

Serum Carcinoembryonic Antigen Levels Before the First Curative Hepatectomy for Metastatic Colorectal Cancer Is a Predictor of Recurrence

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Abstract. *Background/Aim:* The aim of this study was to evaluate the usefulness of serum carcinoembryonic antigen (CEA) levels before the first curative hepatectomy for metastatic colorectal cancer as a predictor of recurrence. *Patients and Methods:* Between 2003 and 2010, 66 patients (45 male and 21 female) who underwent a first curative hepatectomy for metastatic colorectal cancer in our hospital were evaluated retrospectively. The mean patient age was 65.2 years (range=31-80 years). A total of 28 patients had synchronous liver metastasis, and the other 38 patients developed metachronous liver metastasis. *Results:* The 5-year relapse-free survival rate after the first hepatectomy of the 16 patients with normal serum CEA level was 61.1%, whereas that of the 50 patients with abnormal serum CEA level was 34.3% ($p<0.001$). Among patients whose serum CEA levels were abnormal, the 5-year relapse-free survival rate after the first hepatectomy of the 34 patients with serum CEA levels less than 50 ng/ml was 48.1%, whereas that of the 16 patients with serum CEA level equal to or greater than 50 ng/ml was 6.3% ($p<0.001$). All eleven patients whose serum CEA levels were at least 100 ng/ml developed recurrence within one year after hepatectomy. *Conclusion:* Serum CEA levels before the first curative hepatectomy for metastatic colorectal cancer seem to be a predictor of recurrence.

The liver is the most frequent recurrence site in patients with colorectal cancer (1, 2). A resection of liver metastasis is

recommended in many situations, since it is currently the most effective therapy (3-5). However, 60% of patients experience tumor recurrence after the first liver resection (6-8), whereas only 20% to 30% of patients experienced curative treatment after the initial liver resection (5, 9, 10). Carcinoembryonic antigen (CEA) is the most widely used tumor marker for patients with colorectal cancer. High preoperative serum CEA level indicates poor prognosis, and a postoperative increase or persistently high CEA level indicates disease recurrence. The aim of this study was to evaluate the usefulness of serum CEA level before the first curative hepatectomy for metastatic colorectal cancer as a predictor of recurrence.

Patients and Methods

Patients. Between 2003 and 2010, 66 patients (45 male and 21 female) underwent a first hepatectomy for metastatic colorectal cancer in our hospital and were evaluated by reviewing medical records. The mean patient age was 65.2 years (range=31-80 years). Twenty-eight of the patients (42%) developed synchronous liver metastasis, and the other 38 patients (58%) developed metachronous liver metastasis. Thirty of the patients (45%) underwent partial liver resection, 20 (31%) underwent segmentectomy, and the other 16 (24%) underwent lobectomy. Serum CEA level before the first hepatectomy of 16 patients (24%) was normal (Table I). No patients received chemotherapy after the first hepatectomy.

Our indication criteria for hepatectomy were according to the 2016 guidelines for the treatment of colorectal cancer (11), which consisted of the following five items. 1) The patient is capable of tolerating surgery, 2) the primary tumor has been controlled or can be controlled, 3) the metastatic liver tumor can be completely resected 4) there are no extrahepatic metastases, or they can be controlled, 5) The function of the remaining liver will be adequate.

Treatment schedule. Physical examinations, routine blood analyses, and serum CEA measurements were performed every two months after hepatectomy. Computed tomography (CT) was performed every six months or when a patient's serum CEA level was higher than the normal level of 5.0 ng/ml. Positron emission tomography

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Table I. Clinicopathological features of the patients.

Characteristic	No. of patients
Median age (range), years	65.2 (31-80)
Gender, n (%)	
Male	45 (68)
Female	21 (32)
Primary site, n (%)	
Colon	49 (74)
Rectum	17 (26)
Liver metastasis, n (%)	
Synchronous metastases	28 (42)
Metachrous metastases	38 (58)
Surgical procedure, n (%)	
Partial resection	30 (45)
Segmentectomy	20 (31)
Lobectomy	16 (24)
Number of metastatic lesions, n (%)	
1	34 (52)
2-4	20 (30)
5-	12 (18)
Serum CEA level, n (%)	
Normal	16 (24)
5<, <50	34 (51)
50≤, <100	5 (8)
100≤	11 (17)

Table II. Comparison between normal and abnormal in patients' serum CEA level before hepatectomy.

