Liver Resectability of Advanced Liver-limited Colorectal Liver Metastases Following mFOLFOX6 with Bevacizumab (KSCC0802 Study)

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Abstract. *Background/Aim: The Kyushu Study group of Clinical Cancer (KSCC) conducted phase II trials (KSCC0802 - UMIN000001308) concerning liver resectability after first-line treatment of advanced liver-limited colorectal metastases (CRLM) by a prospective, multi-center study. Patients and Methods: Patients received 6 cycles of mFOLFOX6 with bevacizumab followed by evaluating liver resectability. The primary end-point was liver resection rate. Results: The 40 patients enrolled from September 2008 to August 2010. The median number of administration cycles was 6 (range=1-7). The liver resectability cases were 16/40 (40.0 %) and the number of R0 cases was 10 patients (25.0%). An overall response rate was 30.0% (95% CI=15.2%-44.8%). Median progression-free and overall survival of all patients was 9.7 months and 33.0 months), respectively. Conclusion: mFOLFOX6 with bevacizumab regimen is safe and effective for advanced liver-limited CRLM and might lead to high liver resectability.*

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Key Words: Colorectal liver metastases, hepatic resection, chemotherapy, oxaliplatin, fluorouracil, leucovorin, bevacizumab.

Although the liver is most common metastatic organ from colorectal cancer, complete resection rate of colorectal liver metastases (CRLM) has been unsatisfactory due to the greater tumor number and size, complicated tumor location or the presence of extrahepatic metastases. According to the nation-wide registration database maintained by the Japanese Society for Cancer of the Colon and Rectum (JSCCR), the incidences of

Abbreviations: CRLM, Colorectal liver metastases; JSCCR, Japanese Society for Cancer of the Colon and Rectum; 5-FU, 5-fluorouracil; FOLFOX, Folinic acid, 5-fluorouracil and oxaliplatin; EGFR, epidermal growth factor receptor; KSCC, Kyushu Study group of Clinical Cancer; university hospital medical information (UMIN); ECOG, Eastern Cooperative Oncology Group; PS, performance status; PFS, progression-free survival; OS, overall survival; RR, response rate; RECIST, Response Evaluation Criteria In Solid Tumors; CT, computed tomography; MRI, magnetic resonance imaging, CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CTCAE, Common Terminology Criteria for Adverse Events; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; MST, median survival time; CI, confidence interval.

CRLM were 10.7% of synchronous metastases and 7.1% of the first metachronous metastases (1). The goal of treatment for CRLM patients depends on the initial resectability of the metastases and, according to most known treatment guidelines and algorithms, patients may be categorized in accordance with whether they have 'upfront' resectable metastases, borderline resectable metastases or unresectable disease (2). When complete resection was performed successfully for patients with liver-limited CRLM, a 5-year survival of 40% to 50% could be achieved (3-6). However even for curatively resected patients, the recurrence was frequently observed without perioperative modern chemotherapy.

Folinic acid, 5-fluorouracil (5-FU) and oxaliplatin (FOLFOX) is one of the standard chemotherapy for the patients with advanced CRLM. The mFOLFOX6 regimen can lead to tumors being downstaged in some patients with initially unresectable CRLM and, in a previous study, has allowed hepatic resection in 16-38% of the patients (6). A phase III study of the European Organization for the Research and Treatment of Cancer (EORTC), intergroup Trial 40983, identified that perioperative chemotherapy with FOLFOX4 improved progression-free survival (PFS) after hepatic resection of initially resectable CRLM (7). In recent years, great anti-tumor effects have been demonstrated with targeted agents, such as bevacizumab (anti-vascular endothelial growth factor (VEGF) antibody) or anti-EGFR (anti-epidermal growth factor receptor) antibody. Additional use of bevacizumab on chemotherapy for CRLM can result to increased response rate, prolonged progression-free and overall survival and decreased blue liver (8,9). In Japan, there have been few data concerning liver resectability following mFOLFOX6 with bevacizumab as the first-line treatment of non-resectable liver-limited CRLM.

