Randomized Controlled Trial of Intraportal Chemotherapy Combined With Adjuvant Chemotherapy (mFOLFOX6) for Stage II and III Colon Cancer

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Objectives: The optimal time to initiate adjuvant chemotherapy after surgery in patients with colon cancer is not clear. We investigated the benefit of combined intraportal chemotherapy administered during radical surgery with adjuvant chemotherapy for treating stage II and III colon cancer.

Methods: Patients were randomly assigned to OCTREE arm (intraportal chemotherapy plus mFOLFOX6) or a standard adjuvant chemotherapy arm (mFOLFOX6). The primary study endpoint was disease-free survival. The secondary endpoints included metastasis-free survival, overall survival, and safety.

Results: The intent-to-treat population comprised 237 patients. With a median follow-up of 44 months, the hazard ratio (OCTREE vs mFOLFOX6) was 0.66 (95% confidence interval, 0.43–0.90), a 34% risk reduction in favor of OCTREE ($P = 0.016$). The 3-year disease-free survival rate was 85.2% for OCTREE and 75.6% for mFOLFOX6 alone ($P = 0.030$). The 3-year metastasis-free survival rates were 87.6% for OCTREE and 78.0% for mFOLFOX6 ($P = 0.035$). Patients had lower distant metastatic rate in the OCTREE arm (12.7% vs 22.7%; $P = 0.044$), when compared with the mFOLFOX6 arm. The 3-year overall survival was no significant difference between 2 arms ($P = 0.178$). Neutropenia occurred in 12.7% of the patients receiving OCTREE and in 2.5% of the patients receiving mFOLFOX6 ($P = 0.003$) within 2 weeks of surgery, and grade 3 or 4 toxicity event was no difference between 2 regimens.

Conclusions: Combination of intraoperative intraportal chemotherapy with mFOLFOX6 reduced the occurrence of distant metastases and improved disease-free survival in patients with stage II and stage III colon cancer.

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INTRODUCTION

Colorectal cancer (CRC) is a common malignant tumor with the third leading cause of death from cancer in the Western world. Radical surgery remains the only curative option for these patients, but 40% to 50% of patients who accepted curative surgery alone ultimately experience recurrence and die from metastatic disease.[1] To improve the prognosis of CRC, postoperative adjuvant chemotherapy (AC) has been routinely recommended after radical surgery of high-risk CRC.[2,3]

The role of AC on survival after surgery is the elimination of micrometastatic deposits in a certain proportion of patients who would develop cancer relapse. However, the best time to start AC after surgery in patients with colon cancer is still not clear. Systematic review from retrospective study shows that relative overall survival decreases by 14% for every 4-week delay to the initiation of AC,[4] indicating that AC should be implemented as soon as the patient is recovering from surgery and is medically able. With a caveat of possible bias in the study, the current National Comprehensive Cancer Network recommendations (version 2013) cautiously supported this evidence.[5] However, some critics have pointed out that although starting chemotherapy as soon as practical seems advisable, starting therapy too early may have a negative, rather than a positive, effect. There is a risk that chemotherapy-related deaths may be increased if physicians start treatment before allowing time for a full recovery from surgery.[6]

Regional chemotherapy, such as adjuvant intraportal vein chemotherapy, is another delivery strategy that, if administered early enough, could inhibit tumor cell proliferation. Liver metastases are the most common location of colon cancer relapse after surgery, which originate from the remnants of microscopic tumor cell deposits during surgery resection for the primary cancer. In addition, extrahepatic metastasis is frequently encountered within a short time after colorectal liver metastasis.[7] When 5-fluorouracil is delivered regionally instead of systemically, the liver receives higher levels of active 5-fluorouracil metabolites. Therefore, the regional chemotherapy was used to try to eliminate these deposits.[8,9] Previous studies have demonstrated that 5-fluorouracil delivered directly into the portal vein system during the early postoperative period may decrease some kinds of distant metastases.[10,11] However, the effect and safety of intraportal chemotherapy (IPC) initiated during operation is unknown, and the regimen of combined regional IPC with systemic AC for colon cancer treatment needs to be evaluated,[12] especially in this era of oxaliplatin-based chemotherapy.

