CA19-9 Concentration After First Line Chemotherapy is Prognostic Predictor of Metastatic Colon Cancer

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Abstract. *Background/Aim: To evaluate whether the serum levels of CEA or CA19-9 concentration is a useful predictor of survival in patients with metastatic colon cancer (mCC). Patients and Methods: Between 2012 and 2015, 113 patients with mCC who underwent chemotherapy according to the Japanese Colorectal Cancer Treatment Guidelines at four Jikei university hospitals were enrolled into this study. The two serum tumor makers, CEA and CA19-9 were measured before first-line chemotherapy and at four months thereafter. Results: Serum CA19-9 concentration at four months after first-line chemotherapy (p=0.003, HR=3.761) and first-line chemotherapy including oxaliplatin (p=0.038, HR=0.312) were independent predictors of survival in patients with mCC. By excluding the transverse colon, only serum CA19-9 concentration at four months after first-line chemotherapy (p=0.005, HR=3.660) was identified as the predictor of survival. Conclusion: The serum CA19-9 concentration after first-line chemotherapy seems to be a useful predictor of survival in patients with mCC.*

Until 1980s, colorectal cancer had been regarded as a cancer marginally affected by chemotherapy. In the early 1990s, two new anticancer drugs, irinotecan (CPT-11) and oxaliplatin (1-15) attracted attention, and new regimens with strong anticancer effects, such as infusion of fluorouracil and leucovorin combined with either irinotecan (FOLFIRI) (1-3,

5, 8, 14, 15) or oxaliplatin (FOLFOX) (1, 4-8, 12, 13) were introduced for patients with metastatic colorectal cancer (mCRC). During the last decade, the clinical outcomes of patients with mCRC have improved due to combination of the aforementioned regimens with antiangiogenetic drug or anti-epidermal growth factor receptor agents. The median overall survival (OS) for patients with mCRC is currently estimated to exceed 30 months (6-8, 12-15).

RAS, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and BRAF have gained attention as predictors of the effect of chemotherapy and have been used to determine the indications for combined treatment with anti-epidermal growth factor receptor agents (9-11). Generally, predictors used in colorectal cancer include serum levels of the tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9); however, whether serum CEA and CA19-9 concentrations are useful predictors of survival in patients with metastatic colon cancer (mCC) remains unclear. The aim of this retrospective study was to evaluate whether serum CEA and CA19-9 concentration are useful predictors of survival of patients with mCC.

Patients and Methods

The Ethics Committee for Biomedical Research of the Jikei Institutional Review Board approved the protocol of this retrospective study (30-431(9452)). Between 2012 and 2015, 113 patients with mCC whose primary tumor lesion was resected, and were 80 years of age or younger, underwent chemotherapy according to the Japanese colorectal cancer treatment guidelines at four Jikei university hospitals, who were enrolled into this study. Serum CEA and CA19-9 levels were measured twice: once before first-line chemotherapy and then at four months after starting chemotherapy, the latter being performed to evaluate the resectability of metastatic lesions. The cutoff values for serum CEA and CA19-9 concentrations were 50 ng/ml and 37 U/ml, respectively.

This study consisted of 64 male and 49 female patients with a mean age of 66.1 years (range: 38-80 years). Eighty-seven patients (77%) had metastatic recurrence in only one organ, and the other 26 patients (23%) had metastatic recurrence in two or more organs. The liver was the most common organ with metastatic recurrence, occurring in 77 patients (68%), followed by lung in 24 patients (24%) and peritoneal dissemination in 35 patients (31%). One hundred and two patients (90%) were administered oxaliplatin-based regimen (FOLFOX, S-1 plus oxaliplatin (SOX) (6,12), capecitabine plus oxaliplatin (XELOX) (13)) as the first-line chemotherapy, while 11 patients (10%) were given CPT-11-based regimens (FOLFIRI, irinotecan plus S-1 (IRIS) (14), irinotecan plus capecitabine (XELIRI) (15)) as the first-line chemotherapy. Only two patients (2%) underwent conversion surgery (Table I).

