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ORIGINAL ARTICLE

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전이성 대장암에서 1차 치료로 FOLFOX-4 또는 FOLFIRI 복합화학약물 치료 후의 예후 인자 분석

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Prognostic Factors for Metastatic Colorectal Cancer after First-line Chemotherapy with FOLFOX-4 or FOLFIRI Regimen

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Background/Aims: Information on prognostic factors for metastatic colorectal cancer is an important basis for planning the treatment and predicting the outcomes of the patients; however, it has not been well established. The aim of this study was to identify factors that predict results of chemotherapy and to establish a plan for treatment of patients whose tumors are inoperable due to metastatic colorectal cancer.
Methods: We conducted a retrospective review of records from 75 patients treated for colorectal cancer in Kosin University Gospel Hospital, from October 2004 to September 2008. Patients with inoperable tumors due to metastasis at the time of diagnosis who were treated with oxaliplatin or irinotecan as the first-line treatment were included in this study. We investigated the factors that might have an effect on overall survival.
Results: A total of 75 patients were included in this study. Results of univariate analysis showed that hemoglobin (Hb) $\geq$10 g/dL at the time of diagnosis, no increase in CEA on the follow-up examination after chemotherapy, chemotherapy plus surgery, and better response to chemotherapy were significant prognostic factors. Results of multivariate analysis showed that Hb $\geq$10 g/dL at the time of diagnosis ($p<0.001$), surgery after chemotherapy ($p=0.001$), and better response to chemotherapy ($p=0.014$) were significant prognostic factors.
Conclusions: In this study, Hb $\geq$10 g/dL at the time of diagnosis, surgery after chemotherapy, and better response to chemotherapy were significant prognostic factors for metastatic colorectal cancer. **(Korean J Gastroenterol 2014;63:209-215)**

Key Words: Colorectal neoplasms; Prognostic factors; Chemotherapy

INTRODUCTION

Colorectal cancer, one of the most common malignant tumors, ranks as the third leading cause of cancer-related death worldwide.[1] According to data from the Korean National Cancer Center, the age-standardized incidence rate of colorectal cancer was 27.0 per 100,000 persons in 1999 and 49.8 per 100,000 persons in 2010 in men, and 17.1 per 100,000 persons in 1999 and 26.4 per 100,000 persons in 2010 in women.[2] The overall five- year survival rate of colorectal cancer was 72.6% (74.5% for men and 69.9% for women) in 2006-2010.[2] However, this rate was lower in cases of metastatic disease. A radical cure for colorectal cancer is complete surgical excision; however, in the case of meta-

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static colorectal cancer, chemotherapy is the treatment of choice.

As the occurrence of colorectal cancer in Korea increases, interest in survival rates after treatment is also increasing. Some studies have reported several prognostic factors.[3-7] Some factors appear to have overt effects on cancer prognosis, such as progression of the tumor, depth of invasion, metastasis to other organs, distant metastasis, and lymph node metastasis. Clinical variables, such as age, gender, presence of intestinal obstruction or perforation, location and form of major lesion, and presence of symptoms, bleeding, or transfusion, may also affect prognosis. In addition, pathological prognostic factors have been reported, including DNA ploidy, expression of oncogenes, and tumor associated antigens. However, there are few data on the factors affecting prognosis after initial treatment with chemotherapy for inoperable patients. The aim of this study is to identify factors predicting the results of chemotherapy and to establish a plan for treatment of patients whose tumors are inoperable due to metastatic colorectal cancer.

MATERIALS AND METHODS

1. Patients

Records from 770 patients treated for colorectal cancer in Kosin University Gospel Hospital (Busan, Korea) from October 2004 to September 2008 were reviewed. Patients with inoperable tumors due to metastasis at the time of diagnosis and treated with oxaliplatin or irinotecan as the first-line treatment ($\geq$3 cycles) were included. Exclusion criteria included presence of other co-existing malignant tumors, metastases to the central nervous system, active infection Eastern Cooperative Oncology Group (ECOG) performance $\geq$3, age under 18 years, predicted survival time less than 12 weeks, and decreased liver, pancreas, or bone marrow function. Following application of these criteria, a total of 75 patients were included in this study. This study was approved by the Institutional Review Board of Kosin University Gospel Hospital (KUGH IRB No. 13-089).