To determine whether IPC started at the time of operation plus standard AC can benefit patients with colon cancer, we conducted a randomized controlled trial in patients with stage II or III colon cancer (OCTREE study).

MATERIALS AND METHODS

Eligibility Criteria

The inclusion criteria were age 18 years or more and 75 years or less, with histologically proven adenocarcinoma of the colon, stage II (T3–T4, N0, M0) or stage III (Any T, N1–N2, M0) disease (according to the 2007 revision of the International Union Against Cancer TNM staging system), no severe major organ dysfunction, no prior cancer therapy, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Colon cancer was defined as the tumor localized above the peritoneal reflection (≥15 cm from the anal margin). Eligible patients were randomly assigned into one of the treatment arms described in the following text (Fig. 1).

Treatment

The patients assigned to the OCTREE arm received 2 therapies (IPC and AC). The control arm did not receive IPC. For all patients, modified FOLFOX6 was planned to start, given at 2 to 6 weeks after surgery.

1) Intraoperative IPC: During the operation, 1 dose of IPC including 1000 mg fluorodeoxyuridine and 100 mg oxaliplatin were administered as a bolus into the regional vein just before ligation. The vein chosen for IPC infusion was based on the location of the primary colon cancer. The ileocolic vein, middle colic vein, and inferior mesenteric vein were used separately for primary cancers from the cecum or ascending colon, transverse colon, descending colon, or sigmoid colon (see Supplemental Digital Content Fig. 1, available at http://links.lww.com/SLA/A818).
2) Postoperative AC: All patients were planned to receive AC (mFOLFOX6), including a 2-hour infusion of 85 mg/m^2 oxaliplatin given simultaneously with a 2-hour infusion of 400 mg/m^2 leucovorin (LV), followed by 400 mg/m^2 5-fluorouracil. Subsequently, the patients accepted a continuous infusion of 2400 mg/m^2 5-fluorouracil for more than 46 hours by intravenous pumping every 2 weeks for 12 cycles.[13]

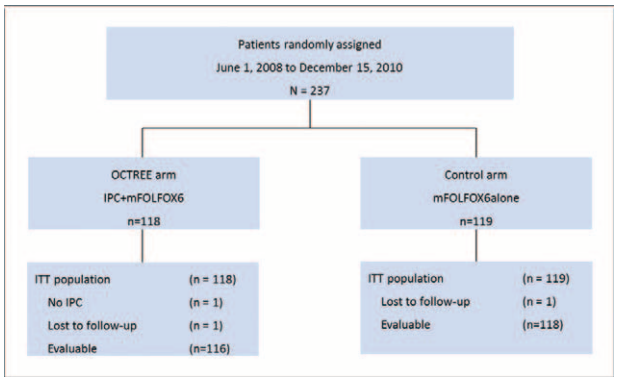

FIGURE 1. CONSORT diagram. OCTREE indicates intraportal chemotherapy (fluorodeoxyuridine and oxaliplatin) plus mFOLFOX6; mFOLFOX6, modified leucovorin, fluorouracil, and oxaliplatin.

Trial Design

The data analysis was based on the intention-to-treat population. The patients were randomly assigned on the basis of the preoperative evaluation and exploratory surgery. This study was approved by the Institutional Review Board of Fudan University, and all patients signed the informed consent before randomization.

The sample size of 230 patients was calculated on the basis of the assumptions of 3 years of disease-free survival (DFS) rate of 70% in the control arm and a hazard ratio (HR) of 0.50 in the OCTREE arm, with an α value of 0.05, and a statistical power of 80% and 2-sided P values on the basis of the log-rank test.