Statistical analysis. Continuous variables were expressed as a mean and range. χ^2 test was used for comparison of categorical data, and *t*-tests were used for comparison of continuous variables. The Kaplan–Meier method was used to calculate survival rates, and the Wilcoxon test was used for comparison of survival rates. Cox proportional hazard regression model was used to analyze the predictive factors for the effect of chemotherapy. A *p*-value of less than 0.05 was considered to indicate significance. All data were analyzed with the IBM SPSS Statistics software, version 22.0 (IBM Japan, Ltd, Tokyo, Japan).

Results

Correlation between the effect of chemotherapy and each factor (Table II). To determine the variables affecting survival after starting chemotherapy, 10 parameters (age, gender, pathological type of the primary tumor, number of metastatic sites, CEA and CA19-9 levels before and at four months after starting chemotherapy, and first-line regimen) were analyzed using Cox proportional hazard regression. Only two factors, serum CA19-9 levels (*p*=0.003; HR=3.761) at four months after starting chemotherapy and the use of an oxaliplatin-based regimen as first line chemotherapy (*p*=0.04; HR=0.312) were independent contributing factors to predict survival after chemotherapy.

Comparison of primary cancer sites in the right- and left-side colons (Table III). In subgroup analysis for primary tumor located in right or left side colon, 15 patients with transverse colon cancer were excluded and the other 98 patients, 47 right-sided and 51 left-sided were selected. The number of patients with the serum CA19-9 levels above 37.0 U/ml at four months after starting chemotherapy was significantly higher in patients with right-side colon cancer as compared to those with left-side colon cancer (*p*=0.05). A larger percentage of patients with left-sided colon cancer were treated with bevacizumab as compared to patients with right-sided colon cancer (84% *vs*. 53%, *p*=0.002).

Correlations between the effect of chemotherapy and various factors depending on location of the primary cancer site (Table

Table I. *Characteristics of the patients with colon cancer*

Variable	n=113
Age (years)	66.1 (38-80)
Gender	
Male	64 (57)
Female	49 (43)
Pathology of primary tumor	
Well differentiated adenocarcinoma	49 (43)
Moderately differentiated adenocarcinoma	59 (55)
Other	5 (5)
Number of metastatic sites	
Only one site	87 (77)
More than two sites	26 (23)
Metastatic site	
Liver	77 (68)
Lung	24 (21)
Peritoneum	35 (31)
Other	4 (4)
Regimen of the first line	
FOLFOX, SOX, XELOX	102 (90)
FOLFIRI, IRIS, XELIRI	11 (10)
Conversion surgery	2 (2)

The data are presented as mean (range) or as n (%).

IV). In order to determine the variables affecting survival after starting chemotherapy, 12 parameters (age, gender, pathological type of the primary tumor, number of metastatic sites, CEA and CA19-9 levels before and four months after starting chemotherapy, and first line regimen including Bmab or Cmab) were analyzed using the Cox proportional hazard regression in the subgroup. Only one factor, serum CA19-9 levels (*p*=0.005; HR=3.660) at four months after starting chemotherapy were the independent contributing factor to predict survival after starting chemotherapy. However, no significant difference was observed regarding the site of the primary cancer (left or right) (*p*=0.65).

Comparison of cumulative survival rates depending on the location of the primary cancer (Figure 1). We compared the prognosis based on the site of the primary cancer. We found no significant difference in overall survival between left-sided and right-sided colon cancer (*p*=0.50) and demonstrated no significant superiority of prognosis in patients whose primary cancer site were left-side colon, over those whose primary cancer site were right-side colon.

