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# Prospective multicenter phase II clinical trial of FOLFIRI chemotherapy as a neoadjuvant treatment for colorectal cancer with multiple liver metastases

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**Purpose:** This study evaluated the efficacy of neoadjuvant chemotherapy combining 5-flurouracil/folinic acid with irinotecan (FOLFIRI) in colorectal multiple liver metastases regardless of resectability.

**Methods:** Forty-four patients with multiple (at least two) colorectal liver metastases were enrolled at seven tertiary referral hospitals between May 2007 and September 2010. All patients received the FOLFIRI chemotherapeutic regimen. Response to chemotherapy was assessed after three cycles (6 weeks) and once more after six cycles (12 weeks) of treatment.

**Results:** Objective response was noted in 27 patients (61.4%) and 4 patients (9.1%) had progressive disease. Of 44 patients, 10 patients (22.7%) underwent curative surgery (R0 resection) and 34 patients did not receive R0 resection. Grades 3 to 4 hematological toxicity was noted in 12 patients (27.3%) and grades 3 to 4 nonhematologic toxicity was identified in 5 patients (11.4%).

**Conclusion:** FOLFIRI chemotherapy as a neoadjuvant chemotherapy for multiple colorectal liver metastases regardless of resectability demonstrated the possibility of R0 resection, high rate of objective response, and tolerable toxicities in this study.

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**Key Words**
Colorectal cancer, Neoadjuvant therapy, Metastasis, Chemotherapy

## INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers occurring worldwide and the second leading cause of cancer-related deaths in Europe and the United States [1,2]. Approximately 50% of CRC patients will experience metastases [3], and patients with stage IV disease were deemed incurable, previously. However, if patients with colorectal liver metastases treated with extirpative surgery and proper chemotherapy, 5-year survival rates would reach up to 58% in the recent reports [4-6]. But, this survival benefit is limited among patients with liver metastases since only 10% to 20% of these patients are candidates for liver resection [4]. There are several reasons for unresectable liver metastases, including large size of metastasis, multiple bilateral lesions, and close proximity of major vessels (the hepatic veins, the inferior vena cava or the liver hilum). This indicates that 80% to 90% of patients with liver metastases received palliative or neoadjuvant chemotherapy.

Commonly available chemotherapy for liver metastases consists of 5-flurouracil

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(5-FU) with leucovorin (LV), irinotecan or oxaliplatin. Significant response rates of up to 56% have been reported by combining 5-FU/LV with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) for metastatic CRC [5-7]. Moreover, good responses to palliative chemotherapy enabled surgical resection with curative intent for some patients who initially had unresectable liver metastases by downsizing and down-staging the effect of chemotherapy [8]. In the past, the use of neoadjuvant chemotherapy was indicated for patients with unresectable colorectal liver metastasis, but recently, current trends of neoadjuvant chemotherapy is expanding to patients with initially resectable colorectal liver metastasis using an innovative combination of chemotherapeutic regimens. The most recent, a systematic review of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases, demonstrated that objective responses of neoadjuvant chemotherapy can improve disease-free survival in patients with resectable colorectal liver metastases [9]. Furthermore, The National Comprehensive Cancer Network guideline recommended neoadjuvant chemotherapy for 2-3 months in patients with resectable colorectal metastases [10]. Thus, neoadjuvant chemotherapy prior to hepatectomy has become the standard treatment option. Herein, we attempted to develop a treatment strategy in the treatment of multiple colorectal liver metastases by using the FOLFIRI regimen. Patients who have more than two colorectal liver metastases were initiated with FOLFIRI chemotherapy, and then resectability was determined after three or six cycles of chemotherapy. Surgical treatment was performed in resectable cases, or, if progressive disease (PD) was observed during chemotherapy regimen-changed chemotherapy was delivered. If metastatic tumor showed controlled disease after 6 cycles of chemotherapy, further treatment was determined through resectability evaluation.

The aim of our prospective study was to evaluate the efficacy of neoadjuvant chemotherapy with FOLFIRI in colorectal multiple liver metastases regardless of resectability. The primary end point of the study was to observe the effects of treatment on the response rate. The secondary objectives were to observe R0 resection rate, complete response (CR) rate, and chemotherapy safety.

## METHODS

### Patients

Patients with multiple (at least two) colorectal liver metastases were enrolled in this study. Patients were recruited at seven tertiary referral hospitals. This study was approved by the Institutional Review Board of participating hospitals and written informed consent was obtained from each patient. Inclusion criteria were as follows: 1) histologically proven adenocarcinoma of colon and rectum, 2) multiple liver metastases confirmed by imaging study regardless of extrahepatic metastases, 3) age more than 18 years, 4) Eastern Cooperative Oncology Group performance status ≤2, 5) no history of previous chemotherapy, immunotherapy, or radiotherapy, 6) adequate bone marrow function (neutrophil counts, $\geq 1.5 \times 10^9$/L; hematocrit, ≥30%; and platelets, $\geq 100 \times 10^9$/L), liver function (total bilirubin ≤1.5 × the upper limit of normal), and renal function (serum creatinine ≤1.25 × the upper limit of normal). Patients having previously received adjuvant chemotherapy for a stage III colorectal cancer were eligible if the treatment had ended more than 6 months prior to enrollment in this study. Exclusion criteria included liver involvement of more than 70%, other malignancy, severe cardiac or pulmonary disease, pregnancy, severe medical disease, and intestinal obstruction or perforation.

