Preoperative Chemotherapy with Bevacizumab Extends Disease-free Survival After Resection of Liver Metastases from Colorectal Cancer

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Abstract. *Background: The benefit of preoperative chemotherapy for patients with liver metastases from colorectal cancer remains unclear. We evaluated the efficacy of preoperative chemotherapy with bevacizumab in such patients, and attempted to identify clinical predictors of recurrence. Patients and Methods: Between February 2007 and December 2013, a total of 65 liver resections for colorectal metastases were performed at our Institution; 47 patients underwent preoperative chemotherapy, which consisted of modified FOLFOX6 (mFOLFOX6) in 42 cases. The last clinical follow-up was in December 2014. Demographic and clinico-pathological factors were reviewed for each patient, and potential predictors of recurrence after liver resection were evaluated. Disease-free survival (DFS) and overall survival (OS) were compared with respect to clinicopathological factors. Results: The 3- and 5-year OS rates were 73.9% and 62.5%, respectively. The time at which metastases appeared, and the extent of metastasis according to the Japanese classification did not significantly affect OS or DFS. However, mFOLFOX6 plus bevacizumab significantly improved DFS compared to mFOLFOX6 alone. Patients did not experience worsening of hepatic dysfunction during preoperative chemotherapy, and tolerated surgical stress well. Conclusion: Preoperative chemotherapy with bevacizumab appears to be an effective treatment modality for liver metastases from colorectal cancer, and results in prolonged DFS.*

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Liver metastases from colorectal cancer remains one of the significant prognostic factors for treatment outcome. Approximately 50% of patients with colorectal cancer develop liver metastases during the course of their disease, and surgical resection is currently considered the only potentially curative option. Following resection, the 5-year overall survival (OS) rates have been reported to be 50-55% in several recent studies (1-3). These favorable outcomes are attributed to advances in chemotherapy protocols, surgical techniques, and perioperative management. In particular, perioperative chemotherapy plays a pivotal role in multidisciplinary therapy for liver metastases. Nordlinger *et al*. showed that perioperative chemotherapy with oxaliplatin, folinic acid and 5-fluorouracil (FOLFOX4) reduced the risk of events that reduced the 3-year progression-free survival (PFS) rate by approximately 25% in patients with resectable liver metastases (4). However, the optimal timing of chemotherapy with respect to liver resection has not yet been determined. Preoperative administration of chemotherapy has a number of potential advantages. Firstly, it may down-size the tumor and increase the probability of curative resection. Secondly, it may allow for previously unresectable tumors to become resectable. Thirdly, it may help identify responders amongst patients who are at high risk of recurrence so that postoperative medication can be optimized and individualized. Fourthly, in patients with multiple tumors, chemotherapy may reveal particular biological behaviors and hence identify non-responders who may not benefit from resection. Even in patients whose disease is considered resectable, preoperative chemotherapy may treat micrometastatic disease, and hence prevent recurrences that can arise from microscopic residual disease after surgery.

Bevacizumab, a monoclonal humanized antibody directed against vascular endothelial growth factor (VEGF), was initially approved by the U.S. Food and Drug Administration

Table I. *The patient characteristics and perioperative factors between the modified FOLFOX6 (mFOLFOX6) and mFOLFOX6+Bevacizumab (Bev) groups.*

		Preoperative chemotherapy		
		mFOLFOX (n=15)	mFOLFOX+Bev (n=27)	*p*-Value
Age, years	Median (interquartile range)	57 (54-70)	63 (56-67)	0.63
Gender	Male, n (%)	9 (60.0)	13 (48.1)	0.46
	Female, n (%)	6 (40.0)	14 (51.9)	
Grade	A, n (%)	11 (73.3)	16 (59.3)	0.36
	B+C, n (%)	4 (26.7)	11 (40.7)	
RECIST	CR+PR, n (%)	7 (46.7)	15 (55.6)	0.58
	SD+PD, n (%)	8 (53.3)	12 (44.4)	
Operative times (×10 minutes)	Median (interquartile range)	23.2 (16.6-27.7)	22.9 (16.4-29.3)	0.91
Blood loss (×100 g)	Median (interquartile range)	5.8 (4.3-10.4)	5.1 (3.5-14.3)	0.89
Postoperative chemotherapy	Yes, n (%)	5 (33.3)	8 (29.6)	0.8
	No, n (%)	10 (66.7)	19 (70.4)	

RECIST: Response Evaluation Criteria in Solid Tumors, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

in 2004 for the first-line treatment of metastatic colorectal cancer based on its survival benefit (5-7). It has been increasingly used in combination with chemotherapy before hepatic resection in patients with colorectal liver metastasis (8-10), despite no proven benefit. Hence, there is an urgent need to clarify whether preoperative treatment with bevacizumab combined with cytotoxic agents can improve the outcome in these cases.