The primary endpoint of this study was DFS, and the secondary endpoints included overall survival, metastasis-free survival (MFS), and safety by intent-to-treat analysis.[14] DFS was measured from randomization to date of tumor recurrence or death from any cause. Overall survival was defined as the time from randomization to date of death from any cause. MFS was measured from randomization to metastasis if metastasis was the first event.

Follow-up

Patients were evaluated after randomization, every 14 days during treatment, and then every half a year for 5 years. During treatment, biochemistry analyses were repeated before each treatment cycle. Tumor assessments were done with calculation of the carcinoembryonic antigen level, magnetic resonance imaging, and chest and abdominal computed tomography. The diagnosis of relapse was done on the basis of imaging and biopsy, if necessary. Adverse effects of patients were monitored throughout the treatment period of IPC and AC and for 1 month after the last cycle of mFOLFOX6 chemotherapy. Adverse events were observed and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

Statistical Analysis

Patient baseline characteristics and outcome factors were summarized and calculated using descriptive statistics. Student t test was used for the continuous variable data analysis. Pearson χ^2 test or Fisher exact test was used to analyze the categorical parameters, as appropriate. According to the Kaplan-Meier method and the log-rank test, survival statistics on time-to-event variables were calculated and compared. SPSS software (version 16.0; SPSS, Chicago, IL) was used for statistical analyses. The tests were considered significant when a 2-sided P value of less than 0.05 was obtained.

RESULTS

Patient Baseline Characteristics

From June 2008 to December 2010, 118 patients were randomly assigned into the OCTREE arm and 119 patients into the control arm and were then assembled in the intent-to-treat (ITT) population accordingly. Among the ITT population, 19 patients did not complete the 12th cycle of mFOLFOX6 chemotherapy and 2 patients were lost to follow-up (Fig. 1). There were no major imbalances between the 2 arms with regard to baseline characteristics (Table 1). As of the last follow-up on September 31, 2013, the median follow-up period was 44 months (range, 34–63 mo). In total, 140 of 237 patients (59.1%) received AC within 4 weeks after surgery, and 97 patients (40.9%) received AC between 4 and 6 weeks, because of perioperative complications, at their request or poor performance status (Table 1). The number of patients receiving first circle of AC for more than 4 weeks was similar between the 2 groups ($P = 0.262$).

TABLE 1. Baseline Characteristics of the Patients

Characteristic	OCTREE (n = 118)	mFOlFOX6 (n = 119)	P*
Age, yr			
Median	59.0	60.0	0.646
Range	19–75	22–75	
Sex, n (%)			0.398
Male	66 (44.1)	73 (38.7)	
Female	53 (55.9)	46 (61.3)	
ECOG PS, n (%)†			0.745
0	100 (84.7)	99 (83.2)	
1	18 (15.3)	20 (16.8)	
Stage II, n (%)‡	47 (39.8)	47 (39.5)	0.391
Low risk	19 (16.1)	15 (12.6)	
High risk	28 (23.7)	32 (26.4)	
Stage III, n (%)	71 (58.5)	72 (58.8)	0.439
1–3 positive nodes	46 (37.3)	51 (41.2)	
≥4 positive nodes	25 (21.2)	21 (17.6)	
Pathology, n (%)			0.826
Adenocarcinoma	109 (92.4)	109 (91.6)	
Well differentiated	4 (3.4)	5 (4.2)	
Moderately differentiated	90 (76.3)	91 (76.5)	
Poorly differentiated	15 (12.7)	13 (10.9)	
Mucinous	9 (7.6)	10 (8.4)	
CEA, n (%)†			0.245
>5 ng/mL	39 (33.1)	48 (40.3)	
≤5 ng/mL	79 (66.9)	71 (59.7)	
Time to AC initiation (wk)§			0.262
≤4 wk, n (%)	71 (60.8)	69 (57.9)	
>4 wk	47 (39.2)	50 (42.1)	
Chemotherapy cycles			0.424
Average, n	11.50	11.66	
Completed cycles, n (%)			0.796
≤6	4 (3.4)	3 (2.5)	
7–11	6 (5.1)	6 (5.1)	
12	108 (91.5)	110 (92.4)	

*P values were calculated using the Pearson χ^2 test for categorical variables and the *t* test for continuous variables.