It is quite difficult to divide CRLM patients to be initially resectable or unresectable, especially in a multi-center study. Limitations of hepatic resection or resection skills are different by each center. Therefore, in the present study, we decided to select H-factor categories according to the issues by JSCCR; H1, four or less metastases with the largest diameter being 5 cm or less; H2, other than H1 or H3; H3, five or more metastases with the largest diameter being more than 5 cm (10). Patients with H2 and H3 have been reported to have significantly poor prognosis compared to H1 (3, 11). The aim of this prospective multicenter study was to evaluate the resectability and safety of mFOLFOX6 plus bevacizumab on H2 and H3 liver-limited CRLM.

Patients and Methods

H2 or H3 liver-limited CRLM patients were enrolled to a multicenter phase II trial of Kyushu Study group of Clinical Cancer (KSCC) 0802 study. The study was registered with a national review board; university hospital medical information (UMIN) 000001308. Institutional Review Board (IRB) approval was obtained from all institutions participating in this study. Written informed consent was obtained from all patients prior to enrollment.

Eligibility criteria. Patients with histologically proven colorectal cancer and at least one measurable lesion in the liver (with no non-hepatic distal metastasis/relapse) were eligible for this study if they met all of the following criteria: H2 or H3 CRLM (either synchronous or metachronous); age ≥20 and ≤ 75 years; no prior chemotherapy except adjuvant chemotherapy if ended ≥6 months before study entry; no prior radiotherapy for advanced/recurrent colorectal cancer; Eastern Cooperative Oncology Group performance status (PS) 0 to 1; life expectancy estimated ≥ 3 months; adequate bone marrow and renal function.

Study design. This is a single-arm study based on the Southwest Oncology Group (SWOG's) standard two-stage design. Assuming null and alternative liver resection rates as 20% and 40%, respectively, 35 patients would be required to achieve 80% power at binomial test with one-sided alpha <0.05. To allow for a 10% drop-out, the number of patients was set to 39. After examining the primary endpoint of the first 20 patients in the first stage, the study was planned to stop if less than 3 patients of liver had been resectable because of low expectation to achieve the alternative liver resection rate. After the second stage, the null liver resection rate was tested for all patients eligible for the analysis.

In principle, 5 cycles of preoperative chemotherapy (mFOLFOX6: oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2 d1 followed by 400 mg/m^2 bolus 5-FU and a 46-h 2,400 mg/m^2 5-FU infusion every 2 weeks+bevacizumab (5 mg/kg)) was administered within 2 weeks after enrollment. Patients who appeared to be amenable to curative resection after completion of mFOLFOX6+bevacizumab received 1 cycle of mFOLFOX6, in principle, and then underwent liver resection after additional reassessment of liver resectability. Liver resection should be performed between 6 and 9 weeks after the final use of bevacizumab and at least 2 weeks after the final use of mFOLFOX6.

End-points. The primary endpoint was the proportion of patients who underwent liver resection. Secondary endpoints were the percentage of H2 patients and percentage of H3 patients who underwent liver resection, 3-year PFS rate, 3-year overall survival (OS) rate, the objective response rate (RR) according to the

Response Evaluation Criteria In Solid Tumors (RECIST ver. 1.0) criteria (12), safety (adverse events, percentage of patients who completed preoperative chemotherapy, incidence of liver disorder, incidence of postoperative complication, postoperative duration of hospital stay), percentage of R0 resection and histological response. The operative indication was decided according to the policy of each institution.

Assessment of efficacy and adverse events of chemotherapy. During protocol treatment, computed tomography (CT) or magnetic resonance imaging (MRI) and tumor markers (CEA and CA19-9) were basically performed every month. A physical examination, blood counts and blood chemistry were performed at every cycle. Patients were assessed before starting and at each 2-week cycle according to the National Cancer Institute-Common Toxicity Criteria (CTCAE ver. 3) (13).

Liver resection. After 5 cycles of preoperative mFOLFOX6+ bevacizumab, surgical resection in curative intent must be performed as soon as possible after 1 cycle of additional mFOLFOX6. After recognition of enough function of the future liver remnant, hepatic resection was conducted. The operative procedure, as to whether anatomical or non-anatomical hepatic resection is performed, is not instructed and is decided by each surgeon. Treatment of the disappeared lesions is not provided and observation of such lesions is acceptable. Preoperative portal vein embolization was authorized to this study but concomitant use of intraoperative radiofrequency ablation or two-stage hepatectomy was prohibited.