In the current study, we analyzed the outcomes in patients who underwent modified FOLFOX6 (mFOLFOX6)-based chemotherapy administered before hepatic resection in order to identify clinical prognostic predictors. We also evaluated the efficacy of combined preoperative bevacizumab and cytotoxic agent administration.

Patients and Methods

The study was performed in accordance with the Helsinki Declaration of the World Medical Association. To meet our criteria of liver resection for colorectal metastases, patients were required to be between the ages of 18-80 years and to have histologically proven colorectal cancer with a World Health Organization performance status of 2 or less, potentially resectable liver metastases, and no detectable extrahepatic tumors. The primary tumor was required to have been previously resected (R0 resection). Clinical examination, chest radiography, an abdominal-pelvic computed tomographic (CT) scan with contrast medium or magnetic resonance imaging (MRI), electrocardiography, and a standard laboratory work-up were performed within 14 days before surgery. Written informed consent was obtained from all patients before the procedure.

In the case of a solitary tumor less than 2 cm in size and located on the surface of the liver, we selected upfront surgery without preoperative chemotherapy. Otherwise, preoperative mFOLFOX6 consisted of six 14-day cycles of oxaliplatin (85 mg/m^2), folinic acid (L form; 200 mg/m^2) on day 1, and fluorouracil (400 mg/m^2 bolus and 2,400 mg/m^2 46 h continuous infusion). Bevacizumab (5 mg/m^2) was administered on day 1 in the mFOLFOX6 plus bevacizumab (mFOLFOX+Bev) group. Operations were performed 6 weeks after the last administration of chemotherapy.

We reviewed the demographic and clinicopathological factors for each patient, including age, sex, and grade classification for colorectal cancer liver metastasis based on the extent of metastasis plus the status of the nodal involvement of the primary tumor according to Japanese Classification of Colorectal Carcinoma (JCCRC) (11). We also evaluated the neutrophil-to-lymphocyte ratio (NLR), carcinoembryonic antigen level before hepatic resection, response according to the Response Evaluation Criteria in Solid Tumors (RECIST) (12), type of hepatic resection, operative time, blood loss, postoperative hospital stay, and postoperative chemotherapy. Disease-free survival (DFS) and OS were calculated from the date of surgery to the diagnosis of progressive disease or death, or else the most recent follow-up visit.

Differences between the mFOLFOX6 and mFOLFOX6+Bev groups were analyzed by univariate analysis using the Mann-Whitney *U*-test for patient age, operating time, and blood loss; and the chi-square test for sex, grade, RECIST, and postoperative chemotherapy. Patient survival curves were plotted using the Kaplan–Meier method, and the differences between groups were analyzed using the log-rank test. A two-sided *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using IBM SPSS 21.0 statistical software (IBM, Armonk, NY, USA). Data from the statistical analysis are presented as the median and interquartile range.

Results

Between February 2007 and December 2013, a total of 65 liver resections for colorectal metastases were performed at our Institution. The last clinical follow-up was in December 2014. Preoperative chemotherapy was administered to 48 patients, 42 of whom were treated with mFOLFOX6-based preoperative chemotherapy. The mFOLFOX6+Bev group comprised 27 patients who were administered bevacizumab

