# Time course of carcinoembryonic antigen after resection of lung cancer: A predictor of recurrence

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**We investigated whether the early postoperative time course of carcinoembryonic antigen (CEA) level after resection of lung cancer could be used to predict patients' prognosis. Fifty-three lung cancer patients were included in this study. Postoperative serum CEA levels were calculated by means of non-linear least-squares fitting to the equation $C(t)=(C_0-C_p)\exp(-kt)+C_p$, where $C(t)$ is postoperative CEA level, $t$ is days after surgery, $C_0$ is CEA level at postoperative time 0, $C_p$ is CEA level at plateau, and $k$ is the rate constant of elimination. Postoperative CEA production ($P_p$) was calculated as $C_p$ multiplied by $k$. $C_p$ and $P_p$ represent the numbers of residual tumor cells after surgery. More residual tumor cells yield higher values of $C_p$ and $P_p$, and result in earlier recurrence. [Results] Kinetic parameters could be obtained for 30 patients whose preoperative CEA levels were sufficiently elevated. Cutoff levels as predictors for recurrence were 1.1 ng/ml for $C_p$ and 0.9 ng/ml/day for $P_p$. The accuracy of prediction of recurrence using these cutoff levels was 79% with $C_p$ and 89% with $P_p$. A very poor prognosis was observed for patients with $P_p$ over 0.9 ng/ml/day. [Conclusion] Analysis of the time course of changes in CEA levels after resection of lung cancer appears to be useful for predicting patient prognosis. $C_p$ and $P_p$ are very precise predictors of recurrence. (Cancer Sci 2003; 94: 741–744)**

Measurement of serum tumor marker levels in patients with malignancy is useful for monitoring responses to therapy. When serum tumor marker levels do not normalize after treatment, the existence of residual tumor cells is strongly suspected.[1–6] After surgical resection of tumors, serum tumor marker levels decrease in accordance with their individual elimination kinetics to a certain plateau level,[6–10] which is determined by the amount of postoperative tumor marker-producing cells remaining. These remaining tumor marker-producing cells may consist in part of residual tumor cells when the plateau level is higher than the normal range.

Serum carcinoembryonic antigen (CEA) levels in lung cancer patients exhibit monophasic elimination patterns after surgical resection of tumors.[11] Evaluation of postoperative CEA time-course changes by using non-linear least-squares analysis considering residual CEA-producing cells enables calculation of postoperative CEA level at plateau and postoperative CEA production. We previously reported that these two parameters provided information about the prognosis of patients after surgery.[11, 12] High postoperative CEA level at the plateau, as well as large postoperative CEA production, indicate the presence of remaining CEA-producing cancer cells. These two parameters may thus be able to predict tumor recurrence.

This study examined the diagnostic accuracy of the CEA time-course after surgery as a predictor of recurrence after resection of lung cancer.

## Patients and Methods

**Patients.** A total of 53 patients who underwent radical resection for primary lung cancer at our institute from February 1993 to June 1997, and from whom informed consent for blood sampling was obtained, were included in the study. The patients were 42 males and 11 females, ranging in age from 30 to 81 years (average 65±11 years). Patients' characteristics are summarized in Table 1. No patients had hepatic or gastrointestinal inflammatory disease, or underwent artificial dialysis.

The patients were followed every month within the first 6 months after surgery at the outpatient clinic and every 2 months thereafter, when plain chest X-rays and serum CEA levels were obtained. Brain, chest, and abdominal computed tomography scans, as well as bone scintigraphy, were performed every 6 months to detect tumor recurrence. The follow-up period after surgery was 40±29 (3–102) months.

**Determination of CEA disappearance curve.** Determination of CEA disappearance curves was performed with the same methods as we previously reported.[11, 12] Blood sampling was performed once within the 1-week period preceding surgery, and four or more times within 3 weeks after surgery. To reduce patient discomfort, blood samples for this study were obtained as far as possible simultaneously with routine clinical blood sampling. The serum CEA level of all blood samples was measured by an enzyme immunoassay sandwich method (Glaozyme CEA, Wako, Osaka), the cutoff value of which was 5.0 ng/ml.