†ECOG PS and CEA determination were performed 7 or less days after random assignment.

‡Evaluation according to the 2007 revision of the International Union Against Cancer TNM staging system. Stage II patients were classified as at high risk when they had at least one of the following: T4 staging, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, or fewer than 10 lymph nodes examined. Patients with none of these prognostic factors were classified as low-risk stage II patients.

§Among ITT population, 97 patients were receiving first AC for more than 4 weeks because of delayed recovery, such as perioperative complications (n = 36), poor performance status (n = 26), and delayed decision of the patients' request (n = 35).

CEA indicates carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; mFOLFOX6, modified leucovorin, fluorouracil, and oxaliplatin; OCTREE, intraportal chemotherapy (fluorodeoxyuridine and oxaliplatin) plus mFOLFOX6.

Toxicity and Complications

Chemotherapy toxicities that occurred in more than 5% of patients, according to the treatment regimens, are summarized in Tables 2 and 3. No death was attributable to IPC, and 1 patient died within 6 month of receiving AC in the control arm. Elevation of serum aminotransferase occurred in 5.9% of patients for OCTREE treatment compared with 0.9% in the mFOLFOX6 arm within 2 weeks after surgery ($P = 0.033$); grade 3 hepatic toxicity occurred in 1.7% of the patients for OCTREE treatment. The frequencies of all-grade neutropenia and thrombocytopenia were higher for OCTREE treatment (12.5% vs 2.5%, $P = 0.003$; 7.6% vs 1.7%, $P = 0.034$), but no grade 3 or 4 toxicity was observed in either arm (Table 2). In addition, there were no differences noted between the 2 arms in regard to postoperative complications, including infections and anastomotic leakage. The average hospitalization times after surgery were also similar between the 2 arms (Table 2). During the period of AC, the frequencies of grade 3 or 4 toxicity were similar in both arms; grade 3 or 4 neutropenia occurred most frequently in both arms (40.7% vs 38.6%, $P = 0.750$) (Table 3).

TABLE 2. Adverse Events of Intraportal Chemotherapy and Surgical Complications*

Adverse Event	OCTREE (n = 118)	mFOlFOX6 (n = 119)	P†
Toxicity events, n (%)			
Neutropenia			
All grade	15 (12.7)	3 (2.5)	0.003
Grade 3 or 4	0	0	NA
Hepatic toxicity			
All grade	7 (5.9)	1 (0.9)	0.033
Grade 3 or 4	2 (1.7)	0	0.247
Thrombocytopenia			
All grade	9 (7.6)	2 (1.7)	0.034
Grade 3 or 4	0	0	NA
Postoperative complications, n (%)	20 (16.9)	15 (12.6)	0.224
Wound infection	5	4	
Pneumonic infection	13	9	
Anastomotic leakage	2	2	
Hospital stays (d)	9.2 ± 2.6	8.3 ± 2.8	0.169

*Adverse events were categorized according to National Cancer Institute Common Toxicity Criteria, version 3.0.

†Pearson χ^2 test or Fisher exact test was used for categorical variables, and the *t* test was used for continuous variables.

mFOLFOX6 indicates modified leucovorin, fluorouracil, and oxaliplatin; NA, not applicable; OCTREE, intraportal chemotherapy (fluorodeoxyuridine and oxaliplatin) plus mFOLFOX6.

