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Early Serum Carcinoembryonic Antigen Reduction Predicts Tumor Shrinkage and Overall Survival in Colorectal Cancer Patients with Distant Metastasis, after Primary Surgery Followed by Mfolfox6 Plus Bevacizumab Treatment

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Abstract

Advances in chemotherapy and molecular targeting therapy have significantly improved the overall survival of colorectal cancer patients with distant metastasis. Our therapeutic strategy for colorectal cancer patients with distant metastasis is to perform surgery for the primary lesion for preventing bowel obstruction and tumor hemorrhage, followed by intensive chemotherapy. From 2008 to June, 31 colorectal cancer cases were retrospectively analyzed. Initially, the primary lesion was surgically resected. Subsequently, the mFOLFOX6 plus bevacizumab regimen was initiated. The response rate was 48%, and the disease control rate was 79%. After a median follow-up of 15.4-month, the median overall survival (OS) was 23.9 months. Therapy was not stopped in any patients because of hemorrhage or bowel obstruction. The reduction rate of the serum carcinoembryonic antigen (CEA) level correlated with the objective response. Patients who had at least a reduction in the serum CEA level seemed to have a longer OS than those who had no reduction (median OS: 23.9 vs 15.3 months, $p = 0.015$). The results showed that our strategy of combining primary surgery with chemotherapy is safe and effective. Furthermore, serum CEA level reduction seems to be a good prognostic predictor for colorectal cancer patients for whom this strategy is used.

Keywords

Colorectal Cancer, Systemic Chemotherapy, Carcinoembryonic Antigen (CEA), mFOLFOX6

1. Introduction

Advances in chemotherapy and molecular targeting therapy have significantly improved the overall survival (OS) of colorectal cancer patients with distant metastasis [1] [2] [3]. Cytoreductive surgery followed by intensive multimodality therapy has been gaining acceptance in selected patients [4]. Our therapeutic strategy for colorectal cancer patients with distant metastasis is to perform surgery for the primary lesion to prevent bowel obstruction and tumor hemorrhage, followed by intensive chemotherapy. However, the efficacy of the therapy varies widely in each case. Thus, it is worth investigating what factors can predict the efficacy of chemotherapy at an early stage of therapy. Many biomarkers have been reported to predict the efficacy of chemotherapy and molecular targeting therapy, including the *KRAS* gene mutation [5], expression of the epidermal growth factor receptor (EGFR) protein, and microsatellite instability (MSI) testing [6] [7]. More easily, it was reported that the values of serum tumor markers well reflected the total volume of the targeted tumors [8]. If validated, early changes in tumor markers may be used as a guide for on-treatment decisions, such as continuation or discontinuation of therapy. Here, we report the outcomes of our retrospective analysis for a colorectal cancer cohort of 31 patients upon whom this strategy was used, and the usefulness of the carcinoembryonic antigen (CEA) ratio to predict the effect of continuous therapy.

2. Patients and Methods

Consecutive thirty-one colorectal cancer cases presenting at Dokkyo Medical University from June 2008 to June 2011 were retrospectively analyzed (men/women, 21/10; median age, 59 years (35 - 77)). Sites of primary cancer were 8 right-side colon cancers, 8 left-side colon cancers, and 15 rectal cancers. Metastasis occurred in a total of 42 organs, including 25 liver metastases, 8 lung metastases, 4 peritoneal disseminations, 4 lymph node metastases, and one bone metastasis. Single-organ metastasis occurred in 22 cases, whereas multi-organ metastases occurred in 9 cases. The histology of the primary lesion was differentiated tubular adenocarcinoma in 26 cases, and poorly differentiated or mucinous adenocarcinoma in 5 cases. Initially, the primary lesion was surgically resected. Subsequently, the mFOLFOX6 regimen (oxaliplatin 85 mg/m^2 on day 1, folinic acid 200 mg/m^2 on day 1 and 5-fluorouracil 400 mg/m^2 by 2-h i.v. bolus on day 1, followed by 2400 mg/m^2 by 46-h continuous infusion starting on day 1, biweekly) was initiated, within one month of resection, if possible. After one month of resection, 5 mg/kg of bevacizumab was added to each cycle. The effectiveness and the safety of the combined therapy were analyzed. Descriptions of the therapeutic effects were evaluated using RECIST version 1.1. Adverse effects were described with NCI-CTCAE ver 4.0. The serum CEA level was measured at baseline and checked again after 3 months. Fisher exact test was performed for categorical analysis. Survival curves were plotted according to the Kaplan-Meier method and any differences were analyzed using the log-rank test. All statistical

analyses were performed by R statistical software. Written informed consent was obtained from all patients.

