




Original Article

## Effects of 7~11 cycles adjuvant FOLFOX chemotherapy on the prognosis of patients with stage III colon cancer

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**Abstract** Adjuvant fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy for 6 months is the standard treatment of stage III colon cancer to improve patient survival. Recent studies have shown that restricting the treatment to 3 months to reduce toxicity negatively affects the outcome. However, the effect of FOLFOX treatment for a duration of between 3 and 6 months (7~11 cycles) on survival is not known. The effect of a reduced duration of FOLFOX chemotherapy on the prognosis of stage III colon cancer was examined. The 5-year disease-free survival in patients receiving 7~11 cycles of FOLFOX was lower than those receiving 12 cycles (72.9% vs. 87%, respectively). Patients receiving 7~11 cycles who had a bowel obstruction at diagnosis had a significantly higher recurrence rate (66.7% vs. 15.0%) and shorter median disease-free survival (24.7 months vs. not reached) than those receiving 12 cycles. Among patients receiving 12 cycles of FOLFOX, there was no difference in the outcome between those with and those without intestinal obstructions at diagnosis. These results suggest that the completion of 12 cycles FOLFOX chemotherapy is important to improve the patient's prognosis, especially for with intestinal obstructions at diagnosis.

**Key words:** Colon cancer, Adjuvant chemotherapy, FOLFOX


### INTRODUCTION

Colon cancer is one of the leading causes of death from cancer worldwide.<sup>1)</sup> In Korea, colorectal cancer ranks fourth among cancer deaths in men and second in women.<sup>2)</sup> In stage III colon cancer, a combination chemotherapy of fluoropyrimidines and oxaliplatin after the resection of the primary tumor is recommended to improve survival, with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) combination chemotherapy as the currently accepted standard adjuvant treatment regimen.<sup>3-5)</sup> However, the appropriate period of FOLFOX chemotherapy

to minimize toxicity from chemotherapy while maximizing the improvement of survival has not been determined. Early clinical studies in the 1990's on adjuvant treatment of colon cancer with 5-fluorouracil and leucovorin showed there was no survival benefit from extending treatment from 6 months to 8 or 12 months.<sup>6,7)</sup> Based on the results from these studies, adjuvant chemotherapy for 6 months has been recommended for standard treatment in stage III colon cancer patients.

With FOLFOX chemotherapy, there is a concern for oxaliplatin-induced peripheral neuropathy (OIPN) from 12 cycles of treatment over 6 months.<sup>3)</sup> The results from a study of Western patients showed that >90% of patients exhibited signs of OIPN during the chemotherapy, and 15% had residual signs even several years after the completion of chemotherapy.<sup>5)</sup> This chronic OIPN is associated with the cumulative dose of oxaliplatin.<sup>8)</sup> Therefore, studies have recently been conducted to determine

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**Table 1.** Baseline characteristics

Variable	Number (%) of patients			P value
	Total (n = 49)	Short-course group (n = 26)	Standard group (n = 23)	
Age (years)				1.0
< 65	36 (73.5)	19 (73.1)	17 (73.9)	
≥ 65	13 (26.5)	7 (26.9)	6 (26.1)	
Sex				0.357
Female	18 (36.7)	8 (30.8)	10 (43.5)	
Male	31 (63.3)	18 (69.2)	13 (56.5)	
Tumor stage				0.728
T1	0 (0)	0 (0)	0 (0)	
T2	1 (2.0)	0 (0)	1 (4.3)	
T3	38 (77.6)	21 (80.8)	17 (73.9)	
T4	10 (20.4)	5 (19.2)	5 (21.7)	
Nodal stage				0.777
N1	29 (59.2)	16 (61.5)	13 (56.5)	
N2	20 (40.8)	10 (38.5)	10 (43.5)	
Risk group				1.0
T2 or T3 N1	26 (53.1)	14 (53.8)	12 (52.2)	
T4, N2 or both	23 (46.9)	12 (46.2)	11 (47.8)	
Angiolymphatic invasion				0.222
Negative	16 (32.7)	6 (23.1)	10 (43.5)	
Positive	33 (67.3)	20 (76.9)	13 (56.5)	
Perineural invasion				0.102
Unknown	1 (2.0)	0 (0)	1 (4.3)	
Negative	17 (34.7)	12 (46.2)	5 (21.7)	
Positive	31 (63.3)	14 (53.8)	17 (73.9)	
Perforation				1.0
Negative	46 (93.9)	24 (92.3)	22 (95.7)	
Positive	3 (6.1)	2 (7.7)	1 (4.3)	
Obstruction				0.731
Negative	39 (79.6)	20 (76.9)	19 (82.6)	
Positive	10 (20.4)	6 (23.7)	4 (17.4)	