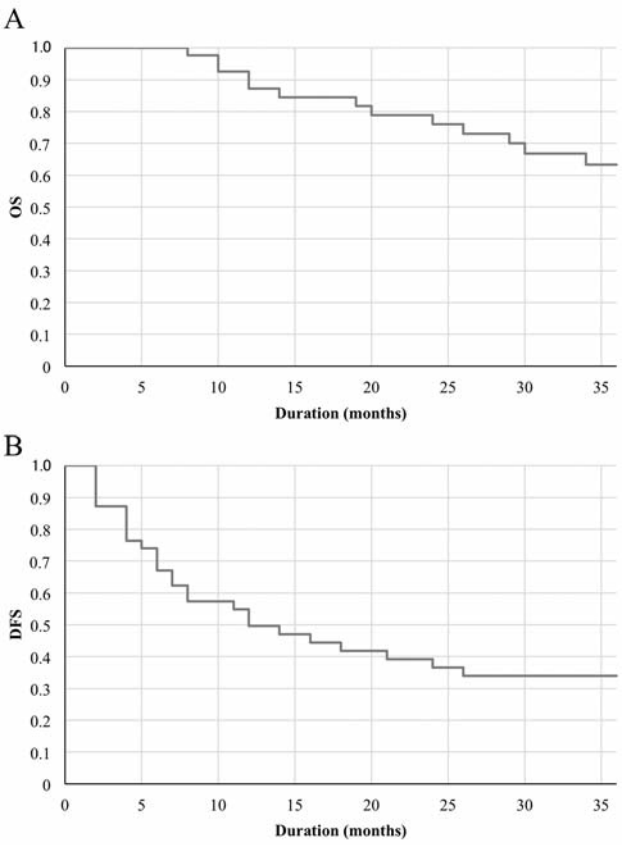

Figure 1. *Three-year overall survival (OS) (A) and disease-free survival (DFS) (B) in the preoperative chemotherapy group.*

in combination with cytotoxic agents, and the remaining 15 patients (the mFOLFOX6 group) were treated without bevacizumab. Although progressive disease was observed in three out of 47 patients (6.4%) who received preoperative chemotherapy, all of these patients were still able to undergo resection of metastases. During the observation period, 28 out of 48 patients experienced disease recurrence after liver resection. In 17 cases, we selected upfront surgery without preoperative chemotherapy. We performed R0 resection for all cases, and there were no major complications.

In the whole patient cohort, including those who underwent preoperative chemotherapy and upfront surgery, the 3-year OS rate was 73.9% (by JCCRC grade classification for liver metastasis: grade A: 81.8%, grade B: 77.8%, and grade C: 0%), and the 5-year OS rate was 62.5%.

There were no statistical differences in the profile and perioperative factors between the preoperative chemotherapy group and the upfront surgery group. All patients who underwent upfront surgery survived for at least 3 years after resection. The response rate, which included complete response and partial response to preoperative chemotherapy, was 46.8%. The baseline tumor and patient characteristics were similar for the recurrence and recurrence-free group, and there were no statistical differences in the patient characteristics and perioperative factors between the mFOLFOX6 and mFOLFOX6+Bev groups (Table I).

The 3-year OS and DFS rates in the preoperative chemotherapy group were 63.3% and 33.9%, respectively (Figure 1). Although OS and DFS did not differ significantly between patients with respect to the time at which metastases appeared or grade classification for liver metastasis of colorectal cancer according to the JCCRC (Figure 2), DFS was significantly longer after mFOLFOX6+Bev therapy compared to mFOLFOX6 therapy alone (p=0.015) (Figure 3).

Finally, multivariate analysis revealed no statistical differences between risk factors for recurrence (Table II).

Discussion

In the current study, preoperative mFOLFOX6 with bevacizumab significantly improved DFS compared to mFOLFOX6 alone. The basis for this improved efficacy is unclear. However, the importance of the morphological response to chemotherapy, in which metastases change from heterogeneous masses with ill-defined margins into homogeneous, hypo-attenuating lesions with sharp borders, has recently been addressed (13). The RECIST guideline has proven to be useful in evaluating the response to chemotherapy. However, this size-based evaluation method is not predictive of residual viable burden in regression analyses (14); indeed, RECIST was not associated with survival after bevacizumab administration in our study. Shindoh *et al*. reported that the CT morphological response to preoperative chemotherapy is a good predictor of long-term outcomes after surgery in patients treated with or without bevacizumab (15). An optimal morphological response was associated with high 5-year OS and DFS rates of 74% and 47%, respectively, and was observed in 47% of patients treated with bevacizumab and 12% of patients treated without bevacizumab in their report. We observed this response in 57.1% of the mFOLFOX6+Bev group and 28.6% of the mFOLFOX6 group. It is, therefore, possible that preoperative chemotherapy with bevacizumab induced a morphological tumor response in our patients, which in turn improved DFS rates in the current study.

Furthermore, pathological tumor response after bevacizumab administration was recently recognized as an important prognostic factor. Ribero *et al*. reported that the addition of bevacizumab to fluoropyrimidine and oxaliplatin-based chemotherapy improved pathological response in patients with metastatic colorectal cancer (16). Moreover, Klinger *et al*. found that the histological response based on tumor regression grades was related to patient outcomes, and bevacizumab significantly increased tumor regression after chemotherapy (17).