Postoperative CEA time-course was represented using two alternative equations, 1 or 2. Eq. 1: $C(t)=C_0$, represents no detectable change in serum CEA level after surgery, and Eq. 2: $C(t)=(C_0-C_p)\exp(-kt)+C_p$, represents a monophasic elimination pattern, where $t$ is time after surgery; $C(t)$ is postoperative serum CEA level; $C_0$ is the serum CEA level at postoperative time 0; $k$ is the rate constant of CEA elimination; and $C_p$ is the postoperative serum CEA level at plateau.

Postoperative serum CEA levels in each patient were fitted to each of the two equations using non-linear least-squares analysis to obtain the values of $C_0$, $C_p$ and $k$ in each patient. The equation that yielded a smaller AIC[13] was adopted for each patient. When Eq. 2 was adopted, the biological half-life of CEA ($t_{1/2}$) was calculated as $\log_e 2$ divided by $k$, and postoperative CEA production rate ($P_p$) was calculated as $C_p$ multiplied by $k$. An example of the CEA disappearance curve calculated by this method is given in Fig. 1.

**Statistical analysis.** All values are given as means±SD (min–max). The $\chi^2$ test and ANOVA were employed to evaluate the significance of differences between groups. The Kaplan-Meier method was used for evaluation of patients' prognosis. $P$ values less than 0.05 were taken to indicate statistical significance.

## Results

**1. CEA elimination kinetics.** Eqs. 1 and 2 were adopted for 23 (group 1) and 30 (group 2) patients, respectively. The kinetic

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parameters of CEA elimination are summarized in Table 2. Preoperative serum CEA level was significantly higher in group 2 than group 1 ($P$=0.02). Patients' characteristics in groups 1 and 2 are shown separately in Table 3. There was no significant difference in age, gender, histological diagnosis, surgical procedures, or pathological stage between groups 1 and 2.

**2. Diagnostic accuracy of prediction for recurrence.** The following investigations of the diagnostic accuracy of prediction of recurrence were performed using only group 2 patients, since no kinetic parameters of CEA elimination were obtained in group 1.

*2.1. $C_p$ and $P_p$ cutoff values and their diagnostic accuracy*: In group 2, tumor recurrence was observed in 20 of 30 patients during 34±27 (4–100) months of follow-up. There were 19 distant metastases and 1 local recurrence (malignant pericardial effusion). Adjuvant chemotherapy was performed in 11 patients. Cutoff values for the prediction of recurrence were determined using the 19 patients who did not undergo any adjuvant therapy. They consisted of 13 patients with recurrence of tumor and 6 patients without recurrence. Cutoff values as predictors of recurrence were determined to obtain the highest accuracy with $C_p$ and $P_p$. They were 1.1 ng/ml with $C_p$ and 0.9 ng/ml/day with $P_p$, respectively (Fig. 2). Values representing diagnostic accuracy using these cutoff values are summarized in Table 4. Accuracy as a predictor of recurrence was 79% with $C_p$ and 89% with $P_p$. $P_p$ exhibited diagnostic properties superior to those of $C_p$.

*2.2. Relationship between prognosis and $P_p$*: $P_p$ was higher than 0.9 ng/ml/day in 11 patients (group H) and lower than 0.9 ng/ml/day in 8 patients (group L) of the 19 patients without adjuvant therapy. The disease-free survival and actual survival of these 2 groups are illustrated in Fig. 3. A striking difference in prognosis was observed between groups H and L.

The disease-free survival of group H was significantly inferior to that of group L ($P$<0.0001). Median disease-free survival time in group H was 3.5 months, and the 1-year disease-free survival rate was 9.1%. Two- and 5-year disease-free survival rates were not obtained. The 1-, 2- and 5-year disease-free survival rates in group L were 100%, 87.5% and 70.0%, respectively.

Actual survival of group H was also significantly inferior to that of group L ($P$=0.001). Median survival time in group H was 16.2 months. The 1- and 2-year survival rates were 71.6% and 20.5%, respectively. Five-year survival was not obtained. The 1-, 2- and 5-year survival rates in group L were 100%, 100% and 83.3%, respectively. Cox's proportional hazards model analysis showed that $P_p$ is a significant ($P$=0.008) prognostic factor for patient survival (Table 5).

