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☐ Original Article ☐

Significance of Postoperative Serum Level of Carcinoembryonic Antigen (CEA) and Actual Half Life of CEA in Colorectal Cancer Patients

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The postoperative levels of carcinoembryonic antigen (CEA) and the actual half life ($T_{1/2}$) of CEA were evaluated to ascertain their potency in predicting the recurrence of colorectal cancer after curative surgery in patients who had an abnormally high level of preoperative carcinoembryonic antigen (CEA, ≥5 ng/ml). Ninety-four patients who underwent curative surgery were enrolled and 24 patients (25.5%) had recurrence during the follow-up period (median: 30 months, range: 2~69 months). $T_{1/2}$ of CEA for all patients ranged from 1.2 days to 88.1 days, with a median of 4.4 days. $T_{1/2}$ of CEA (mean±standard deviation) was 11.7±17.9 days in recurrent patients, whereas it was 6.2±4.9 days in patients without recurrence ($p=0.0224$). The patients' age, gender, size of the tumor, location of the tumor, pre-, and postoperative CEA level, pathologic type of the tumor and Dukes stage had no significance in recurrence. The 1-year, 2-year, and 5-year disease-free survival rates were 95.1%, 81.1%, and 73.8% in patients with postoperative CEA levels less than 5 ng/ml ($n=62$), respectively, and 71.4%, 64.8%, and 64.8% in patients with postoperative CEA levels higher than or equal to 5 ng/ml ($n=32$), respectively ($p=0.04$). Patients were divided into Group S ($T_{1/2}$ of CEA<4.4 days, $n=43$) and Group L ($T_{1/2}$ of CEA≥4.4 days, $n=51$). The 1-year, 2-year, and 5-year disease-free survival rates were 95.3%, 85.1%, and 77.7% in Group S, respectively, and 80%, 67.5%, and 64.1% in Group L, respectively ($p=0.0261$). In conclusion, the disease-free survival of colorectal cancer patients was prolonged in patients who had a short $T_{1/2}$ of CEA or a low level of postoperative CEA. In high-risk colorectal cancer patients with an abnormally high level of preoperative CEA, recurrence may be predicted by checking an early postoperative CEA level and/or by a simple calculation of the actual half life of CEA.

Key Words: Actual half life, carcinoembryonic antigen, recurrence, colorectal cancer

Carcinoembryonic antigen (CEA) is one of the most widely used tumor-associated markers. Because of its close correlation to the recurrence of the disease, regular and sequential assay of the serum CEA is an available method for postoperative surveillance to colorectal cancer patients, especially in predicting a recurrence and in evaluating the effectiveness of postoperative adjuvant therapies.

Patients with preoperative CEA levels higher than 5 ng/ml have been regarded as a high- risk group for the recurrence of colorectal cancer after curative treatment (Wanebo *et al.* 1978).

If a tumor was completely extirpated by surgery, there was no source of CEA production and the rate of normalization of the tumor marker (CEA) can be

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assumed to follow exponential (first-order) kinetics. However, if CEA-producing tumor tissue remained, the level of CEA decreased more slowly and its rate of normalization may be more prolonged than expected.

In this retrospective study, we examined the early postoperative levels of CEA at 7 days postoperatively and calculated their actual half life ($T\frac{1}{2}$) to evaluate their potential as prognostic indicators of a recurrence of colorectal cancer in patients who had an abnormally high level of preoperative CEA (≥ 5 ng/ml).

MATERIALS AND METHODS

Patients

Colorectal cancer patients who underwent surgical treatment between 1991 and 1993 were retrospectively evaluated. Patients who had abnormal liver functions or liver cirrhosis, which were confirmed clinically or pathologically, were excluded because of a possibility of abnormal degradation of CEA. Patients with normal preoperative CEA levels and/or distant metastasis of primary colorectal cancer were also excluded. Ninety-four patients with an abnormally high level of preoperative CEA (≥ 5 ng/ml) were enrolled. All of them underwent curative surgery for their primary colorectal cancers. The curative surgery meant that any gross residual tumor did not remain in the surgical bed and the surgical resection margin was pathologically negative for tumor invasion.