Differences in tumor marker changes before and after chemotherapy (Table V). Evaluation of the changes in serum CEA levels before and at four months after starting chemotherapy revealed that 50 patients (44%) had serum CEA levels of 50 ng/ml or more before starting chemotherapy; this number decreased significantly to 31

Table II. *Correlation between the effect of chemotherapy and each factor*

Variable	Hazard Ratio (95% confidence interval)	*p*-Value
Age (years)		
≤70	1.350 (0.739-2.466)	0.329
>70	1	
Gender		
Female	1.319 (0.758-2.296)	0.328
Male	1	
Pathological type of primary tumor		
Other	0.983 (0.566-1.706)	0.951
Well differentiated adenocarcinoma	1	
Number of metastatic sites		
More than two	1.204 (0.637-2.277)	0.567
Only one	1	
Conversion therapy		
Yes	1.088 (0.105-11.313)	0.944
No	1	
Serum CEA level before chemotherapy		
>50.0 ng/ml	2.131 (0.881-5.152)	0.093
≤50.0 ng/ml	1	
Serum CEA level 4 months after starting chemotherapy		
>50.0 ng/ml	0.933 (0.428-2.034)	0.861
≤50.0 ng/ml	1	
Serum CA19-9 level before chemotherapy		
>37.0 U/ml	0.536 (0.217-1.324)	0.177
≤37.0 U/ml	1	
Serum CA19-9 level 4 months after starting chemotherapy		
>37.0 U/ml	3.761 (1.558-9.081)	0.003
≤37.0 U/ml	1	
First line regimen including oxaliplatin		
No	0.312 (0.104-0.936)	0.038
Yes	1	

patients (27%) at four months after starting chemotherapy (*p*=0.008). In contrast, 59 patients (52%) and 51 patients (45%) had serum CA19-9 levels of 37 U/ml or more before and at four months after starting chemotherapy, with no statistically significant difference (*p*=0.29).

Discussion/Conclusion

With the recent advent of CPT-11, oxaliplatin and molecularly targeted agents, chemotherapy for unresectable recurrent colon cancer has made remarkable progress (6-8, 12-15). Genetic variants of RAS, PIK3CA, BRAF, and UGT1A1 are regarded as prognostic factors for therapeutic agents (9-11, 16). Circulating tumor cells (CTCs) are also considered as a prognostic factor (17, 18) but determining CTC levels is not currently commonly used due to its high cost and complicated protocol. The most general and inexpensive chemotherapy predictors are serum levels of the tumor markers CEA and CA19-9.

Morita *et al*. (19) and Louhimo *et al*. (20) have reported that preoperative serum CEA but not CA19-9 level is a prognostic factor in patients with resectable colon cancer. Conversely, Park *et al*. (21) have measured preoperative and postoperative levels of serum CEA and CA19-9 in patients with resectable colon cancer and reported that high preoperative levels of serum CA19-9 were an independent risk factor for recurrence, while the postoperative elevation of serum CA19-9 was a factor associated with an increased risk of peritoneal recurrence.

Adam *et al*. (22) have reported that elevated serum CA19-9 levels after chemotherapy in unresectable recurrent colon cancer correlated with shortened recurrence-free and overall survival. Similarly, Sakamoto *et al*. (23) have reported that elevated serum CA19-9 levels after chemotherapy shortened recurrence-free and overall survival, while elevated serum CEA level after chemotherapy was a risk factor for recurrence. Mitsuyama *et al*. (24) have reported that serum CEA levels of ≥100 ng/ml and CA19-9 levels of ≥100 U/ml before chemotherapy in patients with colon cancer and unresectable liver metastasis were prognostic factors for poor prognosis. Thus, given that there is no consensus on this matter, we evaluated serum CEA and CA19-9 before

Table III. *Comparison of primary cancer sites in the right- and left-side colons.*