3. Results

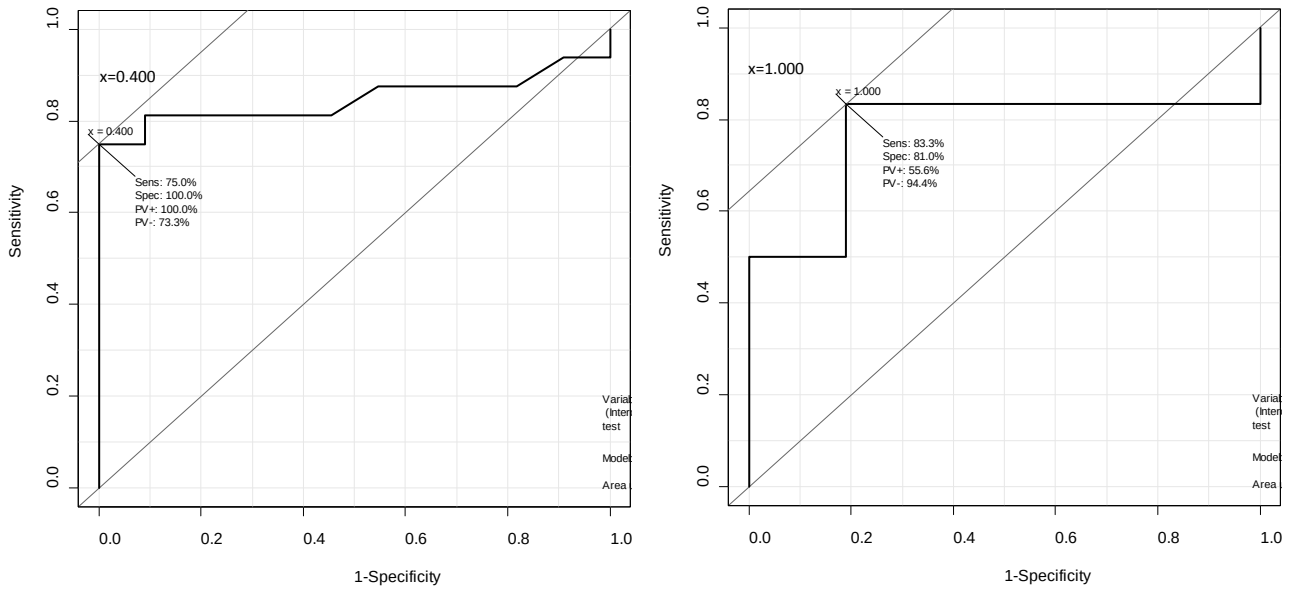
Characteristics of patients were summarized in Table 1. Fourteen colectomies and 17 rectal resections were performed. Two patients experienced postsurgical complications. One was anastomotic leakage, and the other was necrosis of the colostomy. These patients underwent 9.5 cycles (median) of the mFOLFOX6 plus bevacizumab regimen. mFOLFOX6 was continued until disease progression, symptomatic deterioration or the occurrence of unacceptable toxicity. An objective response was documented in 29 cases, according to RECIST criteria. The overall objective response rate (RR), complete response (CR) plus partial response (PR), was 48%, and the disease control rate (DCR) including stable disease (SD) was 79%. After a median follow-up of 15.4 months, the median OS

Table 1. Patient characteristics.

