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Carcinoembryonic antigen and carbohydrate antigen 19-9 are prognostic predictors of colorectal cancer with unresectable liver metastasis

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Abstract. No evidence currently exists to demonstrate the prognostic value of serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) in patients with unresectable colorectal cancer liver metastases (CRLM). Therefore, we retrospectively investigated the correlation between serum CEA and CA19-9 levels and overall survival in patients with unresectable CRLM. The study involved 40 patients who were diagnosed with unresectable CRLM between March 2000 and August 2010 at Jikei University Hospital, Japan. We retrospectively investigated the correlation between patient characteristics, including serum CEA and CA19-9 levels, and overall survival using univariate and multivariate analyses. In the univariate analysis, the absence of primary tumor resection (p=0.0161), the absence of systemic chemotherapy (p=0.0119), serum CEA ≥100 ng/ml (p=0.0148) and CA19-9 ≥100 U/ml (p<0.0001) were significant predictors of poor survival. In the multivariate analysis, the absence of systemic chemotherapy (p=0.0356), serum CEA ≥100 ng/ml (p=0.0079) and CA19-9 ≥100 U/ml (p=0.0002) were independent predictors. Serum CEA and CA19-9 levels are therefore independent prognostic predictors of survival in patients with unresectable CRLM.

Introduction

Colorectal cancer is the third leading cause of cancer and the fourth leading cause of cancer mortality worldwide (1). Liver metastasis is one of the most significant prognostic factors in patients with colorectal cancer, and approximately 25% of patients present with liver metastases at the time of initial diagnosis of colorectal cancer. A further 40-50% of patients develop colorectal liver metastases (CRLM) within 3 years of resection of the primary tumor (2). Hepatic resection is the most effective and potentially curative therapy for CRLM (3-6). The 5-year overall survival rate following hepatic resection is reported to range from 28 to 50% (7-11). Liver resection, however, can only be performed in approximately 10-20% of patients with CRLM due to unresectable multiple and bilobar metastasis (12). The survival rate of patients who do not undergo resection is poor and does not exceed 2% at 5 years (13,14). Therefore, the assessment of prognostic predictors is essential in the management of patients with unresectable CRLM.

Carcinoembryonic antigen (CEA) has been widely accepted as a significant prognostic factor (15,16) and an indicator of recurrence or therapeutic effect in patients with colorectal cancer (17-21). Carbohydrate antigen 19-9 (CA19-9) is another tumor marker for gastrointestinal cancers (22,23), and certain authors have proposed that it has prognostic significance in cases of colorectal cancer (24-26). With regard to CRLM, the prognostic value of serum CEA and CA19-9 levels remains controversial, and specifically, no such study has been carried out in patients with unresectable liver metastasis.

The purpose of this study was to clarify the clinical significance of serum CEA and CA19-9 levels with regard to the diagnosis of unresectable CRLM.

Patients and methods

Patients. Between March 2000 and August 2010, 55 patients were diagnosed with unresectable liver metastasis from colorectal cancer at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Of the 55 patients, 15 patients were excluded from the study; 6 due to concomitant microwave coagulation or radiofrequency ablation therapy, 4 due to lack of data, and 5 who were lost to follow-up, leaving a remaining 40 patients who participated in this study. This study was approved by the Ethics Committee of Jikei University school of Medicine.

Methods. Prior to 2003, we determined that 5 or more bilobar metastases of the liver were unresectable according to the definition of H3 liver metastasis by the Japanese classification

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Key words: colorectal cancer, liver metastasis, carcicoembryonic antigen, carbohydrate antigen 19-9, prognosis

Table I. Univariate analysis of overall survival following the diagnosis of unresectable colorectal cancer liver metastases.

Characteristics	N	Overall survival	
		Median (years)	p-value
Age (years)			
<60	10	1.18	0.8451
≥60	30	0.66	
Gender			
Male	30	1.18	0.7956
Female	10	0.74	
Timing of tumor			
Synchronous	26	0.74	0.0853
Metachronous	14	1.65	
Primary cancer site			
Colon	23	1.46	0.5902
Rectum	17	0.90	
Primary tumor resection			
Yes	32	1.43	0.0161
No	8	0.48	
Primary tumor stage			
II, III	11	1.59	0.1227
IV	29	0.78	
Extrahepatic disease			
Yes	24	1.10	0.4308
No	16	0.88	
Chemotherapy for CRLM			
Yes	34	1.18	0.0119
No	6	0.51	
CEA (ng/ml)			
<100	22	1.55	0.0148
≥100	18	0.62	
CA19-9 (U/ml)			
<100	30	1.55	<0.0001
≥100	10	0.62	

CRLM, colorectal cancer with liver metastases; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table II. Multivariate analysis of overall survival following the diagnosis of unresectable colorectal cancer with liver metastases.

