

Efficacy and Safety of mFOLFOX6 as Perioperative Chemotherapy for Resectable Liver Metastases from Colorectal Cancer: A Case–Control Study

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Abstract. *Background/Aim:* Although resection is effective for managing resectable liver metastases from colorectal cancer, the clinical significance of chemotherapy for such metastases has remained undetermined. Therefore, we conducted a phase II trial of perioperative chemotherapy with mFOLFOX6 to examine its efficacy. *Patients and Methods:* A total of 41 patients were examined. The liver resection rate was the primary endpoint, whereas the response rate, adverse events, completion rate, liver injury rate, R0 resection rate, and histological results were the secondary endpoints. *Results:* Overall, 34 (82.9%) patients underwent liver resection, and 77.4% and 100% had synchronous and metachronous liver metastases, respectively. The seven remaining patients did not undergo resection because of progressive disease. Moreover, 2, 15, 17, and 7 patients had a complete response, partial response, stable disease, and progressive disease, respectively, which indicated that the response rate was 41.5%. Regarding adverse events, three patients exhibited Grade 3 myelosuppression and one patient had gastrointestinal

symptoms. On the basis of histopathological examination, 27, 5, and 2 patients belonged to grades 1a:1b, 2, and 3, respectively. Regarding liver injury, 29.4% had liver sinusoidal injury, whereas 11.7% had steatohepatitis. Meanwhile, all patients underwent postoperative chemotherapy. *Conclusion:* mFOLFOX6 is safe and yields favorable therapeutic effects. The indication for liver resection after a certain waiting period is clinically significant.

In Japan, colorectal cancer has become dramatically prevalent and is recognized as a leading cause of cancer-related deaths next to gastric cancer and lung cancer (1). Stage IV colorectal cancer, which involves distant metastasis, is generally treated with resection; unresectable cases are treated with systemic chemotherapy. For stage I-III cases that are resectable, the cumulative 5-year survival rate is approximately 80%. For stage IV cases, the therapeutic outcomes remain unsatisfactory. Therefore, improving the therapeutic outcomes for colon cancer, particularly regarding metastasis and recurrence, is critical.

The most common distant metastasis in colorectal cancer is liver metastasis; hence, improving the therapeutic outcomes for liver metastasis would have a significant impact on the survival rates of this leading cause of cancer. The indication of liver resection for liver metastases from colorectal cancer remains uncertain; nonetheless, curative resection is recommended when residual liver function is maintained after liver resection (2). The 5-year survival rate survival curative resection ranges from 15% to 59% among various studies (3-13). Although resection is effective for managing resectable colorectal liver metastases, the clinical significance of chemotherapy for such metastases has been insufficiently investigated. A novel chemotherapy-based therapeutic strategy must be developed to improve the outcomes for patients undergoing resection.

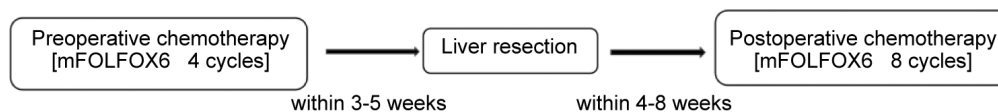
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Key Words: mFOLFOX6, perioperative chemotherapy, liver metastases, colorectal cancer.

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Primary endpoint: liver resection rate
Secondary endpoints: response rate (RR), adverse events, completion rate, liver injury rate, R0 resection rate, and histological results.

Figure 1. Overview of clinical trial.

Thus, in this study, we aimed to conduct a multicenter phase II clinical trial to evaluate the efficacy and safety of mFOLFOX6 as a chemotherapeutic regimen before and after liver resection for resectable liver metastases from colorectal cancer.

Patients and Methods

A total of 42 patients diagnosed with resectable liver metastases between April 2010 and September 2018 underwent treatment. The present trial was approved by the institutional review boards of each participating center (ethics committee that approved the study protocol: Tokyo Medical University Medical Ethics Review Committee) UMIN-CTR registration no. UMIN000009725-2020/0716).

The liver resection rate was the primary endpoint, whereas the response rate (RR), adverse events, completion rate, liver injury rate, R0 resection rate, and histological results were secondary endpoints. We assessed adverse events according to the Common Terminology Criteria for Adverse Events version 4.0.