2. Prognostic factors

We investigated patient characteristics that might have an effect on overall survival. These factors are as follows: age, gender, BMI, ECOG, area of lesions, form of lesions, tumor grade, operation after chemotherapy, number of metastases, presence of anemia at the time of diagnosis, value of serum albumin and CEA at the time of diagnosis, increasing serum CEA level, weight loss at initial presentation and during the study period, and degree of response to chemotherapy. Patients were categorized into three groups according to BMI as follows: under 25 kg/m^2, 25-30 kg/m^2, and over 30 kg/m^2. Patients were also divided into two groups based on other characteristics, including level of hemoglobin at presentation ($<$10 g/dL or $\geq$10 g/dL), level of albumin at presentation ($<$3.5 g/dL or $\geq$3.5 g/dL), serum CEA value ($<$10 g/dL or $\geq$10 g/dL), and an operation after chemotherapy (operation or no operation).

3. Treatment schedule and assessment of efficacy after chemotherapy

Combination of oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX)-4 or combination of irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) regimen as initial chemotherapy consisted of oxaliplatin 85 mg/m^2 or irinotecan 180 mg/m^2, and leucovorin 100 mg/m^2 as a two-hour intravenous infusion on day 1 and 5-fluorouracil 400 mg/m^2 as a bolus, followed by 600 mg/m^2 as a 22-hour intravenous infusion on days 1 and 2. The interval of these regimens is two weeks. After initial chemotherapy (three cycles), abdominal CT scan was performed. Tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease, according to response evaluation criteria in solid tumors criteria. After initial chemotherapy, all CR and PR required confirmation for at least four weeks after they were first noted. If there was no measurable lesion, the evaluable lesion was assessed. The overall survival was measured from the first day of chemotherapy until death or the date of the last follow up.

4. Statistical analysis

Kaplan-Meier analysis was used for evaluation of overall survival, log rank test was used for comparison of differences in prognostic factors, and multivariate analysis by Cox regression proportional hazard model was used for estimation of the prognostic factors affecting overall survival. Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA), and a p-value $<$5% was considered significant.

RESULTS

Of 770 colorectal cancer patients, 75 (9.7%) were treated with chemotherapy and included in this study. Patient characteristics are summarized in Table 1. Fifty one patients were treated with FOLFOX-4 regimen, and the other 24 patients were treated with FOLFIRI regimen. We performed univariate and multivariate analyses for evaluation of the significant prognostic factors (Tables 2, 3).

In univariate analysis, age, gender, BMI, and ECOG performance status were not significant prognostic factors af-

Table 1. Characteristics of Patients (n=75)

Characteristic		Data
Age (yr)		64 (42-85)
Sex	Male	40 (53.3)
	Female	35 (46.7)
Regimen	FOLFOX-4	51 (68.0)
	FOLFIRI	24 (32.0)
Chemotherapy cycle		6
		2-15
Metastasis site	Liver	49 (55.7)
	Lung	11 (12.5)
	Lymph node	21 (23.8)
	Others	7 (8.0)
BMI (kg/m^2)	<25	54 (72.0)
	25-30	18 (24.0)
	>30	3 (4.0)
ECOG	0-1	56 (74.7)
	2	19 (25.3)
Location	Right	19 (25.3)
	Left	56 (74.7)
Borrmann type	1-3	71 (94.7)
	4-5	4 (5.3)
Pathology	Well - moderate	54 (72.0)
	Poorly - SRC	21 (28.0)
Initial CTx+surgery	Yes	12 (16.0)
	No	63 (84.0)
Metastasis (n)	1	63 (84.0)
	≥2	12 (16.0)
Initial BW loss	Yes	28 (37.3)
	No	47 (62.7)
Initial Hb (g/dL)	≥10	62 (82.7)
	<10	13 (17.3)
Initial albumin (g/dL)	≥3.5	50 (66.7)
	<3.5	25 (33.3)
Initial CEA (ng/mL)	≥10	55 (73.3)
	<10	20 (26.7)
Follow-up BW loss	Yes	26 (34.7)
	No	49 (65.3)
Follow-up CEA elevation	Yes	26 (41.3)
	No	49 (58.7)
Response of CTx	CR, PR, SD	62 (82.7)
	PD	13 (17.3)

Values are presented as median (range) or number of patients (%). FOLFOX-4, Oxaliplatin, Leucovorin, and 5-Fluorouracil regimen; FOLFIRI, Irinotecan, Leucovorin, and 5-Fluorouracil regimen; ECOG, Eastern Cooperative Oncology Group; SRC, signet ring cell; CTx, chemotherapy; BW, body weight; Hb, hemoglobin; CR, complete remission; PR, partial remission; SD, stable disease; PD, progression disease.