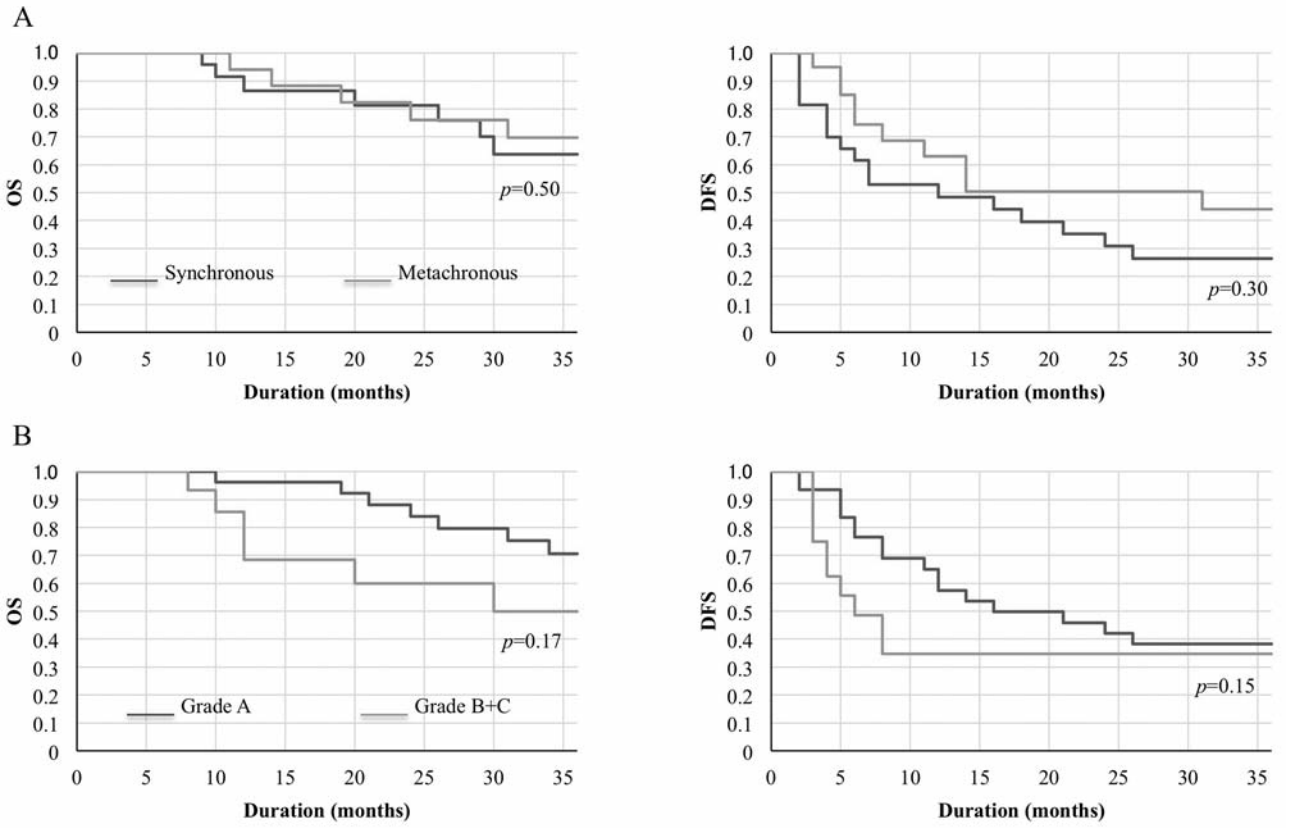

Figure 2. *Overall survival (OS) and disease-free survival (DFS) according to the time at which metastases appeared (A), and the extent of metastasis according to the Japanese classification (B).*

Table II. *Multivariate analysis of the risk factors for recurrence.*

Factor	Odds ratio	95% CI	*p*-Value
Occurrence of metastases: Synchronous *vs*. metachronous	1.4	0.3-5.6	0.67
Grade: A *vs*. B+C	0.4	0.1-1.9	0.24
Preoperative administration of bevacizumab: Yes vs.no	3.5	0.8-16.3	0.11
RECIST: CR+PR *vs*. SD+PD	2.4	0.6-9.8	0.21
NLR: >2.0 *vs*. <2.0	1.7	0.2-2.5	0.52
Postoperative chemotherapy: Yes *vs*. no	1.1	0.4-6.9	0.48

NLR: Neutrophil-to-lymphocyte ratio, 95%CI: 95% confidence interval.