Factors	Number of cases (n = 31)	Frequency (%)
Age, years, median	59	(35 - 77)
Gender		
Male	21	68%
Female	10	32%
Location		
Right colon	8	26%
Left colon	8	26%
Rectum	15	48%
Histology		
tubular	26	84%
poorly	1	3%
mucinous	4	13%
Metastatic site		
Liver	25	81%
Lung	8	26%
Peritoneum	4	13%
Lymph node	4	13%
Bone	1	3%
Number of site		
1	22	71%
2	8	26%
3	1	3%

was 23.9 months in all cases, 16.0 months in colon cancer cases, and 23.9 months in rectal cancer cases, respectively. As for safety, adverse effects were described with NCI-CTCAE ver 4.0. Neutropenia and leucopenia of grade 3/4 occurred in 19% of all cases. Peripheral neuropathy of grade 3/4 was occurred in 6% of all cases. The therapy was not stopped in any patients because of hemorrhage or bowel obstruction. Second-line treatments were not specified, the regimen administered after disease progression was recorded.

Serum CEA levels were recorded initially at baseline and after 3 months from the start of treatment. Serum CEA was elevated initially in 87% of these cases, whereas CA19-9 was elevated in 61% of the cases. Then we calculated CEA ratios -CEA values at 3 months were divided by CEA values at baseline and studied the relationships with overall responses. Receiver operating characteristic (ROC) curves were used to obtain cutoff values to optimally predict the objective responses with CEA ratios (**Figure 1**). With ROC analyses, CR plus PR, or the responders, was correlated with a CEA ratio of 0.4, with a sensitivity of 75% and specificity of 100%, respectively (**Figure 1(a)**). CR plus PR plus SD, or disease control, was correlated with a CEA ratio of 1.0, with a sensitivity of 83% and specificity of 81%, respectively (**Figure 1(b)**). Using the obtained cutoff values, the CEA ratio was significantly correlated with objective responses for both in the values, 0.4 and 1.0 (**Figure 1(a)** and **Figure 1(b)**, bottom).



	CEA ratio < 0.4	> 0.4
CR + PR	11	0
SD + PD	4	12
		p<0.001

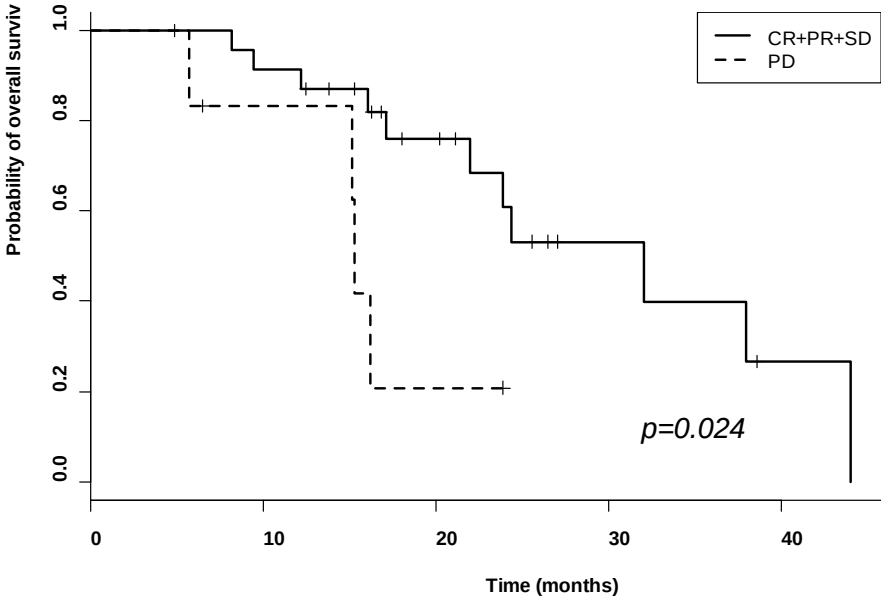
(a)