Table 2. Univariate Analysis of Overall Survival (OS)

		Patient (n)	Median OS (mo)	p-value
Age (yr)	≤ 64	32	16.27	0.290
	>64	43	14.40	
Sex	Male	40	10.73	0.156
	Female	35	20.33	
BMI (kg/m^2)	<25	54	14.00	0.563
	25-30	18	15.87	
	>30	3	16.27	
ECOG	0-1	56	15.87	0.078
	2	19	10.73	
Location	Right	19	9.03	0.263
	Left	56	15.87	
Borrman type	1-3	71	14.40	0.957
	4-5	4	20.33	
Pathology	Well - moderate	54	15.17	0.848
	Poor - SRC	21	10.73	
Initial CTx+surgery	Yes	12	54.49	0.002
	No	63	16.15	
Metastasis (n)	1	63	14.00	0.919
	≥2	12	16.27	
Initial BW loss	Yes	28	14.00	0.726
	No	47	15.87	
Initial Hb (g/dL)	≥10	62	16.27	<0.001
	<10	13	4.50	
Initial albumin (g/dL)	≥3.5	50	15.87	0.444
	<3.5	25	14.00	
Initial CEA (ng/mL)	≥10	55	14.27	0.636
	<10	20	19.10	
Follow-up BW loss	Yes	26	14.27	0.843
	No	49	15.87	
Follow-up CEA elevation	Yes	26	8.87	0.030
	No	49	16.87	
Disease response	CR, PR, SD	62	15.87	0.020
	PD	13	5.53	

ECOG, Eastern Cooperative Oncology Group; SRC, signet ring cell; CTx, chemotherapy; BW, body weight; Hb, hemoglobin; CR, complete remission; PR, partial remission; SD, stable disease; PD, progression disease.

Table 3. Multivariate Analysis of Overall Survival

	OR	95% CI	p-value
Initial CTx+surgery	9.769	2.464-38.727	0.001
Initial Hb (g/dL)	7.600	2.638-21.898	<0.001
Follow-up CEA elevation (ng/mL)	0.660	0.306-1.428	0.292
Disease response	3.396	1.282-9.001	0.014

CTx, chemotherapy; Hb, hemoglobin.

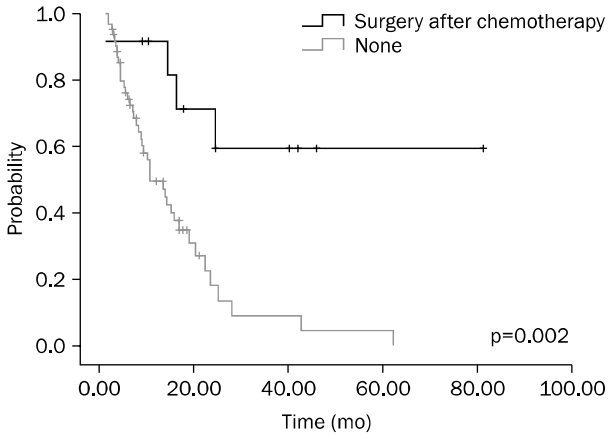

Fig. 1. Overall survival according to whether or not surgery was performed after initial chemotherapy.

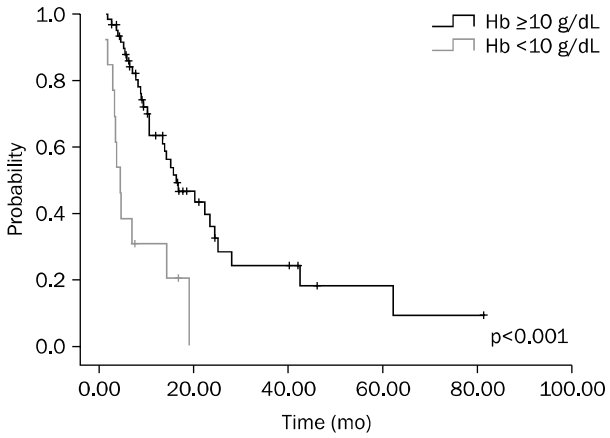

Fig. 2. Overall survival according to initial hemoglobin (Hb) level.

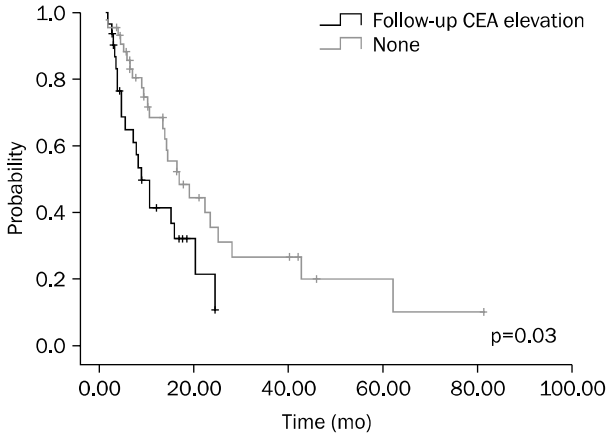

Fig. 3. Overall survival according to whether or not follow-up CEA level was elevated.