Factor	Odds ratio (95% CI)	p-value
Primary tumor resection (No)	0.976 (0.229-4.159)	0.9738
Chemotherapy for CRLM (No)	4.016 (1.098-14.683)	0.0356
CEA (100 ng/ml ≥100)	3.302 (1.367-7.976)	0.0079
CA19-9 (100 U/ml ≥100)	13.450 (3.459-52.300)	0.0002

CRLM, colorectal cancer with liver metastases; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CI, confidence interval.

of colorectal carcinoma (27). Since 2004, we determined that cases with insufficient hepatic reserve or remnant liver volume were unresectable. During both the periods studied, cases with poor performance status and metastasis to other organs (excluding the lungs, local recurrence or para-aortic lymph node metastasis) were generally diagnosed as unresectable. In cases of unresectable liver metastasis, systemic chemotherapy was administered based on the performance status. Prior to 2003, we generally selected leucovorin (LV)/5-fluorouracil (5FU) or irinotecan (CPT-11) chemotherapy. Since 2003, we have generally administered LV and 5FU combined with CPT-11 (FOLFIRI) or oxaliplatin (FOLFOX). A resection of the primary tumor in the rectum or colon was performed in patients with a good performance status and in those with an intestinal obstruction.

The chemistry profile was routinely measured upon diagnosis of CRLM prior to systemic chemotherapy. The serum biochemistry data included serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil) and tumor marker levels, including CEA and CA19-9. Serum CEA and CA19-9 were classified into the groups: <100 or ≥100 ng/ml and <100 or ≥100 U/ml, respectively.

Firstly, using univariate and multivariate analyses, we investigated the correlation between patient characteristics and overall survival following the diagnosis of unresectable CRLM. Patient characteristics included age, gender, synchronous or metachronous CRLM, site of primary tumor (colon or rectum), presence or absence of primary tumor resection, primary tumor stage (II, III or IV) according to the International Union Against Cancer TNM classification (28), presence or absence of extrahepatic disease, presence or absence of systemic chemotherapy for CRLM, and serum CEA and CA19-9 levels.

We then compared patient characteristics of the CEA <100 and ≥100 ng/ml groups, as well as the CA19-9 <100 and ≥100 U/ml groups using the following parameters: age, gender, synchronous or metachronous CRLM, site of primary tumor, presence or absence of primary tumor resection, primary tumor stage, presence or absence of extrahepatic metastases, presence or absence of systemic chemotherapy for CRLM, and serum AST, ALT and T-Bil levels.

This study was approved by the Ethics Committee of Jikei University School of Medicine.

Statistical analysis. The data were presented as the means ± standard deviation (SD). Univariate analysis was performed using the non-paired t-test and the Chi-square test. The analysis of overall survival was performed using the log-rank test. $P<0.05$ was considered to indicate statistical significance.

Results

Univariate and multivariate analysis of overall survival following the diagnosis of unresectable CRLM and patient

Table III. Univariate analysis of patient characteristics in relation to carcinoembryonic antigen upon diagnosis of unresectable colorectal cancer with liver metastases.

Characteristics	CEA level		p-value
	<100 ng/ml (n=22)	≥100 ng/ml (n=18)	
Age (years)	68.8±9.9[a]	62.8±10.4	0.0716
Gender (male:female)	17:5	13:5	0.7136
Timing of tumor (synchronous:metachronous)	14:8	12:6	0.8416
Primary site (colon:rectum)	12:10	11:7	0.6760
Primary tumor resection (yes:no)	18:4	14:4	0.7506
Primary tumor stage (II, III:IV)	6:16	28:7	0.9456
Extrahepatic disease (yes:no)	12:10	12:6	0.4363
Chemotherapy for CRLM (yes:no)	19:3	15:3	0.7895
AST (IU/l)	23.7±12.9	37.2±26.7	0.0613
ALT (IU/l)	17.9±12.7	28.9±31.3	0.1748
Total-bilirubin (mg/dl)	0.78±0.36	0.91±1.02	0.6181

CRLM, colorectal cancer with liver metastases; CEA, carcinoembryonic antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase. [a]Mean ± SD.

Table IV. Univariate analysis of patients characteristics in relation to carbohydrate antigen 19-9 upon diagnosis of unresectable colorectal cancer with liver metastases.

Characteristics	CA19-9 level		p-value
	<100 U/ml (n=30)	≥100 U/ml (n=10)	
Age (years)	66.3±9.3[a]	65.5±13.7	0.8362
Gender (male:female)	23:7	7:3	0.6733
Timing of tumor (synchronous:metachronous)	18:12	8:2	0.2508
Primary site (colon:rectum)	18:12	5:5	0.5796
Primary tumor resection (yes:no)	26:4	6:4	0.0679
Primary tumor stage (II, III:IV)	10:20	1:9	0.1524
Extrahepatic disease (yes:no)	18:12	8:2	>0.9999
Chemotherapy for CRLM (yes:no)	26:4	8:2	0.6091
AST (IU/l)	28.3±15.2	34.4±34.0	0.5930
ALT (IU/l)	20.6±12.2	29.4±42.7	0.5366
Total-bilirubin (mg/dl)	0.73±0.34	1.15±1.33	0.3495

CRLM, colorectal cancer with liver metastases; CA19-9, carbohydrate antigen 19-9; AST, aspartate aminotransferase; ALT, alanine aminotransferase. [a]Mean ± SD.