The explanations for CT morphological changes and pathological responses after bevacizumab administration continue to be debated, and may relate to the mode of action of this antibody. When combined with cytotoxic chemotherapy, bevacizumab normalizes tumor vasculature and decreases intra-tumoral pressure, which subsequently leads to the increased delivery of chemotherapeutic agents to the tumor cells (18, 19). Moreover, bevacizumab predominantly leads to an overgrowth of fibrosis at the expense of viable tumor cells (20, 21). Taken together, these events can lead to specific morphological and pathological changes, rather than further tumor shrinkage.

The oxaliplatin associated sinusoidal obstruction syndrome (SOS) usually results in a bluish discoloration and spongiform consistency of the liver. Pathologically, this syndrome is characterized by hepatic sinusoidal dilatation, hepatocyte atrophy, perisinusoidal fibrosis, and nodular regenerative hyperplasia. The presence of SOS is also

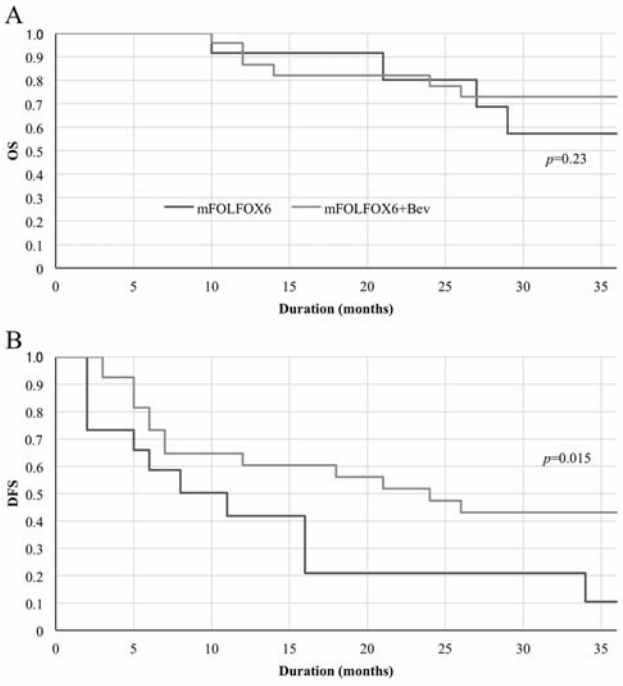

Figure 3. *Overall survival (OS) (A) and disease-free survival (DFS) (B) in the modified FOLFOX6 (mFOLFOX6) plus bevacizumab (mFOLFOX6+Bev) and mFOLFOX6 groups.*

associated with increased transfusion requirements and higher complication rates after major hepatectomy (22). Recent studies have demonstrated a relationship between SOS and early recurrence, including poorer long-term survival, and, in particular, an increased risk of intrahepatic recurrence (23, 24). The molecular pathogenesis of SOS has been studied, and a recent examination of gene-expression changes using microarray technology revealed a number of key processes that may be involved in this process. These include activation of the interleukin 6/ signal transducer and activator of transcription 3 pathway and coagulation system with the overexpression of plasminogen activator inhibitor-1 and von Willebrand factor, and up-regulation of extracellular matrix remodeling proteins (25, 26). An increased expression of VEGF was also reported in experimental SOS models (26). The blockade of VEGF possibly reduces these changes, thus attenuating the progression of SOS. Klinger *et al*. reported that bevacizumab administration can protect against SOS, and bevacizumab correspondingly reduced the pathological changes associated with this syndrome (17). In this study, we likewise found no cases of progression of hepatic dysfunction during preoperative chemotherapy, and patients tolerated the surgical stresses well. We also did not observe a bluish liver at laparotomy in any of the patients in the FOLFOX+Bev group, and we therefore suggest that approximately six preoperative courses of mFOLFOX6+Bev are acceptable for liver surgery for colorectal liver metastases.

In the current study, we found no significant improvement in OS in patients treated with mFOLFOX6+Bev compared to those treated with mFOLFOX6 alone. Nevertheless, the observed increase in DFS was encouraging. The 3-year observation period in this study may be too short for statistical analysis, and we should continue to follow-up these patients. Our study also had several important limitations; it was a retrospective study of a small number of patients, and selection bias may have potentially affected our results. Our findings should thus be confirmed in prospective clinical trials.

In conclusion, preoperative chemotherapy with bevacizumab appears to be an effective treatment modality for treating liver metastases from colorectal cancer, and its administration significantly extends DFS.

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