Pathological effects. The pathological response was depended on the criteria of JSCCR (10) as follows: grade 0: with no necrosis or cellular or structural change; grade 1a: with necrosis or disappearance of tumor in <1/3 of the entire tumor; grade 1b: with necrosis or disappearance of the tumor in <2/3 of the entire tumor; grade 2: with necrosis or disappearance of the tumor in >2/3 of the entire tumor but with viable tumor cells remaining; and grade 3: with the entire tumor presenting necrosis and/or fibrosis and no viable tumor cells identified.

Follow-up. Subsequent therapy, unless decided by each clinician, after this experimental treatment is not stipulated regardless of hepatic resection. As a rule, we followed-up patients by screening of metastases or recurrence with CT or MRI and tumor markers at a 3-month 1-year and 3-year period. The survival and recurrence was estimated every 6 or 12 months.

Statistical considerations. One-sided test on the liver resection rate was conducted with the binomial test. The confidence interval (CI) for the proportion was estimated by the exact method. The duration of survival was measured from the day of entry into the study. PFS and OS were calculated by using the Kaplan-Meier method and were compared by using the log-rank test. All statistical analyses were performed with the Stata version 12 (Stata Corp., College Station, TX, USA). A two sided $p<0.05$ was considered as statistically significant, except at the test of the primary endpoint which adopted one-sided test.

Results

Patients' characteristics. From May 2008 to April 2010, a total of 40 patients with H2 or H3 liver-limited CRLM were enrolled in the study from 19 Institutions. No patients were declared ineligible. The patients' characteristics at study entry are shown in Table I. There were 30 patients for H2 and 10 for H3. Median size and number of CRLM were 52.5 and 5 mm, respectively. The median number of cycles of chemotherapy was 6 (range=1-7).

Table I. *Patients' characteristics at study entry.*

Parameter	No. of patients	%
Age (years)		
median (range)	63 (37-74)	
M/F		
Male	29	72.5
Female	11	27.5
Performance status (ECOG)		
0	38	95.0
1	2	5.0
Primary tumor sites		
Colon	25	62.5
Rectum	15	37.5
Unknown	0	0
Primary lesion		
Yes	35	87.5
No	5	12.5
lymph node		
NX	3	7.5
N0	8	20.0
N1	16	40.0
N2	12	30.0
N3	1	2.5
Histology of primary tumor		
Adenocarcinoma		
Well	13	32.5
Moderately	24	60.0
Poorly	1	2.5
Mucinous carcinoma	0	0
Others	1	2.5
Liver metastatic lesion		
tumor size (range)	52.5 (10-135)	
number of liver metastases (range)	5 (1-20)	
Extent of liver metastatic lesion		
H2	30	75.0
H3	10	25.0
Bilateral lobe/unilateral lobe		
Bilateral lobe	28	70.0
Unilateral lobe	12	30.0
Synchronous/metachronous		
Synchronous	33	85.5
Metachronous	7	17.5
Postoperative complication		
Yes	5	25.0
No	15	75.0
Adjuvant therapy		
Yes	4	20.0
No	16	80.0

ECOG, Eastern Cooperative Oncology Group; N and H staging were according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR).

Table II. *Relative dose intensities.*

	n	Median	5%tile	95%tile	mean	SD	min	max
Oxaliplatin	40	90.1	51.8	100.0	82.8	19.7	0.0	100.0
Levofolinate	40	90.1	59.9	100.0	87.1	12.7	52.0	100.6
5-FU (bolus)	40	90.9	54.8	100.0	84.5	15.6	44.3	100.4
5-FU (continuous)	40	90.8	56.7	100.0	85.5	15.0	41.1	100.0
Bevacizumab	40	88.6	47.4	100.0	82.8	17.4	44.8	101.9

5-FU, 5-fluorouracil; SD, standard deviation.