Clinicopathologic findings of the patients are summarized in Table 1.

Table 1. Clinicopathologic findings of 94 colorectal cancer patients

Age* (years)	8.3±12.8
Sex male	54
female	40
Primary site	
colon	37
rectum	57
Size* (cm)	5.7±2.2
Level of CEA* (ng/ml)	
preop.	21.8±25.2
postop.	9.0±15.0
Pathology	
adenoca.	85
well	12
mod.	70
poor	3
mucinous	7
signet ring cell	2
Dukes stage	
B_2	52
C	42

*: The numbers refer to the mean±standard deviation.

The age of the patients (mean±standard deviation) was 58.3±12.8 years (range: 26-84). There were 54 men and 40 women. Thirty-seven patients had colon cancer and 57 had rectal cancer. Size of the tumor was 5.7±2.2 cm (mean±SD, range: 1.0-12.5). Pathology of the tumor was adenocarcinoma in 85 patients (12 patients were well differentiated, 70 patients were moderately differentiated, and 3 patients were poorly differentiated), mucinous carcinoma in 7 patients and signet ring cell carcinoma in 2 patients. Stage of the tumor according to the Dukes system by Astler-Coller's modification was B_2 in 52 patients and C in 42 patients. All patients were followed until the clinical recurrence of primary colorectal cancer.

The duration of follow-up ranged from 2 to 69 months, with a median of 30 months. The recurrence of primary cancer was identified by clinical evidence (physical examinations, elevation of plasma CEA level, and radiologic evaluations) or by tissue biopsy. During the follow-up period, 24 patients suffered either locoregional failure or distant metastasis.

Carcinoembryonic antigen and its actual half life ($T\frac{1}{2}$)

The level of CEA was checked by commercial kit using immunometric technique (Kodak Amerlite CEA-60 Assay). Preoperative CEA levels of all patients ranged from 5.0 ng/ml to 100.0 ng/ml, with a mean (SD) of 21.8 ng/ml (25.2 ng/ml). Postoperative levels of CEA checked at postoperative day 7 ranged from 0.1 ng/ml to 90.0 ng/ml, with a mean (SD) of 9.0 ng/ml (15.0 ng/ml) (Table 1).

The $T\frac{1}{2}$ of CEA was calculated by the Kohn's equation (Kohn, 1978):

$$T\frac{1}{2}\ (\text{days}) = \frac{0.3 \times \triangle T}{\log_{10}(C_1 / C_0)}$$

$\triangle T$ = time interval between C_1 and C_0 (days)
C_1 = Level of CEA at postoperative day 7
C_0 = Original CEA level

Clinicopathologic parameters for risk-factor analysis were age and gender of the patient, size of the tumor, location of the tumor, pre- and postoperative levels of CEA, pathology of the tumor, Dukes stage of the tumor by Astler-Coller modification and calculated actual half-life of CEA.

Statistical analysis was performed with a SPSS computer program. Chi square test was used to examine the difference between continuous variables while a one-way ANOVA test was used for discrete variables. The Kaplan-Meier method was used to calculate disease-free survival and survival curves, and the difference between survival curves was evaluated using a Breslow test. Significance was accepted at a p value of 0.05 or less.

RESULTS

Clinicopathologic parameters and recurrence of tumor (Table 2)

All patients were categorized group I (recurrent, n=24), and group II (disease-free, n=70). Clinicopathologic parameters of the two groups are summarized in Table 2. The age of patients (mean±SD) was 56.5±11.0 years in group I, and 58.9±13.3 years in group II. There were 12 males and 12 females in group I, and 42 males and 28 females in group II. Location of the primary tumor in group I was the colon in 7 patients, and the rectum in 17 patients, while in group II it was the colon in 30 patients, and the rectum in 40 patients. Size of the tumor (mean±SD) was 6.0±2.8 cm in group I, and 5.6±2.1 cm in group II. Preoperative level of CEA (mean±SD) was 22.2±25.5 ng/ml in group I, and 21.7±25.1 ng/ml in group II. Postoperative level of CEA (mean±SD) was 10.7±16.5 ng/ml in group I, and 8.3±15.3 ng/ml in group II. Twenty patients in group I and 65 patients in group II had adenocarcinomas. Stage of the tumor was B_2 in 10 patients of group I and in 42 patients of group II; C