Prior to liver resection, four mFOLFOX6 cycles were administered. Liver resection was contraindicated in patients who met any of the withdrawal criteria during treatment; in which case, a more suitable treatment was performed. After preoperative chemotherapy, patients were reassessed for liver resectability, and liver resection was performed on those who had resectable livers. If liver resection was not an option, we discontinued the trial and performed a suitable alternative treatment. The criteria for liver resection were as follows: 1) metastatic liver lesions that could be resected without macroscopic residual cancer and 2) at least 40% of the liver could be preserved. This percentage is sufficient to maintain liver function after resection. In liver dysfunction, the maximum liver remnant was determined according to the liver resection criteria of each center. Host factors were as follows: performance status (Eastern Cooperative Oncology Group) score of 0-1 and maintenance of a major-organ function. Such function was defined as meeting all of the following criteria in data <2 weeks before reassessment: white blood cell count 2,500-12,000/mm³, neutrophil count $\geq 1,000/\text{mm}^3$, platelet count $\geq 80,000/\text{mm}^3$, hemoglobin 8.0 g/dl, aspartate transaminase and alanine aminotransferase ≤ 100 IU/l, total bilirubin ≤ 2.0 mg/dl, and creatinine no higher than the center's maximum. Liver resection was possible within 3-5 weeks after preoperative chemotherapy, and an investigator ensured no problems with operability.

Meanwhile, postoperative chemotherapy consisted of eight mFOLFOX6 cycles. For perioperative chemotherapy, the applicability

criteria included meeting all of the aforementioned criteria in <2 weeks before enrollment and the ability to begin treatment within 4-8 weeks after liver resection (Figure 1). The treatment protocol involved curative resection and eight cycles of postoperative chemotherapy. The protocol was discontinued when any of the following occurred: progressive disease (PD) during chemotherapy; curative liver resection deemed impossible after the final cycle of preoperative chemotherapy; inability to perform liver resection within 3-5 weeks after the final cycle of preoperative chemotherapy; inability to perform chemotherapy within a prescribed period after liver resection; adverse events hindering the continuation of chemotherapy; patient's request to discontinue the treatment protocol; and worsening of disease state/death caused by exacerbation of complications.

Results

Of the 42 enrolled patients, one refused treatment; therefore, 41 patients were examined. The liver resection rate (primary endpoint) was 82.9% (34/41 patients). For patients with synchronous liver metastasis, the rate was 74% (24/31), whereas for patients with metachronous liver metastasis, the rate was 100% (10/10) (Figure 2). Of the seven patients who could not undergo liver resection, six had pancreaticoduodenectomy (PD), whereas one patient underwent treatment change because of adverse drug reactions to chemotherapy and later developed PD (Table I and Figure 2).

Complete response, partial response, stable disease, and PD were observed in 2, 15, 17, and 7 patients, respectively; thus, the RR was 41.5%. Regarding adverse events, we observed Grade 3 myelosuppression in three patients and gastrointestinal symptoms in one patient. In addition, one patient had Grade 2 gastrointestinal symptoms. Meanwhile, 97.6% of patients (40/41) had completed the preoperative chemotherapy. A patient who could not complete preoperative chemotherapy withdrew from treatment because of renal impairment associated with Grade 3 gastrointestinal symptoms. All patients (100%) received postoperative chemotherapy, but four failed to complete it because two refused treatment and two suffered from recurrence, thus requiring treatment revision (2 patients).

According to histopathological examination, 27, 5, and 2 patients belonged to grades 1a/1b, 2, and 3, respectively. As