Table III. *Hematologic toxicities (n=40).*

	All grade	%	Grade 3/4	%
White blood cell	25	62.5	4	10.0
Neutrophil	32	80.0	13	32.5
Hemoglobin	31	77.5	0	0
Platelet	13	32.5	0	0
Total bilirubin	7	17.5	0	0
AST	22	55.0	1	2.5
ALT	17	42.5	0	0
ALP	27	67.5	1	2.5
Creatinine	3	7.5	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Table IV. *Non-hematologic toxicities (n=40).*

	All grades	%	Grade3/4	%
Pyrexia	5	12.5	0	0
Febrile neutropenia	3	7.5	2	5.0
Fatigue/malaise	20	50.0	1	2.5
Diarrhea	8	20.0	1	2.5
Constipation	6	15.0	0	0
Nausea	12	30.0	0	0
Vomiting	5	12.5	0	0
Appetite loss	21	52.5	1	2.5
Alopecia	9	22.5	0	0
Hand and foot syndrome	7	17.5	0	0
Taste alteration (taste disorder)	4	10.0	0	0
Hypersensitivity	3	7.5	0	0
Nerve disorder (CTCAE v3.0)	16	40.0	0	0
Neurological symptom (DEB-NTC)	16	40.0	0	0
Hypertension	9	22.5	0	0
Thrombosis/thrombus/embolism	0	0	0	0
Proteinuria	2	5	0	0
Gastrointestinal hemorrhage	0	0	0	0
Bleeding	1	2.5	0	0
Gastrointestinal perforation	0	0	0	0

CTCAE, Common Terminology Criteria for Adverse Events; DEB-NTC, Neurotoxicity Criteria of Debiopharm.

Liver resection rate (primary end-point). One patient who did not undergo liver resection after laparotomy because no hepatic lesion was detected was excluded from the resected patients. The overall resection rate was 40.0% (16/40) and the percentage of H2 and H3 patients who underwent liver resection was 46.7% (14/30) and 20% (2/10), respectively.

Treatments administered and toxicities. The median relative dose intensities of oxaliplatin, levofolinate, 5-FU (bolus), 5-FU (continuous infusion) and bevacizumab were 90.1%, 90.1%, 90.9%, 90.8% and 95.3%, respectively (Table II). Two patients withdrew before the end of the study due to personal reasons (5%) and five received fewer than six cycles of therapy due to toxicity (12%). The combination of bevacizumab plus mFOLFOX6 was relatively well tolerated (Tables III and IV). The most commonly reported hematological toxicity was neutropenia. Grade 3 and 4 neutropenia were observed in 32.5% of patients, however, febrile neutropenia was rare (5.0%). Serious adverse events (Grade 3 and 4) that may be associated with bevacizumab were nil, including thromboembolic events, hypertension and gastrointestinal hemorrhage and perforation. There was no treatment-related death.

Tumor response. All 40 patients were evaluated for their tumor response. No complete response (CR) was observed. The overall objective RR was 30.0% with a 95% CI from 16.6% to 46.5%. Stable disease (SD) was achieved in 55.0% of patients. The tumor control rate (partial response (PR) + SD) was 85.0%. Only three patients (7.7%) experienced progressive disease (PD) during neoadjuvant therapy.

Progression-free and overall survival. The median potential follow-up time from commencement of treatment was 28.9 months (range=9.9-52.3 months). The starting point to calculate survival was the day of registration to this study. The median PFS of all patients (n=40) was 9.7 months (95% CI=6.2-11.8 months). The estimated 1-, 2- and 3-year PFS

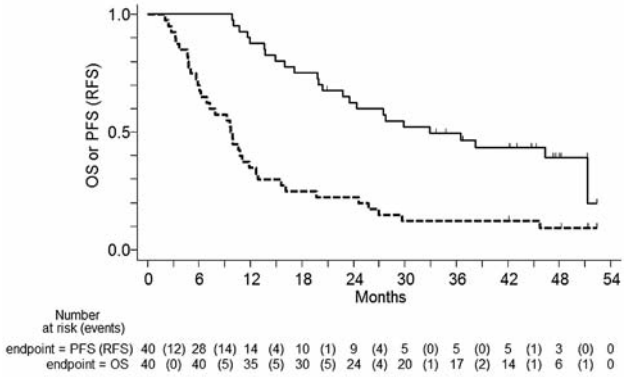

Figure 1. *Cumulative overall survival (OS) and progression-free survival (PFS) rates in all patients with colorectal liver metastases (CRLM). Solid line, OS; dotted line; PFS.*

were 35.0% (95%CI=20.8%-49.6%), 22.5% (95%CI=11.2%-36.3%) and 12.5% (95%CI=4.6%-24.6%), respectively (Figure 1). The median survival time (MST) was 33.0 months (95%CI=22.8 months –not reached). The estimated 1-, 2- and 3-year OS were 87.5% (95%CI=72.5%-94.6%), 62.3% (95%CI=45.4%-75.3%) and 49.3% (95%CI=33.1%-63.7%), respectively (Figure 1).