Disease-free Survival

DFS was the primary endpoint of OCTREE study. Of the ITT population, 54 (22.8%) suffered treatment failures, defined as distant metastasis, local recurrence, or death without relapse. All other patients were censored at the time of the last follow-up. The first relapse events are listed in Table 4. When comparing the total relapse events between the 2 treatment arms, there was an obvious decrease in relapse events in the OCTREE arm (16.9%) versus control arm (28.6%) ($P = 0.033$). The Kaplan-Meier curves of these 237 patients are presented in Figure 2A. The HR for OCTREE versus mFOLFOX6 was 0.66 [95% confidence interval (CI), 0.16–0.90,

TABLE 3. Grade 3 or 4 Adverse Events During Adjuvant Chemotherapy*

Adverse Event	OCTREE (n = 118)	mFOlFOX6 (n = 119)	P†
Neutropenia	48 (40.7)	46 (38.6)	0.750
Neuropathy	6 (5.1)	5 (4.2)	0.494
Diarrhea	6 (5.1)	5 (4.2)	0.494
Nausea	8 (6.8)	6 (5.0)	0.386
Vomiting	6 (5.1)	4 (3.7)	0.369

*Adverse events were categorized according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

†Pearson χ^2 test or Fisher exact test was used to assess the difference in the rate of grade 3 or 4 toxicity across treatments.

mFOLFOX6 indicates modified leucovorin, fluorouracil, and oxaliplatin; OCTREE, intraportal chemotherapy (fluorodeoxyuridine and oxaliplatin) plus mFOLFOX6.

TABLE 4. First Site of Relapse

Site of Relapse	OCTREE (n = 118)	mFOlFOX6 (n = 119)	P*
Distant metastasis	15 (12.7)	27 (22.7)	0.044
Liver	6	12	0.433
Others†	9	15	0.555
Lungs	7	10	
Peritoneum	2	3	
Bone	0	1	
Brain	1	1	
Local site relapse	3 (2.5)	4 (3.4)	0.710
Death without relapse	2 (1.7)	3 (2.5)	0.710
Total	20 (16.9)	34 (28.6)	0.033

*Pearson χ^2 test or Fisher exact test was used for categorical variables.

†One patient developed lung metastases and brain metastases at the same time during follow-up.

mFOLFOX6 indicates modified leucovorin, fluorouracil, and oxaliplatin; OCTREE, intraportal chemotherapy (fluorodeoxyuridine and oxaliplatin) plus mFOLFOX6.

$P = 0.016$], corresponding to a 34% relative risk reduction. The 3-year DFS rates were 85.2% (95% CI, 81.9–88.4) for OCTREE treatment and 75.6% (95% CI, 71.7–79.4) for mFOLFOX6 alone (an absolute difference of 9.6%, $P = 0.030$).

Metastasis-free Survival

MFS was measured from randomization to metastasis, if metastases were the first events, and was a secondary endpoint of this study and exhibited similar results with those for DFS. As seen in Table 4, further analysis of the total relapse events indicated that 42 patients developed distant metastasis, which accounted for 77.8% of the total events. When comparing the distant metastases events between the 2 treatment arms, there was an obvious decrease in the OCTREE arm (12.7%) versus the control arm (22.7%) ($P = 0.044$). However, the local site recurrence and nontumor death events did not differ between 2 arms ($P = 0.710$, Table 4). In addition, patients in OCTREE arm experienced an improved survival than those in the control arm in terms of MFS (3-year survival, 87.6% vs 78.0%; $P = 0.035$); the HR for OCTREE versus mFOLFOX6 was 0.59 (95% CI, 0.38–0.92, $P = 0.023$) (Fig. 2B).

