because most of them give up smoking before surgery.[14] It has also been reported that in p-stage I NSCLC patients, a high postoperative CEA level is a strong indicator of postoperative recurrence or poor prognosis.[15–17] Okada et al.[18] has

reported that normalization of CEA levels after surgery is a significant favorable prognostic sign in patients with high preoperative CEA levels. We sought to define the optimal cutoff values of the postoperative CEA levels in p-stage I adenocarcinoma patients and to identify those who would benefit for adjuvant chemotherapy by combination of the two conditions of postoperative CEA levels and vascular invasions identified on the resected specimen.

## PATIENTS AND METHODS

We enrolled 163 consecutive patients with a peripheral tumor that was surgically given a diagnosis of p-stage I adenocarcinoma during the 7-year period from January 1, 2000 to December 31, 2006. The indications of segmentectomy or mediastinal lymph node dissection were determined using sentinel node navigation in patients with tumors less than 20 mm in diameter.[19,20] Technetium-99m tin colloid was injected into the peritumoral region before surgery. When an intraoperative frozen material of sentinel nodes, identified by measuring radioactive tracer uptake, did not pathologically have metastasis, segmentectomy was performed and mediastinal lymph node dissection was omitted. Both lobectomy and mediastinal lymph node dissection were performed in all patients with tumors larger than 20 mm. We excluded 27 patients from this study for the following reasons: 10 patients had an Eastern Cooperative Oncology Group performance status 2 or 3 after surgery, 8 patients had other cancers at surgery (2 cases with synchronous lung cancer, 2 breast cancer, 1 colon cancer, 1 hepatic cellular carcinoma, 1 pancreatic cancer, and 1 thyroid cancer) and 9 cases lacked sufficient follow-up data after surgery. A total of 136 p-stage I adenocarcinoma patients were eligible (109 IA cases: 42 men and 67 women, 27 IB cases: 12 men and 15 women) and staged according to the guidelines of the Union Internationale Contre le Cancer Tumor Node Metastasis classification of malignant tumors. Informed consent was obtained from all of the patients at the same time we explained the procedure of diagnostic approach.

We measured serum CEA levels within 1 month before surgery, and 2 months, 6 months and 12 months after surgery. Measurement of serum CEA was performed using a chemiluminescent immunoassay test kits (Abbott Japan Co., Ltd., Chiba, Japan, reference ranges $<5.0$ ng/ml) following the manufacturer's instructions. All current smokers ($n = 36$) gave up smoking before surgery and no one started smoking again for at least 12 months after surgery.

We divided 136 eligible patients into 2 groups: (1) patients who had postoperative recurrence (recurrence group) and (2) patients without recurrence (no recurrence group). Postoperative recurrence such as local metastasis, distant metastasis, and chest wall implantation, was defined as the first appearance of any new lesion suspected to the recurrence of original lung cancer and it was pathologically diagnosed with percutaneous transthoracic needle biopsy or clinically diagnosed by combination of brain magnetic resonance imaging, bone scintigraphy or fluorodeoxyglucose-positron emission tomography tests. Local metastasis was defined as recurrence at the surgical stump or in a lymphatic drainage area. The 5-year recurrence-free survival was determined as the interval between surgery for lung cancer and the appearance of recurrence or metastasis. The survival past December 31, 2007, was classified as censored.

Statistical analysis was performed on a Macintosh computer with a Stat View J 4.5 statistical program (Abacus Concepts Inc., CA). Data are presented as mean ± SD (SD). Differences between two independent samples were tested using the Mann-Whitney *U* test. Analysis of categorical data was performed with Fisher's exact test probability test. The probability of 5-year survival was estimated by the method of Kaplan and Meier. Clinical variables were examined as possible predictors of survival time using the Cox proportional-hazards model. Hazard ratio and corresponding 95% CIs were presented. A $p$ value of less than 0.05 was considered to indicate a statistically significant difference.

## RESULTS

### Disease Recurrence

The median postoperative period was 28.3 months. Fifteen patients had postoperative recurrence (seven p-stage IA cases and eight p-stage IB cases). The median of the time to recurrence was 12.8 months (range: 6.3–46.0 months) for the 15 patients who had recurrence. There were seven patients who had only local metastasis (six cases with mediastinal lymph node metastases, one case with recurrence at the surgical stump), three patients who had both local and distant metastases (two cases with mediastinal lymph node plus brain metastasis and one case with recurrence at the surgical stump plus multiple organ metastasis) and five patients who had only distant metastases (two cases with bone metastasis, two cases with brain metastasis, and one case with intrapulmonary metastasis).

### Postoperative Levels of Serum CEA

We measured CEA in all 136 patients before surgery and 2 months after surgery, but not in 11 cases 6 months after surgery and not in 25 cases 12 months after surgery for the following reasons; 1 patient died of lung cancer less than 12 months after surgery and the other patients did not visit our hospital regularly (Figure 1). In the no recurrence group, the mean levels of serum CEA before surgery significantly decreased from 2.0 ng/ml before surgery to 1.4 ng/ml 2 month after surgery ($p = 0.0081$) and the decrease continued for 12 months. In the recurrence group, there was no difference in the mean levels at 4 different time points. The mean levels 2 months after surgery were lower in the no recurrence group than those in the recurrence group (1.4 ± 0.8 ng/ml versus 3.2 ± 2.8 ng/ml, $p = 0.0057$). There was a significant difference in the chronological change of postoperative CEA levels between the 2 groups ($p < 0.0001$). Postoperative CEA levels were defined as the levels measured 2 months after surgery.

### Variables Associated with Recurrence-Free Survival Time

There was a significant difference between in the recurrence group ($n = 15$) and in the no recurrence group ($n =$

 