The cumulative PFS (Figure 2A) and OS (Figure 2B) curve in patients with finally resectable (n=16) and unresectable (n=24) CRLM were investigated. The median PFS was 10.7 months (95%CI=6.9-25.8) and 7.2 months (95%CI=4.6-12.9) in finally resectable and unresectable CRLM, respectively, while the cumulative PFS was equivalent (p=0.21) in the two groups. In contrast MST was longer than 51 months (95%CI=27.8–not reached) and 22.8 months (95%CI=13.7-38.3) in finally resectable and unresectable patients, respectively, whereas the cumulative OS with resectable CRLM was significantly greater than that of CRLM without hepatic resection (p=0.002).

The cumulative PFS (Figure 3A) and OS (Figure 3B) curve in patients with H2 (n=30) and H3 (n=10) CRLM were studied. The median PFS was 10.6 months (95%CI=6.9-16.1) and 6.0 months (95%CI=2.4-9.9) in H2 and H3 patients, respectively, while the cumulative PFS was marginally better (p=0.055) in H2 patients compared to H3 patients. MST was 51.4 months (95%CI=24.4–not reached) and 20.4 months (95%CI=10.0-33.0) in H2 and H3 patients, respectively, whereas the cumulative OS with H2 patients was significantly greater than that of H3 (p=0.015).

Median PFS and OS in patients with responder (n=12) and non-responder (n=28) CRLM, by the RECIST criteria, were equivalent (both, p=0.11); 10.6 months (95%CI=6.2–not reached) and 7.2 (95%CI=4.8-11.0) in PFS compared to not reached (95%CI=19.8–not reached) and 27.5 months (95%CI=17.2-46.4), respectively.

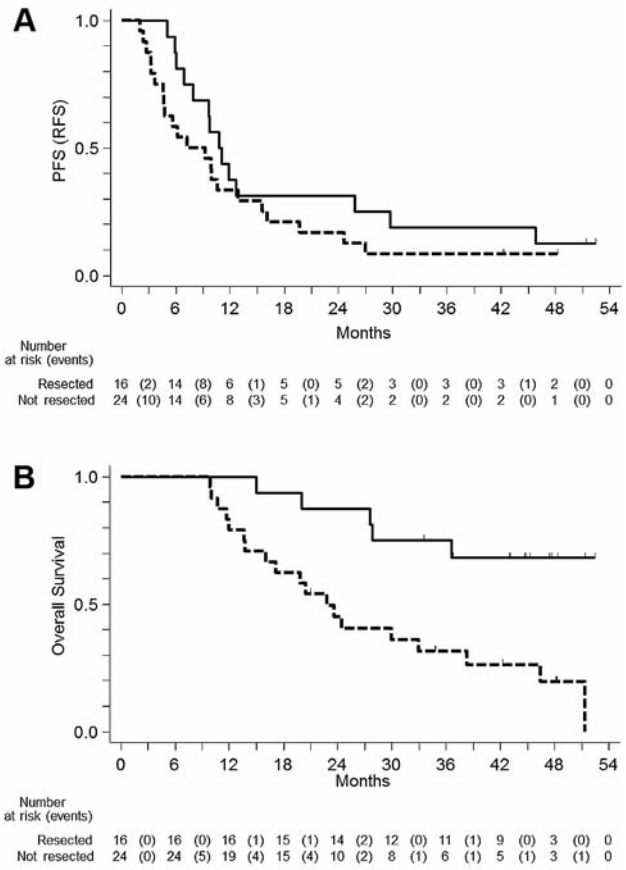

Figure 2. *Cumulative progression-free survival (PFS) (A) and overall survival (OS) (B) curve in patients with initially unresectable liver metastases according to the existence or nonexistence of hepatic resection. Solid line: patients with hepatic resection, dotted line: patients without hepatic resection.*