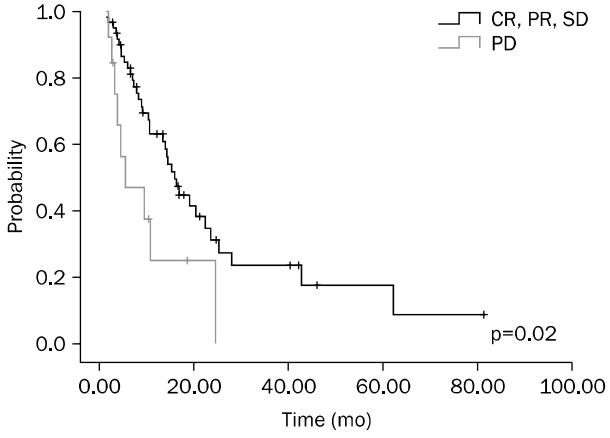

Fig. 4. Overall survival according to disease response.
CR, complete remission; PR, partial remission; SD, stable disease; PD, progression disease.

fecting median overall survival. Twelve patients who showed a response after chemotherapy subsequently underwent an operation, and they had better median overall survival compared to the 63 patients who did not undergo operations (54.49 months *vs.* 16.15 months, p=0.002) (Fig. 1). Of twelve patients who underwent an operation, five patients underwent an operation because they showed much better response than expected after chemotherapy. However, four patients underwent an operation for palliative treatment, and three patients for complications of cancer, including perforation, obstruction, and severe pain. Patients with tumors in the right colon had longer median overall survival than those with tumors in the left colon, although there was no statistical significance (15.87 months *vs.* 9.03 months, p=0.263). Results of analysis including number of metastases and histological tumor grades showed no statistically significant differences in overall survival. At the time of diagnosis and during the follow-up period, weight loss ($\geq$10%) had no significant effect on overall survival. In addition, decrease in albumin level from the time of diagnosis to the follow-up period did not result in any differences in overall survival. In patients whose hemoglobin level decreased below 10 g/dL at the time of diagnosis (13 patients, 17.3%), median overall survival was significantly decreased compared to patients with hemoglobin $>$10g/dL at the time of diagnosis (4.5 months *vs.* 16.27 months). This difference was statistically significant ($p<0.0001$) (Fig. 2). Increased serum CEA level at the time of diagnosis had no significant effect on overall survival; however, a significant difference in median overall survival was observed in patients whose CEA decreased after chemotherapy (16.87 months *vs.* 8.87 months, p=0.03) (Fig. 3).

Patients who had complete remission, partial remission, or SD after chemotherapy had longer overall survival duration than patients who had progression of disease after chemotherapy (15.87 months *vs.* 5.58 months). This difference was also statistically significant (p=0.02) (Fig. 4).

In multivariate analysis, significant prognostic factors for metastatic colorectal cancer were hemoglobin $\geq$10 g/dL at the time of diagnosis (OR 7.60, 95% CI 2.638-21.898; p $<$0.001), surgery after chemotherapy (OR 9.769, 95% CI 2.464-38.727; p=0.001), and better response to chemotherapy (OR 3.396, 95% CI 1.282-9.001; p=0.014).

DISCUSSION

Colorectal cancers that develop before age 40 are known to have a poor prognosis, because they are often diagnosed at a more advanced stage or have more aggressive histological patterns.[8,9] However, Schellerer et al.[10] reported that although young patients present with more aggressive histopathological subtypes and fewer early stages, cancer-related survival is not less favorable when compared with older patients. Cheung et al.[7] found that sex is a modest independent prognostic marker for patients with early-stage colon cancer, particularly in older patients. In this study, there was no significant difference in prognosis based on age or gender. Ishihara et al.[11] reported that proximal tumor location and female gender were independent predictors of fair prognosis in poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma of the colon. Meyerhardt et al.[12] reported that obesity is a risk factor for progression of colorectal cancer; however, in this study, neither BMI nor weight change showed a significant association with an increased risk of cancer recurrence or death. In one study, obstruction and perforation are considered major risk factors that decrease survival rates.[13] In general, prognosis of polypoid or protruding cancer is better than that for flat or ulcerative cancer, as it is usually found at an earlier stage and has a lower frequency of lymphatic metastasis or penetration into the wall of the intestine.[14]