	CEA ratio < 1.0	> 1.0
CR + PR + SD	17	4
PD	1	5
		p<0.01

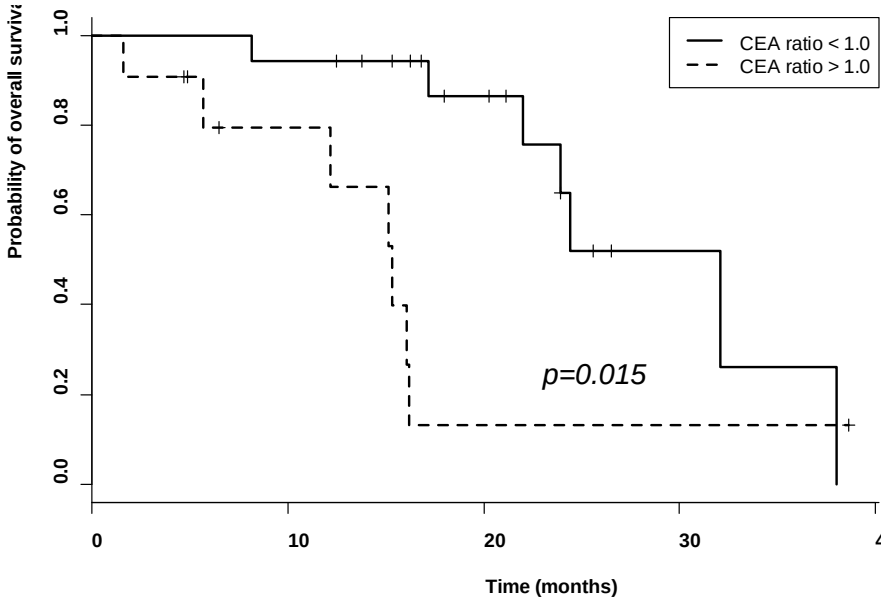
(b)

Figure 1. ROC curves depicting the predictive values of early changes in CEA ratios and objective responses in these patients. (a) CR + PR in the objective response by RECIST was significantly correlated with a CEA ratio of 0.4 ($p < 0.001$); (b) CR + PR + SD in the objective response by RECIST was significantly correlated with a CEA ratio of 1.0 ($p < 0.01$).

Next, we analyzed the overall survivals of these patients with the objective response and the reduction of CEA ratio. Progressive disease (PD) was apparently correlated with poor prognosis. In other words, patients achieving disease control in the objective response showed longer survival than those not showing disease control (median OS: 32.1 vs 15.3 months, $p = 0.024$) (Figure 2(a)).



(a)



(b)

Figure 2. Kaplan-Meier analyses. Overall survival in patients who underwent our therapeutic protocol according to objective response by RECIST and values of CEA ratio. (a) OS based on whether patients achieved a complete response, partial response and stable disease or not according to RECIST ($p < 0.05$); (b) OS based on whether patients achieved a CEA ratio below 1.0 or not. Patients achieving CEA ratio below 1.0 had significantly improved overall survival ($p < 0.05$).

The patients were separated into two groups, using the CEA ratios of 0.4 and 1.0. The reduction rate of the serum CEA level was correlated with the OS. Patients who had a serum CEA ratio < 0.4 seemed to have a longer OS than those whose ratio was > 0.4 (median OS: 32.1 vs 16.0 months, $p = 0.113$). Furthermore, patients who had a serum CEA ratio < 1.0 had significantly longer OS than those whose ratio was > 1.0 (median OS: 23.9 vs 15.3 months, $p = 0.015$) (**Figure 2(b)**). These findings demonstrate a strong relationship between early change in the CEA ratio and OS in patients with metastatic CRC receiving primary surgery followed by intensive chemotherapy.

4. Discussion

Here, we describe the relationships between the early CEA change and the patient's OS, and the possibility of using the CEA ratio to predict the patient's prognosis. This analysis suggests a possible use for an early tumor marker change as a predictor of outcomes in this setting. Clinicians often use a reduction of CEA value as a surrogate marker for therapeutic response [9] [10]. Recently, the kinetics of serum CEA during chemotherapy has been reported to be useful in predicting the objective response. In this study, CEA slopes were calculated using multi-point value during chemotherapy, and the value would be a surrogate marker for objective response and prognosis [11]. In our study, CEA ratio was defined to calculate much easier and more convenient.

The results showed that our strategy of combining primary surgery with chemotherapy is safe and effective. Furthermore, serum CEA level reduction seems to be a good prognostic predictor for colorectal cancer patients on whom this strategy is used. These assessments can be made early in the course of treatment. The limitation of this study is the small number of cases and conducting a single-institution analysis. Further studies are required to elucidate the impact of early tumor marker change on long-term outcome and on clinical decision making.

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