**Table 1. Patients' characteristics**

| | | |
|---|---|---|
| Gender | male | 42 |
| | female | 11 |
| Age (yrs.) | | 65±11 (30–81) |
| Histology | adenocarcinoma | 24 |
| | squamous cell carcinoma | 21 |
| | large cell carcinoma | 5 |
| | small cell carcinoma | 3 |
| Pathologic stage | Ia | 9 |
| | Ib | 9 |
| | IIa | 0 |
| | IIb | 8 |
| | IIIa | 21 |
| | IIIb | 6 |
| Operative method | partial resection | 1 |
| | segmentectomy | 1 |
| | lobectomy | 42 |
| | bilobectomy | 4 |
| | pneumonectomy | 5 |

Pathological stage is according to UICC-TNM.

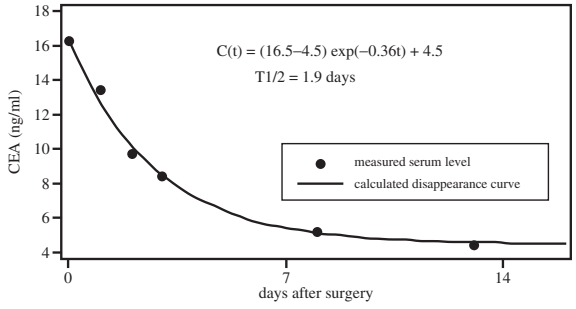


**Fig. 1.** An example of a calculated CEA disappearance curve after surgery.

## Discussion

In cases of surgical treatment of malignancies, tumor recurrence after surgery occurs when surgical procedures fail to remove cancer cells completely. Most cases of recurrence after resection of lung cancer are distant metastases, and some invisible distant metastases must have already existed at the time of surgery. Adjuvant chemotherapy for these invisible metastases may improve the prognosis of patients with lung cancer who

**Table 2. Kinetic parameters of CEA elimination**

| | Equation 1 (Group1) | Equation 2 (Group2) | |
|---|---|---|---|
| $n$ | 23 | 30 | |
| $C_{preop.}$ (ng/ml) | 2.2±3.1 (0.2–15.4) | 15.7±27.6 (0.8–154.6) | $P$=0.02*1)* |
| $k$ (day$^{-1}$) | — | 0.679±0.389 (0.070–1.557) | |
| $C_p$ (ng/ml) | — | 6.8±17.1 (0.33–93.5) | |
| $t_{1/2}$ (day) | — | 1.7±1.8 (0.4–9.9) | |
| $P_p$ (ng/ml/day) | — | 4.9±13.8 (0.02–76.1) | |

$C_{preop.}$, measured preoperative serum CEA level; $k$, rate constant of CEA elimination; $C_p$, serum CEA level at plateau; $t_{1/2}$, CEA half-life; $P_p$, postoperative CEA production. Equation 1: $C(t)=C_p$. Equation 2: $C(t)=(C_0-C_p)\exp(-kt)+C_p$.
$t$, postoperative day; $C(t)$, postoperative serum CEA level; $C_0$, serum CEA level at postoperative day 0.
Group 1: patients for whom Equation 1 was adopted. Group 2: patients for whom Equation 2 was adopted.
*1)* Compared by ANOVA, group 1 vs. group 2.

**Table 3. Patients' characteristics in groups 1 and 2**

| | | Group1 ($n$=23) | Group2 ($n$=30) | |
|---|---|---|---|---|
| Gender | male | 18 | 24 | n.s. |
| | female | 5 | 6 | |
| Age (yrs.) | | 65±12 (30–81) | 65±11 (37–80) | n.s. |
| Histology | adenocarcinoma | 9 | 15 | n.s. |
| | squamous cell carcinoma | 12 | 9 | |
| | small cell carcionoma | 0 | 3 | |
| | large cell carcionoma | 2 | 3 | |
| Operation | partial resection | 0 | 1 | n.s. |
| | segmentectomy | 0 | 1 | |
| | lobectomy | 19 | 23 | |
| | bilobectomy | 1 | 3 | |
| | pneumonectomy | 3 | 2 | |
| Pathologic stage | Ia | 5 | 4 | n.s. |
| | Ib | 4 | 5 | |
| | IIa | 4 | 4 | |
| | IIb | 0 | 0 | |
| | IIIa | 7 | 14 | |
| | IIIb | 3 | 3 | |