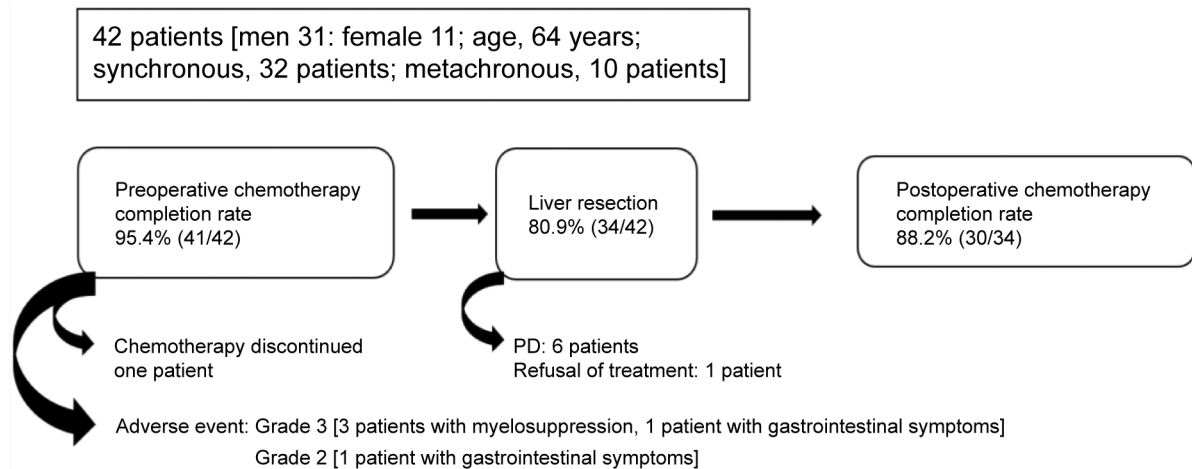


Figure 2. Clinical trial result.

Table I. Details of patients whose treatment could not be continued (age, sex, primary site, outcomes).

Age, Sex, Primary site	Outcomes
75, M, Ascending colon	Pulmonary metastasis, enlargement of pre-existing hepatic metastasis
53, F, Sigmoid colon	Pulmonary metastasis, enlargement of pre-existing hepatic metastasis
69, M, Ascending colon	Para-aortic, hepatic lymph node metastasis
73, M, Sigmoid colon	Pulmonary metastasis, enlargement of pre-existing hepatic metastasis
81, M, Ascending colon	Pulmonary metastasis, enlargement of pre-existing hepatic metastasis
74, M, Colorectal cancer	Novel hepatic lesion in S3, enlargement of pre-existing hepatic metastasis

for liver injury in normal livers, 29.4% of patients had liver sinusoidal injury and 11.7% of patients had steatohepatitis. Meanwhile, macroscopic resection was performed in 34 patients (100%).

Discussion

The liver resection rate was reportedly higher in FOLFOX than in FOLFIRI for unresectable liver metastases (14). For resectable liver metastases, FOLFOX extended progression-free survival after perioperative chemotherapy (15). FOLFOX also extended progression-free survival of postoperative adjuvant chemotherapy for Stage III colorectal cancer and is considered useful for resectable liver metastases. Therefore, the present trial selected mFOLFOX6 for treating resectable liver metastases. The liver resection rate (the primary endpoint) was 82.9%, which was nearly equal to that of the EORTC Intergroup trial 40983 (88.9%, 152/171).

Preoperative chemotherapy is expected to reduce tumor size, control micrometastatic lesions, and increase chemotherapy sensitivity. However, resection may be impossible for patients who were unresponsive to chemotherapy or patients with liver

injury, which increases postoperative complications. Meanwhile, a complete response may prevent the identification of lesions. Although synchronous metastases involve greater biological malignancy than metachronous metastases, no significant difference was found between the two metastasis types in the study of Kato *et al.* on the 5-year survival rates of 763 patients who underwent surgical resection (31% vs. 46%; $p=0.059$) (5). However, of the 41 subjects in the present study, seven patients without liver resection had synchronous metastases. Of these seven patients, one discontinued chemotherapy and later developed PD, whereas the other six had preexisting PD based on preoperative assessments. In addition, these seven patients exhibited new lesions in other organs, and one patient also manifested liver metastasis enlargement. Thus, these patients were excluded from liver resection. On the basis of preoperative tests alone, the potential for a radical cure of synchronous liver metastases is difficult to determine. Patients who develop novel lesions and undergo resection without preoperative chemotherapy are highly likely to experience recurrence of metastases in the liver remnant. Therefore, preoperative chemotherapy, as performed in the present study, was considered to be effective as a “watch and

wait” approach to assess resectability. For patients with unfavorable prognoses, delayed induction of chemotherapy in liver resection is fatal.

In the present trial, the liver resection rate was 100% for metachronous liver metastases. The significance of preoperative chemotherapy for metachronous liver metastases differed clinically from synchronous liver metastases. According to Hasegawa *et al.*, uracil–tegafur with leucovorin demonstrated no significant benefit for synchronous liver metastases (16). Our trial results revealed that liver injury or unrespectability caused by PD is less likely to occur and that chemotherapy induction before liver resection for metachronous liver metastases is highly safe. However, the clinical significance of preoperative chemotherapy remains questionable.