Variable	Right side colon (n=47)	Left side colon (n=51)	*p*-Value
Age (years)			
≤70	19 (40)	20 (39)	0.903
>70	28 (60)	31 (61)	
Gender			
Female	19 (40)	15 (29)	0.252
Male	28 (60)	36 (71)	
Pathological type of primary tumor			
Other	26 (55)	32 (63)	0.455
Well differentiated adenocarcinoma	21 (45)	19 (37)	
Number of metastatic sites			
More than two	12 (26)	12 (24)	0.818
Only one	35 (74)	39 (76)	
Conversion therapy			
Yes	0 (0)	1 (2)	1.000
No	47 (100)	50 (98)	
Serum CEA level before chemotherapy			
>50.0 ng/ml	20 (43)	20 (39)	0.737
≤50.0 ng/ml	27 (57)	31(61)	
Serum CEA level 4 months after starting chemotherapy			
>50.0 ng/ml	15 (32)	15 (29)	0.788
≤50.0 ng/ml	32 (68)	36 (71)	
Serum CA19-9 level before chemotherapy			
>37.0 U/ml	27 (57)	23 (45)	0.222
≤37.0 U/ml	20 (43)	28 (55)	
Serum CA19-9 level 4 months after starting chemotherapy			
>37.0 U/ml	26 (55)	18 (35)	0.046
≤37.0 U/ml	21 (45)	33 (65)	
Additional drug			
None	14 (30)	3 (6)	0.002
Bevacizumab	25 (53)	43 (84)	
Cetuximab	8 (17)	5 (10)	

The data are presented as n (%).

implementing first-line chemotherapy for unresectable colon cancer and again at four months after starting chemotherapy to determine whether serum CEA and CA19-9 were prognostic factors.

We reported a correlation between serum CEA and CTC levels in which CTC appear when the serum CEA levels were at least 10-fold higher than the normal levels (50 ng/ml), and any subsequent increase in serum CEA was associated with an increase in CTC. Accordingly, the serum CEA cutoff levels in the current study were 50 ng/ml (17, 18). The CA19-9 cutoff levels were set at 37 U/ml which was the upper normal value.

Analysis of the Cox proportional hazard model revealed significant differences in two factors: the serum CA19-9 levels at four months after starting chemotherapy and the use of an oxaliplatin-based regimen (FOLFOX, SOX, and XELOX) as the first-line chemotherapy regimen. The pre-chemotherapy serum CEA and CA19-9 levels were not prognostic factors, which was an unexpected finding. The use of potent oxaliplatin-based chemotherapies, such as

FOLFOX, SOX, and XELOX, as first-line chemotherapy could explain why these levels were not prognostic. Also, the life-prolonging effect of second and third-line therapies might have influenced the outcome.

Analysis of the Cox proportional hazard model regarding differences in primary cancer site (right-side or left-side colon), which has recently become a topic of discussion (25-27), revealed a significant difference only in serum CA19-9 levels at four months after starting chemotherapy, and the serum CA19-9 levels had a higher hazard ratio than the difference between the primary cancer being in the left or the right colon. It has been reported that little effect can be expected from anti-epidermal growth factor receptor (EGFR) antibodies as a concomitant drug with chemotherapy in patients with primary cancer in the right-side colon (25-27). In the current study, there were more cases in which angiogenesis inhibitors were used as a concomitant drug with chemotherapy in patients with primary cancer in the right-side colon as compared to anti-EGFR antibodies. In fact, we found no significant difference in overall survival between

Table IV. *Correlations between chemotherapy effect in patients with the primary cancer site in the left or right side of the colon and various factors.*

Variable	Hazard Ratio (95% confidence interval)	*p*-Value
Age (years)		
≤70	0.899 (0.487-1.662)	0.736
>70	1	
Gender		
Female	1.162 (0.627-2.153)	0.632
Male	1	
Primary tumor location		
Left side colon	1.157 (0.613-2.185)	0.653
Right side colon	1	
Pathological type of primary tumor		
Other	0.775 (0.399-10503)	0.451
Well differentiated adenocarcinoma	1	
Number of metastatic sites		
More than two	0.887 (0.456-1.727)	0.724
Only one	1	
Conversion therapy		
Yes	0.214 (0.019-2.378)	0.724
No	1	
Serum CEA level before chemotherapy		
>50.0 ng/ml	2.336 (0.879-6.207)	0.089
≤50.0 ng/ml	1	
Serum CEA level 4 months after starting chemotherapy		
>50.0 ng/ml	0.603 (0.229-1.586)	0.305
≤50.0 ng/ml	1	
Serum CA19-9 level before chemotherapy		
>37.0 U/ml	0.540 (0.212-1.374)	0.196
≤37.0 U/ml	1	
Serum CA19-9 level 4 months after starting chemotherapy		
>37.0 U/ml	3.660 (1.475-9.085)	0.005
≤37.0 U/ml	1	
First line regimen including Bmab		
No	0.478 (0.209-1.092)	0.080
Yes	1	
First line regimen including Cmab		
No	0.563 (0.186-1.702)	0.309
Yes	1	