Table 2. Clinicopathologic findings and actual half life ($T\frac{1}{2}$) of CEA between recurrent and disease-free colorectal cancer patient groups

	Group I (Recurrent, n=24)	Group IIp (Disease-free, n=70)	P value
CEA level* (ng/ml)			
preop.	22.2±25.5	21.7±25.1	ns
postop.	10.7±16.5	8.3±15.3	ns
Pathology			ns
adenoca.	20	65	
well	5	7	
mod.	15	55	
poor	0	3	
mucinous	3	4	
signet ring cell	1	1	
Dukes stage			ns
B_2	10	42	
C	14	28	
$T\frac{1}{2}$ of CEA* (days)	11.7±17.9	6.2±4.9	0.0224

* : The numbers refer to the mean±standard deviation.
Statistic significance was obtained by using Chi square and ANOVA test.
ns: not significant

Table 3. Clinicopathologic parameters of colorectal cancer patients according to serum level of CEA

	Postoperative levels of CEA		P value
	< 5 ng/ml (n=62)	≥ 5 ng/ml (n=32)	
Preoperative CEA* (ng/ml)	9.4±4.9	45.9±30.5	0.001
T½* (days)	6.0±4.2	10.8±16.1	0.028
Cumulative disease-free survival rate			0.04
12 months	0.9508	0.7143	
24 months	0.8112	0.6478	
36 months	0.8112	0.6478	
48 months	0.7375	0.6478	
60 months	0.7375	0.6478	

* : The numbers refer to the mean±standard deviation.
Statistic significance was obtained by using Chi square test, ANOVA test and Breslow test.
ns: not significant

in 14 patients of group I and in 28 patients of group II. T½ of the CEA (mean±SD) was 11.7±17.9 days in group I and 6.2±4.9 days in group II (p=0.0224). All clinicopathologic parameters, except the T½ of CEA, showed no significant differences between the two groups (Table 2).

Level of postoperative CEA and recurrence (Table 3)

All patients were divided into two groups, one with patients who had recovered to normal levels of postoperative CEA (< 5 ng/ml, n=62) and the other with patients who still had abnormally high levels of postoperative CEA (≥ 5 ng/ml, n=32). Their clinicopathologic characteristics are summarized in Table 3.

Preoperative levels of CEA were higher in the abnormal postoperative CEA group than in the normal postoperative CEA group (p=0.0001).

T½ of CEA was 6.0±4.2 days in patients with postoperative CEA less than 5 ng/ml, whereas it was 10.8±16.1 days in patients with postoperative CEA greater than 5 ng/ml (p=0.028).

The 1-year, 2-year, and 5-year disease-free survival rate was 95.1%, 81.1%, and 73.8% in patients with low levels of postoperative CEA, respectively, and 71.4%, 64.8%, and 64.8% in patients with abnormally high levels of postoperative CEA, respectively. The difference in survival rates between the two groups had statistical significance (p=0.04). (Fig. 1).

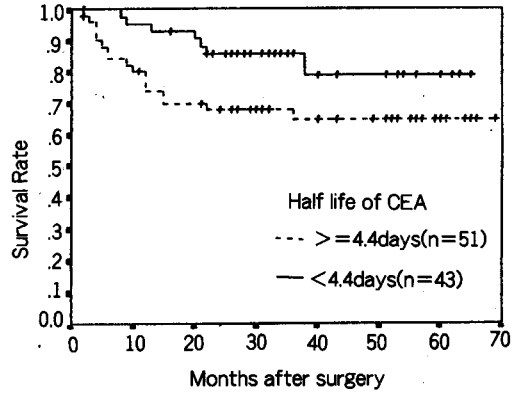

Fig. 1. Disease-free survival curves according to T½ of CEA (p=0.026).