Intra- and postoperative findings. Hepatic resection was performed solely for all 16 patients without synchronous resection of primary tumor. Hepatectomy included hemi-hepatectomy in 4, sectionectomy in 5 and segmentectomy or partial resection in 7. There were no intraoperative complications. Postoperative complications were observed in 5 patients (31.3%), namely biliary leakage in 2 patients (12.5%), intra-abdominal abscess in 1, wound infection in 1 and wound dehiscence in 1. No patient required further surgery. The median postoperative hospital stay was 18 days (range=9-66). Adjuvant chemotherapy after hepatic resection was performed in 7/16 (44%) of the patients (FOLFOX in 2 patients, FOLFOX+bevacizumab in 2, folinic acid, 5-FU and irinotecan (FOLFIRI)+bevacizumab, uracil and tegafur/leucovorin in 1, and S-1 in 1).

Pathological findings. Histological curability was consisted of R0: 10 (62.5%), R1: 2 (12.5%) and R2: 4 (25.0%). The

degree of pathological response of CRLM was classified as Grade 0 in 1, Grade 1a in 2, Grade 1b in 4, Grade 2 in 7 and no Grade3. Pathological examination of background liver showed sinusoidal obstruction (Rubbia-Brandt Grade≥2) (14) in 2 patients (12.5%) and steatosis in 3 (18.8%).

Discussion

The primary end-point of this clinical study was the percentage of CRLM patients who underwent liver resection. To confirm conversion, the rate of initially unresectable CRLM after induction chemotherapy is a completely fascinating issue. However, in a multi-center study it is difficult to analyze the resectability rate because the resection criteria of each Institute differ. Therefore, we decided to enroll H2 or H3 CRLM patients who had poor surgical outcome compared to H1 (3, 11, 15). It is known that patients in the synchronous group demonstrate significantly lower resection rates compared to the metachronous group (5, 16). In the current study, 33 of the 40 patients (82.5%) had synchronous CRLM. Nevertheless, the resection rates were 46.7% for H2 patients and 20% for H3. A similar multi-center study of preoperative chemotherapy using capecitabine, oxaliplatin (CAPOX) plus bevacizumab for patients with poor-risk liver-only CRLM has been initially introduced (17). Of the 30 initially technically unresectable patients in that study, 12 (40%) were considered potentially suitable for resection. Recently, we have reported that conversion rates in a cohort of initially or marginally unresectable 137 CRLM patients were 54.7% for H2 patients and 18.2% for H3 (18).

According to a consensus statement (19) for downsizing of CRLM, while FOLFOX and FOLFIRI represent two chemotherapy backbones of equivalent efficacy, there is a possibility that the three-drug regimen 5-FU, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) may provide a higher likelihood of a response. Recently FOLFOXIRI plus bevacizumab was introduced in the European Cancer Congress 2013 and updated efficacy/safety findings from a randomized, phase II study in patients with initially unresectable CRLM (OLIVIA study) was demonstrated (20). A total of 80 patients were divided to FOLFOXIRI+ bevacizumab (n=41) and mFOLFOX6+bevacizumab (n=39) group. In the FOLFOXIRI+bevacizumab group, increased resection rate (61% *vs*. 49%) and significantly greater R0 rate (48.8% *vs*. 23.1%, p=0.017) was observed. FOLFOXIRI+bevacizumab may be an extremely promising regimen for unresectable CRLM. To calculate the true conversion rate of unresectable CRLM in the current study, we have performed a central review to assess the resectability by checking paired baseline and post-chemotherapy scans being blinded to patient clinical information like CELIM study (21).