left-side and right-side primary cancers. Using angiogenesis inhibitors as a concomitant drug with chemotherapy may be effective for patients with primary cancer in the right side of the colon.

Assessment of the difference in changes in tumor marker levels before and after chemotherapy revealed a significantly reduction of serum CEA levels after chemotherapy and no significant difference in CA19-9 levels. Perhaps, CTC disappeared due to the potent chemotherapy, resulting in the serum CEA levels below the cutoff levels, which disqualified serum CEA as an effective predictor. Patients with a serum CA19-9 levels of ≥37 U/ml at four months after starting chemotherapy had a poor prognosis. Therefore, early switching to a second-line therapy and the selection of a concomitant agent may be worthwhile in this category of patients.

Table V. *Differences in tumor marker changes before and after chemotherapy.*

Variable	Normal	Abnormal	*p*-Value
Serum CEA levels			
Before chemotherapy	63 (56)	50 (44)	0.008
4 months after starting chemotherapy	82 (73)	31 (27)	
Serum CA19-9 levels			
Before chemotherapy	54 (48)	59 (52)	0.287
4 months after starting chemotherapy	62 (55)	51 (45)	

The data are presented as n (%).

In conclusion, serum CA19-9 concentration at four months after first-line chemotherapy seems to be a useful predictor of survival in patients with mCC.
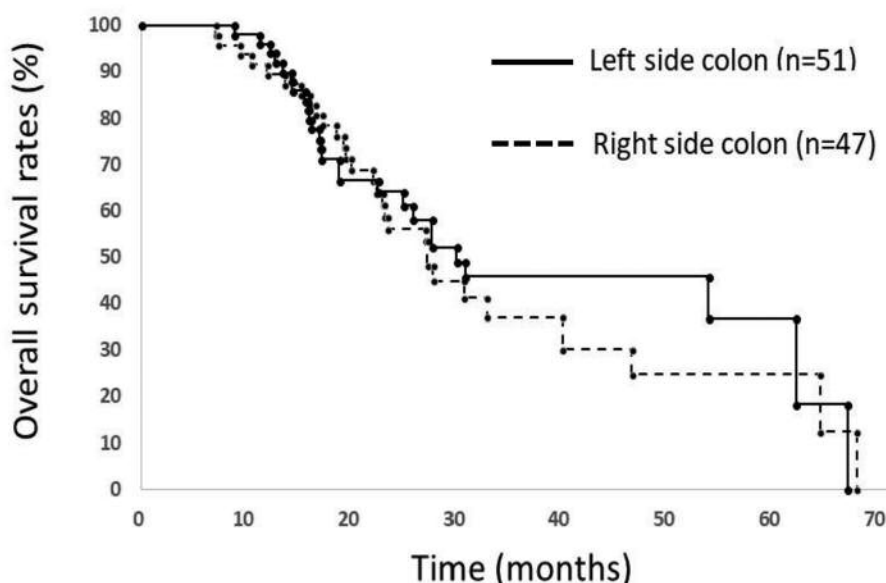
Figure 1. *Comparison of overall survival rate after starting chemotherapy between the two groups. No significant difference was demonstrated.*

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

All Authors performed operations, analyzed the data of patients regarding their clinical features, and have been involved in drafting the manuscript. KY had given final approval of the version to be published. All Authors read and approved the final manuscript.

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