Actual half life (T½) of CEA and recurrence (Table 4)

The T½ of CEA varied from 1.2 days to 88.1 days with a median of 4.4 days. All patients were classified into two groups; those who had a short T

Table 4. Clinicopathologic findings of colorectal cancer patients according to T½ of CEA

	T½ (days)		P value
	short (<4.4, n=43)	long (≥4.4, n=51)	
Level of CEA* (ng/ml)			
preop.	22.1±21.4	21.6±28.7	ns
postop.	5.0±5.2	13.1±20.9	0.01
Cumulative disease-free survival rate			0.026
12 months	0.9529	0.8000	
24 months	0.8513	0.6753	
36 months	0.8513	0.6753	
48 months	0.7773	0.6407	
60 months	0.7773	0.6407	

* : The numbers refer to the mean±standard deviation.
Statistic significance was obtained by using Chi square test, ANOVA test and Breslow test.
ns: not significant

½ of CEA (Group S, < 4.4 days, n=43) and the others who had a long T½ *of CEA* (Group L, ≥ 4.4 days, n=51). The age of patients (mean±SD) was 57.8±12.4 years in group S, and 58.8±13.3 years in group L. There were 23 males and 20 females in group S, and 31 males and 20 females in group L. The size of the tumor (mean±SD) was 6.0±2.4 cm in group S, and 5.4±2.1 cm in group L. There were 14 colon and 29 rectal cancers in group S, and 23 colon, and 28 rectal cancers in group L. Thirty-six patients in Group S and 49 patients in group L had adenocarcinoma. The preoperative CEA level (mean±SD) was 22.1±21.4 ng/ml in group S and 21.6±28.7 ng/ml in group L. The postoperative CEA level (mean±SD) was 5.0±5.2 ng/ml in group S and 13.1±20.9 ng/ml in group L (p=0.01). Regarding stages of tumors, there were 25 patients of B2 and 18 patients of C in group S, while there were 27 patients of B2 and 24 patients of C in group L. There was no significant difference in clinicopathologic parameters between the two groups, except postoperative CEA levels (Table 4).

The 1-year, 2-year, and 5-year disease-free survival rate was 95.3%, 85.1%, and 77.7% in Group S, respectively, and 80.0%, 67.5%, and 64.1% in Group L, respectively. The difference of disease-free survival rates between the two groups had statistical significance (p=0.026), (Fig. 2).

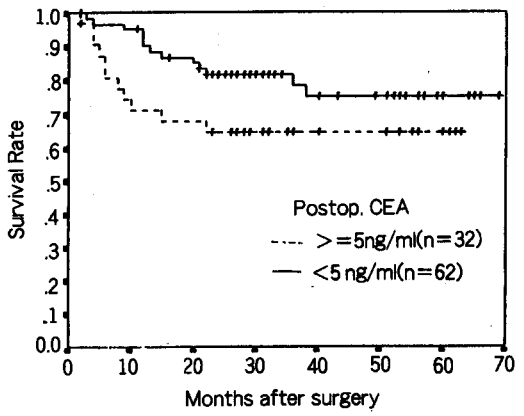

Fig. 2. Disease-free survival curves according to serum CEA levels (p=0.04).

DISCUSSION

There is no precise determinant for tumor recurrence after curative surgery of colorectal cancer, and the probability of remaining disease-free in high-risk patients is still undetermined. CEA was regarded as the most sensitive tool for follow-up and as an indicator of tumor recurrence for both locoregional

failure and distant metastasis in colorectal cancer (Wanebo *et al.* 1978; Boey *et al.* 1984; Moertel *et al.* 1986; Woolfson, 1991).

Martin *et al.* (1980) undertook a second-look operation for patients with elevated levels of CEA and found recurrent tumors in 56 of 60 patients. In the present study, we selected patients who underwent curative surgery and had abnormally high preoperative CEA levels equal or more than 5 ng/ml (i. e. high-risk preoperative CEA).

Preoperative levels of CEA were the prognostic determinant for patients with adenocarcinoma of the colorectum (Moertel *et al.* 1986), and the recurrence rate was higher in those who had elevated CEA levels irrespective of their stage, and patients who had high preoperative levels of plasma CEA of more than 5 ng/ml were regarded as a high-risk group (Wanebo *et al.* 1978). In the present study, the level of preoperative CEA closely correlated to the level of postoperative CEA (p=0.000), and the level of postoperative CEA had a significant relation to disease-free survival (p=0.04).