Overall Survival

At the time of analysis, 38 patients (16%) died during the follow-up period, including 15 for OCTREE treatment and 23 for mFOLFOX6 alone. No significant differences were observed between the 2 arms; the HR was 0.33 (95% CI, 0.182–1.231; $P = 0.186$; see Supplemental Digital Content Fig. 2, available at http://links.lww.com/SLA/A819). These data for survival were immature and further analysis of 5-year survival will be provided in the future.[14,15]

Subgroup Analysis

To observe which population would derive more benefit from OCTREE therapy, a subgroup analysis (stratifying for PTNM (pathologic TNM staging): stage II or stage III) was performed. We analyzed and compared patients with stage II and stage III disease separately. The data showed that patients for OCTREE treatment experienced improved survival than those for mFOLFOX6 alone with respect to DFS (3-year survival, 81.2% vs 69.4%; HR, 0.63; 95% CI, 0.40–0.92; $P = 0.022$; Fig. 3A) and MFS (3-year survival, 83.7% vs 70.8%; HR, 0.56; 95% CI, 0.39–0.93; $P = 0.037$; Fig. 3B), but there were no significant differences in the stage II patients with respect to DFS and MFS (Fig. 3).

DISCUSSION

AC has been well established as the standard treatment of high-risk CRC after radical surgery. The efficacy and safety of oxaliplatin-based regimens have been verified in some large, randomized, phase III trials, which demonstrated that these regimens are superior to fluorouracil plus leucovorin alone.[16–19] However, the optimal time to initiate AC after radical surgery in colon cancer patients is not clear. There are some substantial researches that support to initiate adjuvant treatment promptly after radical surgery. The increase in metastatic growth is correlated with the surgical procedure. For example, during primary tumor resection, improper handling of primary tumors may occasionally result in tumor cells shedding into the blood and increase the risk of hematogenous metastases.[20,21] In addition, after surgical resection of the primary tumor, it was shown that reduced angiogenesis inhibitors, such as angiostatin,[22,23] and enhanced production of oncogenic growth factors could increase tumor growth.[24,25] Therefore, these studies indicated that chemotherapy initiated promptly is most effective after resection of primary tumor, when patients' tumor burden is at a low level. However, systemic AC starting therapy too early may increase chemotherapy-related toxicity and affect postoperative recovery.

In this study, we performed a new regimen for stage II or stage III colon cancer using OCTREE, including intraoperative IPC and postoperative AC, which has never been reported. The tumor-killing effect on residual tumor cell is depending on the local concentration of chemotherapy drugs in target organ. This effect can be increased in 10-fold when the local drug concentration doubles.[26] In addition, the micrometastases foci originate from residual tumor cell deposits that are not big enough to be detected during surgical resection of the primary cancer, which are the major targets of OCTREE regimen.[27] For these reasons, IPC is an effective manner to increase the local concentration of the chemotherapy drugs. Also, IPC is started at the time of operation just after radical resection of colon cancer when circulation tumor burden is low, which will eradicate microscopic tumor cell deposits in a certain proportion of patients who are at risk of developing cancer recurrence.

Our trial tested the efficacy of adjuvant treatment with IPC administered during surgery plus AC (mFOLFOX6). Compared to most previous studies of adjuvant treatment of colon cancer with oxaliplatin regimen,[16–19] DFS in the control arm of our study existed in the highest range of these studies. The improved DFS in patients who received OCTREE regimen (IPC plus mFLFOX6) corresponds to a 34% risk reduction of tumor recurrence. In addition, in subgroup analysis, we observed that stage III patients may benefit from OCTREE regimen, whereas no significant benefit was observed for stage II patients, consistent with previous findings in studies of the oxaliplatin-based regimen.[28,29] However, these subgroup analyses should be cautiously considered owing to the limited number of patients.

Interestingly, the distant metastasis accounted for 77.8% of the total relapse events in this study, and there was an obvious decrease in the OCTREE arm versus the control arm. However, the local site relapse exhibited no significant difference between the 2 arms. Combined with the improved MFS for OCTREE treatment, the data indicate that the effect of OCTREE regimen on improved DFS was mainly due to the systemic efficacy of IPC plus AC, which leads to reduction of all kinds of distant metastasis events (liver metastases and other extrahepatic metastases).