Group 1: 23 patients for whom Equation 1"$C(t)=C_0$" was adopted. Group 2: 30 patients for whom Equation 2 "$C(t)=(C_0-C_p)\exp(-kt)+C_p$" was adopted.
$t$, postoperative day; $C(t)$, postoperative serum CEA level; $C_0$, serum CEA level at postoperative day 0; $k$, rate constant of CEA elimination; $C_p$, serum CEA level at plateau.
Each value was compared between groups 1 and 2.

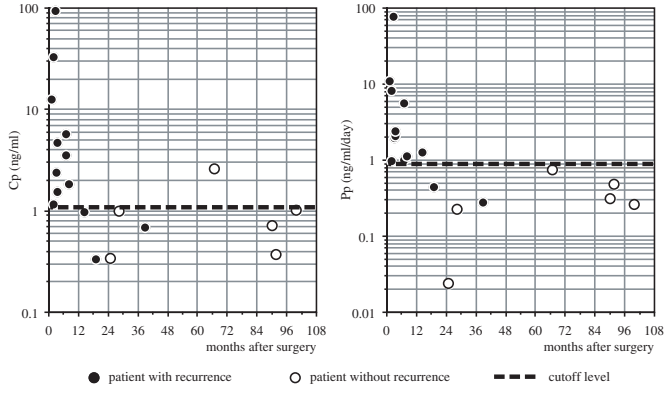


**Fig. 2.** Cutoff levels of $C_p$ and $P_p$ as predictors of recurrence. The X-axis shows the time in months after surgery when recurrence was detected in patients with recurrence and the follow-up period for patients without recurrence. $C_p$, postoperative serum CEA level at plateau; $P_p$, postoperative CEA production.

**Table 4. Diagnostic accuracy for residual tumors**

| Parameter | $C_p$ | $P_p$ |
|---|---|---|
| Cutoff | 1.1 ng/ml | 0.9 ng/ml/day |
| Sensitivity | 77% | 85% |
| Specificity | 83% | 100% |
| True positive rate | 91% | 100% |
| True negative rate | 57% | 75% |
| Accuracy | 79% | 89% |

$C_p$, serum CEA level at plateau; $P_p$, postoperative CEA production.

undergo surgical resections, if detection of such metastases is possible immediately after surgery.

We reported in 1997 that analysis of the postoperative CEA time-course within 3 weeks after resection of lung cancer enables detection of residual cancer cells.[11] Accumulation of additional patients and the retrospective analysis of follow-up results enabled us to evaluate the diagnostic accuracy of prediction of recurrence and its prognostic implications. The results of the present study revealed that postoperative CEA production ($P_p$) could predict recurrence after surgery with an accuracy of 89%.

The parameters $C_p$ and $P_p$ could not be obtained in group 1, and we could not predict the prognosis of these patients. Our method of analysis could not be applied to patients without sufficient elevation of preoperative serum CEA level.

$C_p$ and $P_p$ were both very precise predictors of recurrence, and were superior to the routine measurement of serum CEA level. There were 8 group H patients whose serum CEA levels were normalized during the measurement of this study. These good characteristics of $C_p$ and $P_p$ appeared to have two causes. First, non-linear curve-fitting using two alternative equations enabled us to exclude patients for whom prediction of recurrence was not possible by our method. Secondly, $P_p$ and $C_p$ were calculated using four or more measured serum CEA levels. Daily variations were averaged and measurement errors were minimized, considering the effects of elimination.