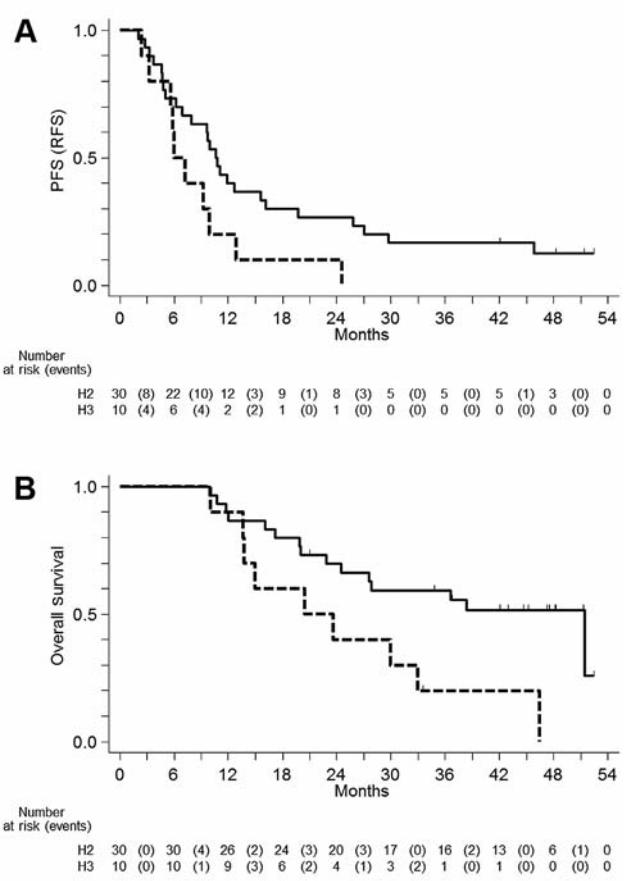

Figure 3. *Cumulative progression-free survival (PFS) (A) and overall survival (OS) (B) curve in patients with H2 and H3 colorectal liver metastases (CRLM). Solid line, H2 CRLM (n=30); dotted line; H3 CRLM (n=10).*

In our study, 40 CRLM patients were safely treated with the preoperative setting of mFOLFOX6 and bevacizumab. The relative doses of the drug administered were satisfactory. Serious adverse events (Grade 3 and 4) were not observed; limited side effects associated with bevacizumab. Maximal 6 courses of FOLFOX and 5 courses of bevacizumab might make this study safer. A total of 6 cycles of preoperative chemotherapy significantly increased the postoperative complication rates (16% to 25%) (7). The incidence rates of biliary fistula or intra-abdominal infection were higher in the patients treated with FOLFOX followed by hepatic resection. In our study, the complication rates were 31.3%, including 2 biliary leakage and 2 infectious complications, however, they were immediately recovered. Median postoperative hospital stay was 18 days enough to the early restart of adjuvant chemotherapy.

In this study, a high disease control rate of 85.0% was obtained, however, the overall objective RR was 30.0%. Bevacizumab can protect against sinusoidal obstruction

syndrome but does not increase the response rate in neoadjuvant XELOX/FOLFOX therapy of CRLM (22, 23). Median PFS and OS in patients with responder and non-responder CRLM were equivalent in our study. In the EORTC 40983 study (7) and in our study PD with RECIST's criteria was observed in 12/182 (7%) and 3/40 (7.5%), respectively. An important finding was the appearance of new intra- and extra-hepatic lesions; it is likely that these new lesions would have occurred immediately after hepatic resection, a presence that might be considered a diagnostic advantage before an unnecessary operation.

Pathological responses to neoadjuvant chemotherapy in CRLM have been shown to correlate with improved survival (24). Bevacizumab in combination with oxaliplatin/fluoropyrimidines was associated with the highest major pathological response rate (25). Extensive pre-operative chemotherapy does not improve the pathological response but can increase the risk for post-operative liver insufficiency (26). In this study, the rate of patients with Grade1b and Grade 2 was 68.8%. Non-invasive CT morphological criteria had also recently been developed that correlated the CT appearances of CRLM after bevacizumab treatment with pathological response and OS (27).

In the present study, pathological sinusoidal obstruction (Rubbia-Brandt Grade≥2) in the background liver was demonstrated only in 2 patients (12.5%) and steatosis in 3 (18.8%). Concomitant use of bevacizumab and oxaliplatin can decrease sinusoidal obstruction (23, 28). We have reported that splenic volume enlargement might be a useful indicator for the protective effect of bevacizumab against oxaliplatin-induced sinusoidal obstruction (28). The presence of sinusoidal obstruction has been shown to impair hepatic regeneration in a rat model (29). Furthermore, sinusoidal obstruction was reported to result in poor recurrent-free and overall survival (30). According to these viewpoints, combination use of bevacizumab and FOLFOX appears reasonable to use before hepatic resection.

In conclusion, mFOLFOX6 with bevacizumab is safe and effective and therefore, is recommended as a preoperative chemotherapy regimen for patients with advanced liver-limited CRLM undergoing potentially curative liver resection.

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