In previous studies,[26] 5-fluorouracil was commonly administered alone, whereas the fluorodeoxyuridine used in our study was suitable for local use, especially administrated with oxaliplatin, which has confirmed effect on CRC liver metastasis.[30] In our study,

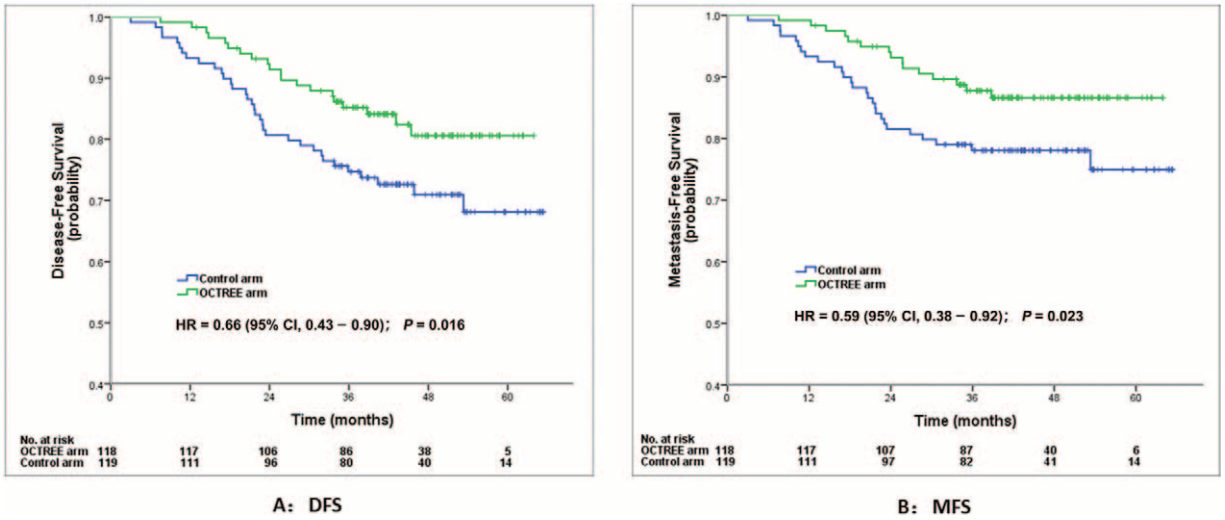

FIGURE 2. A, Disease-free survival curves and (B) Kaplan-Meier metastasis-free survival for the intent-to-treat population in the OCTREE arm and mFOLFOX6 alone arms.

the dose of chemotherapy drugs used for IPC was only a half dose of standard systemic AC. IPC is characterized by low-dose administration but can obtain high local drug concentration in the blood. The results showed that intraoperative IPC neither prolonged hospitalization after surgery nor resulted in significant surgical complications. Furthermore, no IPC-related death was observed, and patients receiving first circle of AC for more than 4 weeks did not increase significantly in OCTREE arm. These data indicate that IPC administered during surgery did not delay recovery or disturb the implementation of postoperative AC in patients after surgery. The incidence of all-grade toxicities was higher in the OCTREE arm within 2 weeks after surgery, but these cases of toxicity could be managed conservatively without severe clinical complications. During the period of AC, our data indicated that the OCTREE regimen exhibited similar toxicity events and safety profiles as mFOLFOX6 alone,which is consistent with the report of an Asian study.[31]

The effect of the traditional IPC with 5-fluorouracil alone after surgery (without any other AC) on CRC has been well researched. These large-scale trials indicated that the possible increase in survival from 5-fluorouracil-based IPC seemed to be less.[32,33] In contrast with the aforementioned studies, our study is the first report that confirmed the efficacy and safety of oxaliplatin-based adjuvant treatment, which combined intraoperative IPC with standard AC. Moreover, the data on the combination of IPC with systemic AC were limited until now. Labianca et al[12] had compared the efficacy of adjuvant 5-fluorouracil-based chemotherapy through 3 different routes of administration. 5-fluorouracil was delivered directly into the portal vein (IP), intravenously (SY), and a combination of both routes (IP + SY). The results show that the 3 routes have similar efficacy. When compared with our study, the differences of chemotherapy regimen, administrating time, and delivery modes of IPC plus AC may be some of the reasons that lead to different results. In