Serum CEA level is determined by both the rate of CEA production by the tumor and the rate of CEA elimination from circulating blood.[14–16] CEA production is related to the number of cancer cells. However, the rate of CEA elimination is unrelated to the nature of cancer. Our previous study revealed that the rate of CEA elimination is closely correlated with renal function.[12] Serum CEA level therefore depends on renal function. This dependency of serum CEA level on renal function decreases the diagnostic accuracy of CEA.

The rate of CEA elimination is calculated individually by our method, and the parameter $P_p$ is independent of the rate of elimination. These advantages of $P_p$ yielded good accuracy of diagnosis of recurrence.

$P_p$ was higher than the cutoff level in 11 of 13 cases with recurrence. Recurrence of tumor was detected within 18 months after surgery in these 11 cases. There were 2 cases with recurrence, with $P_p$ beneath the cutoff level. Recurrence of tumors was detected over 18 months after surgery in these 2 cases. The number of residual tumor cells was probably very low in these 2 cases. $P_p$ could predict recurrence only in the early postopera-

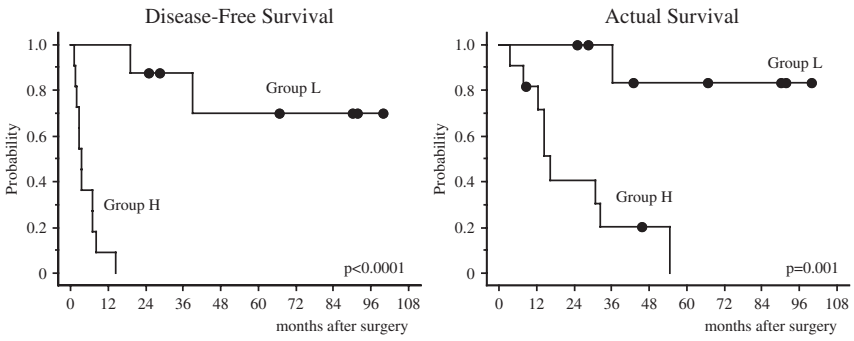


**Fig. 3.** Disease-free survival and actual survival in groups H and L. Group H, patients with $P_p$ above cutoff level; group L, patients with $P_p$ below cutoff level.

**Table 5. Cox's proportional hazards model analysis for patient survival**

| Variable | Coefficient | SE | $\chi$ | *P* value | Risk ratio | 95%CI |
|---|---|---|---|---|---|---|
| Gender (female/male) | 1.273 | 1.444 | 0.777 | 0.378 | 3.57 | 0.21–60.5 |
| Age (≥70 years old) | 2.394 | 1.226 | 3.812 | 0.051 | 10.96 | 0.99–121.3 |
| Histology | 0.040 | 0.886 | 0.002 | 0.964 | 1.04 | 0.18–5.91 |
| Pathological stage (IIIa or IIIb) | 2.929 | 1.316 | 4.955 | 0.026 | 18.71 | 1.42–246.8 |
| Operative method | −1.122 | 1.008 | 1.239 | 0.266 | 0.33 | 0.05–2.35 |
| Preoperative CEA level (≥5.0 g/ml) | 0.128 | 1.026 | 0.016 | 0.901 | 1.14 | 0.15–8.49 |
| $P_p$ (≥0.9 ng/ml/day) | 3.223 | 1.211 | 7.078 | 0.008 | 25.10 | 2.34–269.7 |

tive period, e.g., within 18 months after surgery, in our materials. Recurrence in the late postoperative period could not be predicted with our method.

This study is a retrospective one, and prospective clinical studies should be designed and performed to confirm the usefulness of $P_p$ and $C_p$. However, the very poor prognosis of the 11 patients in group H dissuaded us from additional prospective study. These patients did not undergo any adjuvant therapy. The prognosis of these patients might be improved by employing adjuvant chemotherapy immediately after the detection of residual tumor cells using this method.

The usefulness of adjuvant chemotherapy for lung cancer has not yet been determined. We believe that adjuvant chemotherapy is not needed in patients without residual cancer cells. Our method of analysis of the postoperative CEA time-course in lung cancer patients enabled us to select patients with residual cancer cells and whose prognosis was therefore very poor, and who were therefore candidates for adjuvant chemotherapy.


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