INTRODUCTION

Colon cancer is one of the leading causes of death from cancer worldwide. In Korea, colorectal cancer ranks fourth among cancer deaths in men and second in women. In stage III colon cancer, a combination chemotherapy of fluoropyrimidines and oxaliplatin (FOLFOX) 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. 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. 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. 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. This chronic OIPN is associated with the cumulative dose of oxaliplatin. Therefore, studies have recently been conducted to determine...
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. 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

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**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%) of patients</th>
<th>Total ($n = 49$)</th>
<th>Short-course group ($n = 26$)</th>
<th>Standard group ($n = 23$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) &lt; 65</td>
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<td>1.0</td>
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<tr>
<td>Age (years) ≥ 65</td>
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<td>0.357</td>
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<tr>
<td>Sex</td>
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<td>0.728</td>
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<tr>
<td>Tumor stage T1</td>
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<td>0.777</td>
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<tr>
<td>Tumor stage T2</td>
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<td>Tumor stage T3</td>
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<td>0.222</td>
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<td>Tumor stage T4</td>
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<td>0.102</td>
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<tr>
<td>Nodal stage N1</td>
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<tr>
<td>Risk group T2 or T3 N1</td>
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<td>0.0</td>
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<tr>
<td>Risk group T4, N2 or both</td>
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<td></td>
<td>0.0</td>
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<tr>
<td>Angiolymphatic invasion</td>
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<td>0.0</td>
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<tr>
<td>Perineural invasion</td>
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<td>0.0</td>
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<tr>
<td>Perforation</td>
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<tr>
<td>Obstruction</td>
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<td>0.0</td>
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</tbody>
</table>
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.

RESULTS

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 (± standard deviation) of the patients was 57.4 ± 10.6 years; patients in the short-course group were a mean of 59.6 ± 10.2 years, and those in the standard group were 55.0 ± 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), angiolympathic 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.11) 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.11) Because there is no specific
method to prevent OIPN and treatment entails only con-
servative management, there is continued concern about
how to reduce the use of oxaliplatin.12) 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.13)

The results of the present study reveal that the DFS of
patients receiving fewer cycles of FOLFOX chemothera-
py 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 FOLF-
OX 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 sta-
tistical comparisons. Second, the retrospective design
limited the data to what was present in the medical re-
cords; 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 treat-
ment 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.9)
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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