whether shortening the treatment period reduces toxicity while maintaining efficacy. These studies reported that 3 months of FOLFOX chemotherapy did not show non-inferiority of the survival outcome compared to that with 6 months of treatment.<sup>9,10)</sup> To date, no study has reported the effects of slightly longer durations, we sought to compare the clinical outcomes of stage III colon cancer patients receiving adjuvant FOLFOX chemotherapy for between 3 and 6 months (i.e., 7~11 cycles) with those who completed 6 months (12 cycles) of FOLFOX chemotherapy.

## MATERIALS AND METHODS

### Patients

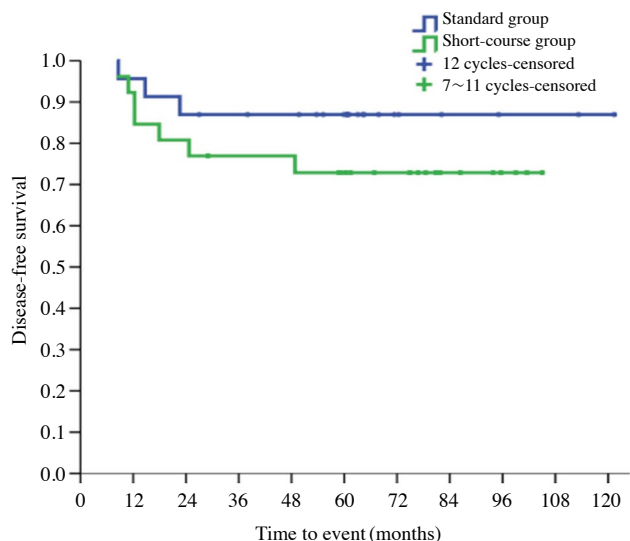
The medical records of colon cancer patients who underwent curative surgery between March 2008 and May 2013 and received adjuvant FOLFOX chemotherapy were reviewed. Among these, the records of patients meeting

the following three criteria were selected for analyses: (i) diagnosis of stage III colon cancer according to the American Joint Committee on Cancer cancer staging manual; (ii) more than 7 cycles of adjuvant FOLFOX were administered; (iii) no recurrence at the time of chemotherapy completion. The patients' clinicopathologic features and clinical outcomes were retrospectively evaluated. This study protocol was approved by the Institutional Review Board (IRB) of the Jeju National University Hospital (IRB protocol number JEJUNUH 2018-05-008).

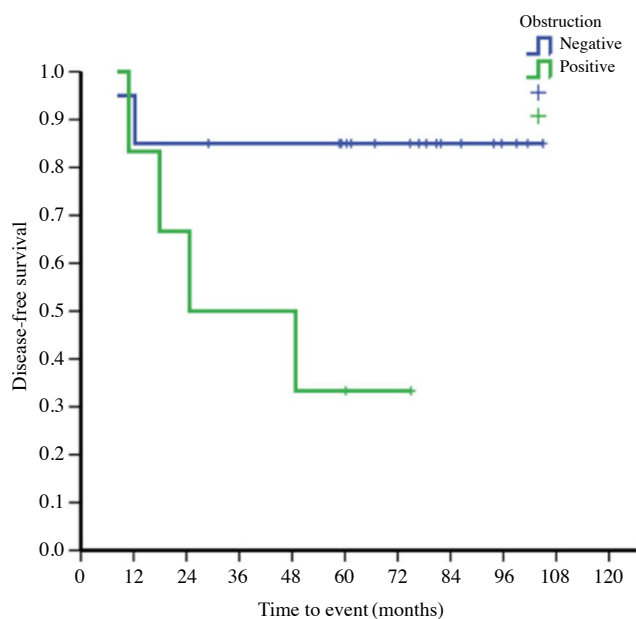
### Statistical analysis

The comparisons of clinicopathologic variables, recurrence of colon cancer, and patterns of relapse between patients receiving 12 cycles of FOLFOX (standard group) and those receiving 7~11 cycles of FOLFOX (short-course group) were made using Pearson's  $\chi^2$  or Fisher's exact tests as appropriate. Two-sided *P* values of <0.05 were considered statistically significant. The associations between clinicopathologic variables, including disease-free

## RESULTS



**Figure 1.** Disease-free survival for patients receiving standard or a short course of adjuvant FOLFOX chemotherapy.



**Figure 2.** Disease-free survival for patients with or without bowel obstructions receiving short-course FOLFOX chemotherapy.

survival (DFS) of patients in both groups, were analyzed by Kaplan-Meier plots and log-rank tests. The DFS was defined as the time from the date of surgery to the first detection of disease recurrence. Multivariate analyses were carried out using the Cox regression model. A significance level of 0.05 was used to select variables for covariate analyses.