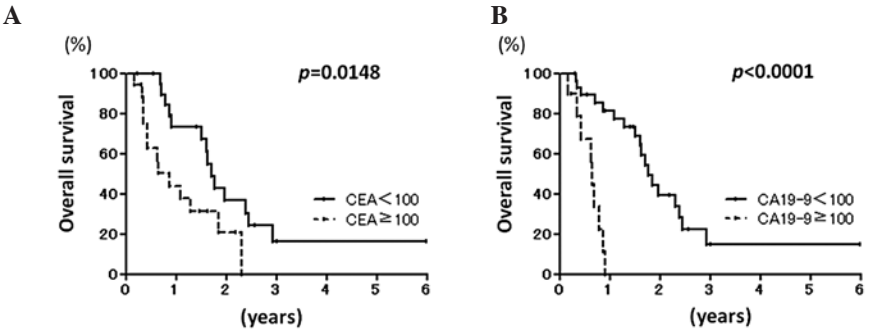

Figure 1. Kaplan-Meier curves of overall survival in patients with CEA <100 and CEA ≥100 ng/ml (A) and those with CA19-9 <100 and CA19-9 ≥100 U/ml (B). CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

characteristics. Table I shows the correlation between the patient characteristics and overall survival following the diagnosis of unresectable CRLM. In the univariate analysis, overall survival was significantly poorer in the case of absence of primary tumor resection (p=0.0161), absence of systemic chemotherapy (p=0.0119), serum CEA level ≥100 ng/ml (p=0.0148; Fig. 1A) and serum CA19-9 level ≥100 U/ml (p<0.0001; Fig. 1B).

In the multivariate analysis, the significant factors from the univariate analysis were used, including the presence or absence of primary tumor resection, presence or absence of systemic chemotherapy, CEA level < or ≥100 ng/ml, and CA19-9 level < or ≥100 U/ml. The absence of systemic chemotherapy (p=0.0356), CEA level ≥100 ng/ml (p=0.0079) and CA19-9 level ≥100 U/ml (p=0.0002) were found to be independent and significant predictors of overall survival (Table II).

Univariate analysis of patient characteristics in relation to serum CEA levels upon diagnosis of unresectable CRLM. Table III shows the correlation between patient characteristics and serum CEA levels. Univariate analysis demonstrated that all factors in both the CEA <100 and CEA ≥100 ng/ml groups were comparable.

Univariate analysis of patients characteristics in relation to serum CA19-9 levels upon diagnosis of unresectable CRLM. Table IV shows the correlation between patient characteristics and serum CA19-9 levels. Univariate analysis demonstrated that all factors in both the CA19-9 <100 and the CA19-9 ≥100 U/ml groups were comparable.

Discussion

Since 20 to 30% of patients with colorectal cancer have synchronous or metachronous liver metastases, their management is a common and significant clinical problem. Several studies have discussed the predictors of long-term survival in patients with CRLM. Jaeck *et al* reported that three factors, serosa infiltration, involvement of peritumoral lymph nodes around the primary colorectal tumor and a liver resection margin of less than 1 cm, proved to be independently significant by multivariate analysis (29). Minagawa *et al* reported that the stage of the primary tumor (III or IV), lymph node metastasis and multiple nodules were significantly associated with a poor prognosis in multivariate analysis (10). In the present study, absence of systemic chemotherapy, serum CEA level ≥100 ng/ml and serum CA19-9 level ≥100 U/ml were independent significant predictors in patients with unresectable CRLM by multivariate analysis.

The preoperative level of tumor markers was also reported to be a predictive factor of survival in patients with CRLM. Adam *et al* reported that high preoperative levels of serum CEA (≥30 ng/ml) and CA19-9 (≥100 U/ml) were poorer predictors of poor survival following liver resection (30). Ishizuka *et al* reported that the preoperative serum CEA level (≥150 ng/ml) and CA19-9 level (≥200 U/ml) were significant predictors of poor survival in patients with CLRM (31). For unresectable CLRM, Hotta *et al* reported that a >1.0 ratio of postoperative/preoperative CEA was a factor of poor prognosis in multivariate analysis (32). However, no evidence is available demonstrating the prognostic value of serum CEA and CA19-9 levels in patients with unresectable CRLM. In this study, we demonstrated that serum CEA (≥100 ng/ml) and CA19-9 levels (≥100 U/ml) were significant and independent predictors of poor survival in patients with unresectable CLRM by multivariate analysis. Recent chemotherapy regimens, including LV and 5FU combined with CPT-11 or oxaliplatin, have demonstrated survival benefits in patients with advanced colorectal cancer including unresectable liver metastasis (33-36). Therefore, the measurement of serum CEA and CA19-9 prior to treatment including both hepatectomy and chemotherapy for CRLM may provide a prognostic indicator, and contribute to advances in therapeutic strategy.

In conclusion, the serum CEA and CA19-9 levels upon diagnosis of unresectable CLRM were independent and significant predictors of overall survival. The measurement of serum CEA and CA19-9 levels may aid in improving the management of patients with CLRM.

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