Patients with symptoms had a better five-year survival rate than patients with no symptoms (71% *vs.* 49%), because the cancer was found at an earlier stage through a screening inspection.[15] Better five-year survival rate was reported for patients with persistent symptoms over six months.[16] This appears to be related to the tumor growth rate. According to the results of stage-controlled multivariate analysis, the duration of presenting symptoms does not have an effect on patient survival.[17] Rectal bleeding was considered to be a prognostic of better outcomes due to early diagnosis and treatment; however, according to the results of multivariate analysis, rectal bleeding also did not show any association with prognosis.[17] History of transfusion is known to be associated with an increase in cancer recurrence rate and decrease in survival rate.[18] In this study, patients with hemoglobin level $\geq$10 g/dL (not requiring transfusion) at the time of diagnosis had a remarkably increased median overall survival compared to those with hemoglobin $\leq$10 g/dL (requiring transfusion). This was a statistically significant difference, and, thus, hemoglobin level at the time of diagnosis was considered to be a helpful prognostic factor.

Most colorectal cancers are histologically consistent with adenocarcinoma. The other histologic types are mucinous-type carcinoma, signet ring cell carcinoma, and undifferentiated carcinoma, which are associated with poor prognoses. The degree of differentiation is an independent factor for survival, as the probability of intestinal wall penetration, lymphogenous metastasis, or remote metastasis increases.[19] In addition to these outcomes, other factors affecting prognosis include invasion of lymphatic vessels, blood vessels, and perineural areas, lymphocytic infiltration around the lesion, and reaction pattern of lymph nodes.[20-22]

One study reported an association between aneuploidy and survival rate, and the stage of disease is known to increase as aneuploidy increases.[23] There is, however, controversy regarding an association between S-phase fraction and survival rate. Allelic loss of chromosome 18q is associated with poor prognosis of colorectal cancer,[24] and DNA index is known to provide better information about prognosis than ploidy.[25] In addition, K-ras mutation or over-expression of ras p21 is related to recurrence of cancer. High expression of p53 has been reported as an independent factor related to decreased survival rate.[26] Mutations in the DCC and nm23 genes may also be related to the prognosis.

An increase in CEA is related to an increase in recurrence rate and lower survival rate. This is more remarkable in an advanced stage of disease and more notable in patients with colon cancer than in those with rectal cancer.[27] In this study, patients with no increase in CEA after chemotherapy had better

median overall survival. Thus, CEA is thought to be a useful prognostic factor during the follow-up period. In addition, patients whose colorectal cancer had mucin-associated antigens experienced worse clinical results. Relation of stronger HLA-DR expression to increased survival rate when controlling for stage of disease was also reported.[28] Growth factors and higher expression of the epidermal growth factor receptor (EGFR) also affect the prognosis. A number of studies on various factors affecting prognosis continue to be published.

Stelzner et al.[29] found that performance status, level of CEA, degree of metastasis, invasion of primary tumor, and chemotherapy were independent factors predicting patient survival. Rougier et al.[30] reported that independent factors affecting survival of colorectal cancer patients with unresectable liver metastasis were ECOG performance status, level of alkaline phosphatase, number of fractions in liver metastasis, chemotherapy, location of primary tumor, prothrombin time, and excision of primary lesion. In this study, we found that level of CEA, operation after chemotherapy, and response to chemotherapy affected the prognosis, and our results are partially consistent with those of other studies.

This study has some limitations. First, this study was retrospective; therefore, we could not avoid selection bias when collecting information. Second, the number of patients with metastatic colorectal cancer included in this study is too small to conclude that these factors are reliable prognostic factors and conduct of further studies including a larger number of patients with metastatic colorectal cancer will be needed in order to verify our findings. Third, this study did not include the response after second line chemotherapy. Therefore, we did not consider the effect of second line chemotherapy on the prognosis.

In summary, the aim of this study is to analyze the prognostic factors affecting patients with metastatic colorectal cancer who were initially treated with chemotherapy. We found some significant prognostic factors. Results of univariate analysis showed that hemoglobin $\geq$10 g/dL at the time of diagnosis, no increase in CEA on the follow-up examination after chemotherapy, surgery after chemotherapy, and better response to chemotherapy were significant prognostic factors. According to the results of multivariate analysis, the significant prognostic factors were hemoglobin $\geq$10 g/dL at the time of diagnosis, surgery after chemotherapy, and better response to chemotherapy.

Conduct of further studies will be needed in order to clarify the prognostic factors affecting metastatic colorectal patients who are initially treated with chemotherapy.

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