Characteristic	Normal (n=16)	Abnormal (n=50)	p-Value
Median age (range), years	62.2 (31-79)	66.2 (31-81)	0.570
Gender, n (%)			0.070
Male	8 (50)	37 (74)	
Female	8 (50)	13 (26)	
Primary site, n (%)			0.743
Colon	11 (69)	38 (76)	
Rectum	5 (31)	12 (24)	
Liver metastasis, n (%)			0.250
Synchronous metastases	9 (56)	19 (38)	
Metachrous metastases	7 (44)	31 (62)	
Surgical procedure, n (%)			0.139
Partial resection	8 (50)	21 (42)	
Segmentectomy	7 (44)	14 (28)	
Lobectomy	1 (6)	15 (30)	
Number of metastatic lesions, n (%)			0.283
1	11 (69)	23 (46)	
2-4	3 (19)	17 (34)	
5-	2 (12)	10 (20)	

(PET) or PET/CT was not routinely performed but was occasionally employed for patients who had equivocal conventional imaging studies to detect occult metastasis if indicated.

Statistical analysis. Continuous variables are expressed as the mean and range. The Wilcoxon rank-sum test was used for the comparison of continuous variables, and the chi-square test was used for the comparison of categorical data. Relapse-free survival rates after hepatectomy were examined by the Kaplan–Meier method and log–rank test. A p-value of less than 0.05 indicated significance. All data were analyzed with SPSS version 24.0 (IBM Japan, Ltd, Tokyo, Japan).

Results

Comparison of patients with normal and abnormal serum CEA levels before the first curative hepatectomy. No significant differences were identified in age, gender, primary tumor site, type of liver metastasis, type of hepatectomy, or number of metastatic lesions (Table II).

Comparison of relapse-free survival rates after the first curative hepatectomy between patients with normal or abnormal serum CEA levels before hepatectomy. The 5-year relapse-free survival rate after hepatectomy for the 16 patients with normal serum CEA level was 61.1%, whereas that of the 50 patients with abnormal serum CEA level was 34.3%. A significant difference was found between the two groups ($p<0.001$) (Figure 1).

Comparison of patients with serum CEA levels of less than or at least 50 ng/ml before the first curative hepatectomy. In the 50 patients whose serum CEA level was abnormal, no significant differences were identified in age, gender, primary tumor site, type of liver metastasis, type of hepatectomy, or number of metastatic lesions (Table III).

Comparison of relapse-free survival rate after the first curative hepatectomy in patients with serum CEA levels less than or at least 50 ng/ml before hepatectomy. The 5-year relapse-free survival rate after hepatectomy of the 34 patients with serum CEA level less than 50 ng/ml was 48.1%, whereas that of the 16 patients with serum CEA level at least 50 ng/ml was 6.3%. A significant difference was found between the two groups ($p<0.001$) (Figure 2).

Comparison of patients with a normal serum CEA level or a level of 100 ng/ml or higher before the first curative hepatectomy. There was a significant difference between the two groups in three factors: gender, number of metastatic lesions and recurrence within one year after the first curative hepatectomy. No significant differences were found in age, primary tumor site, type of liver metastasis, or type of hepatectomy. All eleven patients whose serum CEA levels were 100 ng/ml or higher experienced recurrence within one year after hepatectomy (Table IV).

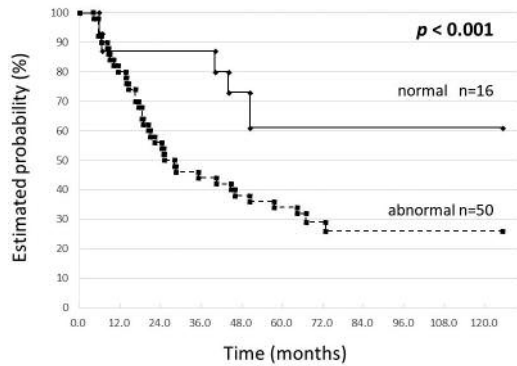


Figure 1. Comparison of relapse-free survival rates after the first curative hepatectomy between patients with normal and abnormal serum CEA level before the hepatectomy. A significant difference was identified between the two groups ($p < 0.001$).

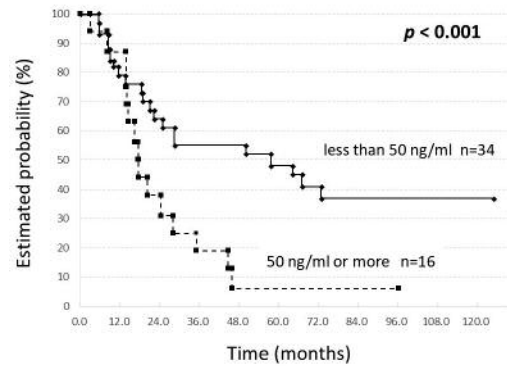


Figure 2. Comparison of relapse-free survival rates after the first curative hepatectomy between patients with serum CEA level of less than 50 ng/ml and equal or more than 50 ng/ml before the hepatectomy. A significant difference was identified between the two groups ($p < 0.001$).