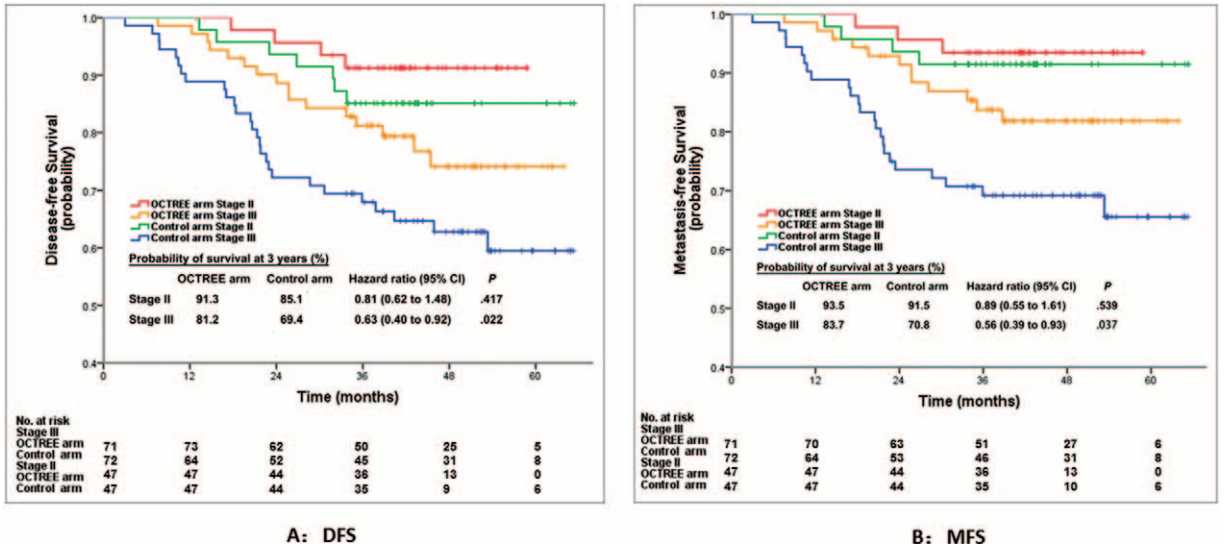

FIGURE 3. Subgroup analysis for patients with stage II and stage III disease. (A) Disease-free survival curves and (B) Kaplan-Meier metastasis-free survival for the intent-to-treat population in the OCTREE arm and mFOLFOX6 alone arms.

addition, the negative results may be due to the design of this multicenter study itself. Only 66% of patients in these 3 groups completed the established treatment plan as initially designed, and the use of ITT analysis may weaken the significant efficacy of the IP + SY regimen, compared with the other 2 groups. The average age of population was 65 years; nearly 30% patients were older than 70 years. The elderly patients had poor prognosis and a worse response to chemotherapy than younger patients,[17] which may also influence the detection of difference in 3 groups.

The follow-up result of our study demonstrated that chemotherapy initiated during operation by way of IPC combined with mFOLFOX6 was a safe and effective method to reduce the occurrence of distant metastasis and, therefore, significantly improves DFS in patients with stage III colon cancer. However, our study has some limitations, including the limited number of patients and the short follow-up period, and the 5-year overall survival rate has not been reached.

CONCLUSIONS

Although the relative importance of OCTREE regimen remains to be determined, the early results suggest that this treatment may represent one among several other promising regimens that contribute to further improving survival in colon cancer.

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