Since Kohn (1978) proposed that the clearance rate of a tumor marker after treatment could have prognostic significance, there have been many reports for the actual half-life of a tumor marker as a prognostic indicator in patients with a germ cell tumor (Horwich and Peckham, 1984; Lo and Johnson, 1984; Toner *et al.* 1990; Semjonow *et al.* 1993; Murphy *et al.* 1994).

But for CEA as a tumor marker of colorectal cancer, there were few reports of the half-life of CEA as the prognostic predictor of colorectal cancer and the half-life of CEA was calculated approximately as 3-to-5 days in the literature (Kiyama *et al.* 1990; Mai and Takahashi, 1993; Rapellino *et al.* 1994).

The production and excretion of CEA by tumor cells is a lineal function of cell number and CEA can be used to define a semiquantitative relationship between CEA levels and tumor volume (Bronstein *et al.* 1980).

The clearance of plasma CEA after tumor resection had two characteristic phases. The first phase was a rapid-equilibrium phase in which the plasma level of CEA rapidly decreased to 69~89% of the initial circulating level and the second phase was the logarithmic decline influenced by metabolism or secretion of CEA in the liver (Lokich *et al.* 1984). We used this second logarithmic decline phase for prognostic-factor analysis in this study.

If the surgical extirpation of a tumor was complete and if no residual tumor was present, there was no source of CEA production in the body and a regression of CEA followed its metabolic clearance rate, which was expressed as a metabolic half-life (the rate of normalization can be assumed to follow exponential [first-order] kinetics, with a constant fraction of marker eliminated per unit time). However, if CEA-producing tumor tissue remains anywhere in the body, the level of CEA decreased more slowly and its half-life was longer than expected.

We calculated the actual half life ($T\frac{1}{2}$) of CEA for patients who had an abnormally high level of preoperative CEA ($\geq$5 ng/ml) in the expectation of a correlation between the $T\frac{1}{2}$ of CEA and recurrence.

In our result, patients with recurrence had a longer $T\frac{1}{2}$ of CEA than disease-free patients (11.7 ± 17.9 vs. 6.2 ± 4.9 days, p=0.0224)

We also found that patients with high postoperative CEA levels ($\geq$ 5 ng/ml) had a significantly longer $T\frac{1}{2}$ of CEA than those who had postoperative CEA levels less than 5 ng/ml (10.8 ± 16.1 vs. 6.0 ± 4.2 days, p=0.028), and patients with longer $T\frac{1}{2}$ of CEA had an elevated level of postoperative CEA than patients with shorter $T\frac{1}{2}$ of CEA (13.1 ± 20.9 vs. 5.0 ± 5.2, p=0.01).

The postoperative level of CEA was significantly influenced by preoperative CEA, in the present study. The disease-free survival rate was significantly higher in patients with a low level of postoperative CEA (p=0.04), and/or with short $T\frac{1}{2}$ of CEA (p=0.026).

From these results, we can confirm the hypothesis in tumor recurrence. That is, in patients with a long $T\frac{1}{2}$ of CEA, and/or high levels of preoperative CEA, and/or high levels of postoperative CEA, there may be a risk of microscopic viable tumor burdens which cannot be detected before or during surgery. The CEA secreted from the remaining tumor causes the $T\frac{1}{2}$ of CEA to be prolonged in the early postoperative period.

In conclusion, a calculation of the $T\frac{1}{2}$ of CEA in the early postoperative period and obtaining an

early postoperative CEA level can both be used as an effective predictor for a recurrence of colorectal cancer in patients who had an abnormally high level of preoperative CEA. Patients who had a prolonged T½ of CEA and an abnormally elevated early postoperative CEA level should be followed carefully. And an appropriate adjuvant therapy should be scheduled for these high-risk patients.

Because the present retrospective study cannot exclude the effects of postoperative adjuvant chemotherapy or radiotherapy, the accurate rate of recurrence of primary disease without adjuvant therapy was not obtained. A randomized prospective study may prove the precise role of the half-life of CEA as a predictor of recurrence.

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