In performing postoperative chemotherapy, it is imperative to consider the likelihood of injury to a normal liver. The EORTC Intergroup trial 40983, which compared differences in the outcome of perioperative chemotherapy with FOLFOX plus surgery and surgery alone for resectable liver metastases from colorectal cancer, found that six preoperative cycles of FOLFOX resulted in Grade 2/3 liver sinusoid damage and steatohepatitis in 41% and 24% of patients, respectively. The rate of liver sinusoidal injury was significantly higher with preoperative chemotherapy than with surgery alone (17) (Table II).

Safely performing liver resection and inducing chemotherapy postoperatively require a reduction of liver injury, based on preoperative FOLFOX. Liver injury can be minimized by decreasing the number of preoperative FOLFOX cycles; its effects on liver injury should also be confirmed. A commonly reported adverse reaction to FOLFOX is peripheral neuropathy, which first presents as functional impairment starting from around the fifth FOLFOX cycle (18). Therefore, discontinuing perioperative FOLFOX before functional impairment can be effective. This approach supports the “stop and go” method for administering oxaliplatin, as reported by Vauthey *et al.* (14). Therefore, in the present trial, we performed four cycles of chemotherapy before liver resection, and we examined subsequent adverse reactions and liver damage. While undergoing postoperative chemotherapy, only one patient required a treatment change because of adverse events, and doses were not reduced for any patient. Cases in which chemotherapy was withdrawn or revised because of neurotoxicity were not noted. Liver sinusoidal injury and steatohepatitis occurred in 29.4% and 11.7% of normal livers, respectively. The extent of liver damage was evidently lower than that of the EORTC Intergroup trial 40983, which involved six cycles of chemotherapy. Performing four mFOLFOX6 cycles yielded minimal effects on normal liver tissue and did not cause adverse drug events, such as neurotoxicity. Therefore, performing four cycles of mFOLFOX6 prior to liver resection is valid.

Table II. *Histological effects of the liver and frequency of hepatic sinusoidal injury and steatohepatitis after preoperative chemotherapy.*

Histological effects	(No. patients)
Grade 1a	22.5% (9/34)
Grade 1b	45% (18/34)
Grade 2	12.5% (5/34)
Grade 3	5% (2/34)
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Liver damage in normal livers	(No. patients)
Hepatic sinusoidal injury	29.4% (10/34)
Steatohepatitis	11.7% (4/34)

Chemotherapy effects were difficult to determine, because we did not compare chemotherapy plus surgery with surgery alone. However, liver metastases were macroscopically resected for all patients who underwent liver resection. Tissue examination of these patients revealed that the tumor margin was almost unrecognizable when the tumor was macroscopically resected in three patients. However, in these three patients, we noted long-term survival and no recurrence in the resection stump. In a study on patients who underwent preoperative chemotherapy, the 5-year overall survival rates for R1 resection and R0 resection were equal (14); however, the small sample size hindered assessment, so performing certain curative resections was necessary.

An optimal regimen for postoperative adjuvant chemotherapy has yet to be established. Nevertheless, FOLFOX reportedly extends progression-free survival in perioperative chemotherapy and is considered effective for resectable liver metastases from colorectal cancer (19). In the present study, postoperative mFOLFOX6 was performed in 100% of patients and was completed in 88.2%, which were considered high rates. Perioperative chemotherapy with mFOLFOX6 in colorectal cancer with resectable liver metastases can be performed safely and extend progression-free survival, thus is considered an effective treatment.

Conclusion

In conclusion, perioperative chemotherapy with mFOLFOX6 for the treatment of colorectal cancer with resectable liver metastases is a safe treatment, and adverse drug reactions were within the acceptable range. The liver resection rate (the primary endpoint) was high although a certain percentage of patients developed PD. Induction of chemotherapy as a “watch and wait” approach before attempting liver resection was effective for assessing the true suitability of liver resection. Furthermore, the induction of preoperative chemotherapy with four mFOLFOX6 cycles was unlikely to affect liver resection, and the postoperative chemotherapy induction rate was high;

thus, four cycles were considered effective. However, the present study is a phase II trial and utilizes a small sample size; therefore, further investigation is necessary to verify and expand upon the findings of the current study.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Substantial contributions to the conception and design of the work and/or the acquisition, analysis, or interpretation of data for the work: Takahiro Wada and Kenji Katsumata. Drafting the manuscript or revising it critically for important intellectual content: Akihiko Tsuchida, Kenta Kasahara, Junichi Mazaki, Masatoshi Shigoka, Hideaki Kawakita, Masanobu Enomoto, Tetsuo Ishizaki, and Yuichi Nagakawa.

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