### Patient characteristics

The medical records from 49 patients were included in this study. Of these, 23 patients were treated with 12 cycles FOLFOX chemotherapy (standard group), and 26 were treated with 7~11 cycles (short-course group). All patients in the short-course group received FOLFOX chemotherapy for more than 4 months: nine patients received 8 cycles, sixteen had 9 cycles, and one had 11 cycles of FOLFOX chemotherapy. The demographic and clinical characteristics of the patients are summarized in Table 1. The overall mean age ( $\pm$  standard deviation) of the patients was  $57.4 \pm 10.6$  years; patients in the short-course group were a mean of  $59.6 \pm 10.2$  years, and those in the standard group were  $55.0 \pm 10.8$  years. The median duration of follow-up was 66.8 months (range, 17.9~121.4 months).

### Clinical outcomes

During the follow-up period, 10 (20.4%) patients experienced recurrence; 7 of these were in the short-course group. The 5-year DFS in the short-course group was slightly lower than that in the standard group (72.9% vs 87%, respectively;  $P=0.244$ ) (Fig. 1). Among the patients in the short-course group, those with a bowel obstruction at diagnosis had a significantly higher recurrence rate (66.7% vs 15.0%,  $P=0.028$ ) and shorter median DFS (24.7 months; 95% confidence interval, 0.0 to 61.8 [CI] vs not reached; 95% CI, not available,  $P=0.017$ ) than those with no obstructions (Fig. 2). There was no significant difference in outcomes between those with and those without an intestinal obstruction among patients in the standard group. None of the other factors, including age, lymph node stage, tumor stage, risk group (T2 or T3 N1 vs. T4, N2 or both), angiolymphatic invasion, perineural invasion, and perforation, had a significant effect on recurrence and DFS.

## DISCUSSION

A prospective study of Korean colorectal cancer patients treated with 12 cycles of adjuvant FOLFOX revealed that 94% showed signs of OIPN after the completion of treatment, and 14% of patients showed grade 3 OIPN.<sup>11)</sup> OIPN persisted in 64% of patients 1 year after the end of treatment, with 11% of patients showing grade 3 toxicity, and the frequency and severity of OIPN increased with repeated cycles of chemotherapy.<sup>11)</sup> Because there is no specific

method to prevent OIPN and treatment entails only conservative management, there is continued concern about how to reduce the use of oxaliplatin.<sup>12)</sup> One way to reduce the frequency and severity of OIPN may be to reduce the number of chemotherapy cycles. And, treatment duration affected to patient's compliance to chemotherapy.<sup>13)</sup>

The results of the present study reveal that the DFS of patients receiving fewer cycles of FOLFOX chemotherapy was lower, though this reduction was not statistically significant. However, patients with bowel obstructions as a risk factor had worse outcomes than those without, but only among patients receiving fewer cycles. This finding suggests that shortening the duration of adjuvant FOLFOX has a negative effect on the clinical outcome of stage III colon cancer patients with bowel obstructions.

There are some limitations in this study. First, the small number of patients included in this study limited the statistical comparisons. Second, the retrospective design limited the data to what was present in the medical records; thus, we were unable to obtain some information, such as why chemotherapy was stopped early in some patients.

The results from this study indicate that patients with bowel obstructions at the diagnosis of colon cancer are at risk for a poorer outcome if a shorter course of FOLFOX chemotherapy is used. Thus, the full 12 cycles of treatment should be administered to these patients to improve the prognosis.

As shown in a recent study, for those with a lower risk for recurrence, a 3-month regimen of capecitabine with oxaliplatin may be as efficacious as a 6-month duration.<sup>9)</sup> Therefore, we also suggest that the choice of regimen should be personalized to the patient's tumor condition and their risk of OPIN. And, further studies are needed to determine the exact mechanism of OIPN and its prevention and treatment.

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