Table III. Comparison of patients' serum CEA level before hepatectomy between less than 50 ng/ml and 50 ng/ml or more.

Characteristic	less than 50 ng/ml (n=34)	50 ng/ml or more (n=16)	p-Value
Median age (range), years	66.7 (31-79)	65.2 (31-80)	0.574
Gender, n (%)			0.508
Male	24 (50)	13 (81)	
Female	10 (50)	3 (19)	
Primary site, n (%)			1.000
Colon	26 (69)	12 (75)	
Rectum	8 (31)	4 (25)	
Liver metastasis, n (%)			1.000
Synchronous metastases	13 (56)	6 (38)	
Metachrous metastases	21 (44)	10 (62)	
Surgical procedure, n (%)			0.555
Partial resection	16 (50)	5 (31)	
Segmentectomy	9 (44)	5 (31)	
Lobectomy	9 (6)	6 (38)	
Number of metastatic lesions, n (%)		0.261	
1	18 (69)	5 (31)	
2-4	11 (19)	6 (38)	
5-	5 (12)	5 (31)	

Table IV. Comparison of patients' serum CEA level before hepatectomy between normal and 100 ng/ml or more.

Characteristic	Normal (n=16)	100 ng/ml or more (n=11)	p-Value
Median age (range), years	62.2 (31-79)	64.5 (31-80)	0.868
Gender, n (%)			0.042
Male	8 (50)	10 (91)	
Female	8 (50)	1 (9)	
Primary site, n (%)			1.000
Colon	11 (69)	8 (73)	
Rectum	5 (31)	3 (27)	
Liver metastasis, n (%)			0.440
Synchronous metastases	9 (56)	4 (36)	
Metachrous metastases	7 (44)	7 (64)	
Surgical procedure, n (%)			0.284
Partial resection	8 (50)	3 (27)	
Segmentectomy	7 (44)	8 (73)	
Lobectomy	1 (6)	0 (0)	
Number of metastatic lesions, n (%)			0.034
1	11 (69)	2 (18)	
2-4	3 (19)	6 (55)	
5-	2 (12)	3 (27)	
Recurrence within one year after hepatectomy, n (%)			<0.001
Presence	1 (6)	11 (100)	
Absence	15 (94)	0 (0)	

Discussion

Colorectal cancer recurrence after liver resection for metastasis remains a great concern, and the reported recurrence rates are up to 60% (6-8). Serum CEA level is the most widely used tumor marker for patients with colorectal cancer. Accordingly, the usefulness of serum CEA level

before the first curative hepatectomy for metastatic colorectal cancer as a predictor of recurrence was evaluated. Circulating tumor cells (CTCs) are also considered a prognostic factor (12-14); however, determining CTC levels is not currently common due to its high cost and complicated

protocol. A correlation between serum CEA and CTC levels was reported: CTCs appear when serum CEA is at least 10-fold higher than normal (50 ng/ml), and any subsequent increase in serum CEA level is associated with an increase in CTCs (15, 16). Therefore, the CEA cut-off levels in this study were 5 and 50 ng/ml.

When patients with normal and abnormal serum CEA levels before the first curative hepatectomy were compared, no significant differences were identified in their background. However, a significant difference in the 5-year relapse-free survival rate after hepatectomy was found between the two groups. When the 50 patients with abnormal serum CEA levels of 50 ng/ml or less before the first curative hepatectomy were compared, no significant differences were identified in their background. However, a significant difference was found between the two groups in the 5-year relapse-free survival rate after hepatectomy. Since CTCs appear in patients with a serum CEA level of 50 ng/ml or higher, which represents a 10-fold increase above normal (15), CTCs seem to contribute to recurrence. These patients may receive chemotherapy, such as an infusion of fluorouracil and leucovorin combined with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), to kill CTCs before hepatectomy. However, in cases of resectable liver metastasis, the administration of chemotherapy before liver resection remains arguable. During the period of chemotherapy, tumor progression could occur, possibly leading to an unresectable status if the metastatic lesion is not susceptible to chemotherapy (17-19).

Mitsuyama *et al.* (20) reported that patients whose serum CEA level was 100 ng/ml or higher before chemotherapy and who had unresectable liver metastasis had a poor prognosis. In this study, all eleven patients whose serum CEA level was 100 ng/ml or higher experienced recurrence within one year after the first curative hepatectomy. These patients may be at high risk for hepatic metastasis if curative hepatectomy is possible. The indication of hepatectomy for these patients should be considered very carefully.

In conclusion, serum CEA levels before the first curative hepatectomy for metastatic colorectal cancer seem to be a predictor of recurrence; however, a large-scale prospective study is needed to clarify this issue.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding this study.

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