Pretreatment evaluation included a physical examination, abdominopelvic computed tomography (CT), and carcinoembryonic antigen (CEA) assay. Positron emission tomography (PET) scanning was performed when possible.

### Chemotherapy

Chemotherapy consisted of a regimen of irinotecan 180 mg/$m^2$ administered intravenously over 30-90 mimutes, LV 400 mg/$m^2$ (200 mg/$m^2$ if L form was used) infused over 2 hours, 5-FU 400 mg/$m^2$ intravenous bolus, and 5-FU 2,400 mg/$m^2$ continuously infused for 46 hours on day 1. Treatment was delayed for 1 week in cases of neutropenia ($\leq 1.5 \times 10^9$/L), platelet reduction ($\leq 100 \times 10^9$/L) or significant nonhematological toxicity. Irinotecan and 5-FU doses were reduced by 25% in cases of grade 3/4 neutropenia or grade 3/4 diarrhea. In cases of grade 3/4 stomatitis, 5-FU doses were also only reduced by 25%. The treatment was interrupted in cases of grade 4 hematological toxicity or grade 4 gastrointestinal toxicity lasting for >1 week after a previous dose reduction or a delay in dose administration exceeding 2 weeks. The treatment was repeated every 2 weeks and response was assessed after completion of 3 cycles (6 weeks). If disease progression was identified, another chemotherapeutic regimen was begun in case of unresectable metastases or curative resection was performed in case of resectable metastases. If response was noted at the first assessment, chemotherapy was resumed until the completion of the other 3 cycles (6 weeks). After the second assessment was done, curative surgery was performed in case of resectable metastases or continuation of chemotherapy with another chemotherapeutic regimen was administered in cases of disease progression according to the discretion of the investigators in each institution (Fig. 1).

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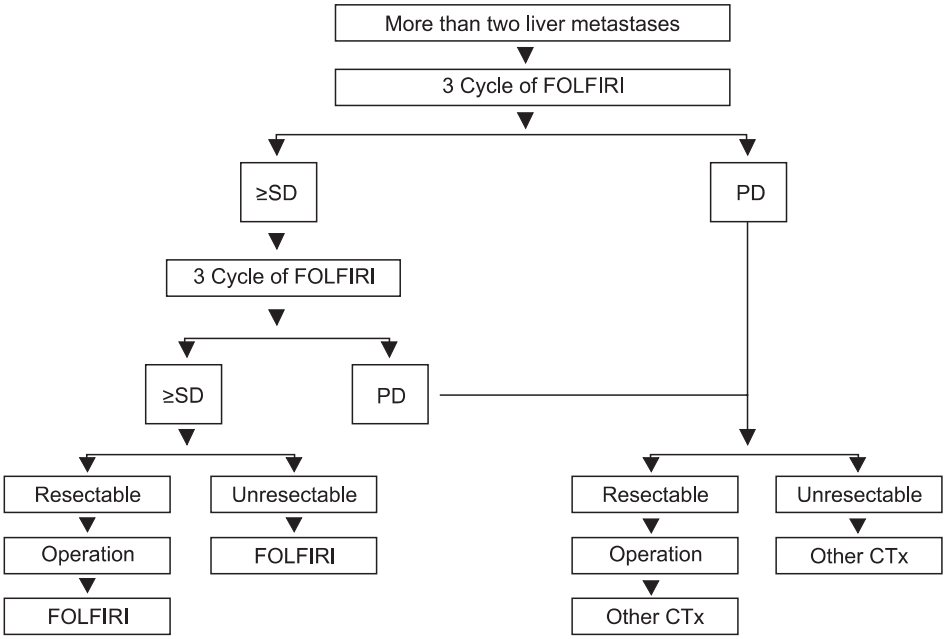


**Fig. 1.** Study design. SD, stable disease; PD, progressive disease; FOLFIRI, 5-fluorouracil/leucovorin with irinotecan; CTx, chemotherapy.

### Assessments

Disease unresectability at the study outset was established for all patients by the hepatobiliary surgeon, oncologist and a radiologist from each institution. Criteria for initial unresectability of hepatic metastases were: unfavorable location of the metastases (contiguity with at least two hepatic veins, the inferior vena cava or the liver hilum); the number of metastases (more than six synchronous metastases in the same lobe and a major hepatectomy [resection of at least four segments] required, or more than three metastases in each of the two involved lobes both for synchronous and metachronous metastases); the size of the lesions (largest diameter >5 cm in at least one metastasis if there were six lesions in the same lobe, or three lesions if there was bilobar involvement); insufficient liver reserve (>70% of the liver was involved); and the presence of extrahepatic disease. Resectability of metastases following chemotherapy was assessed by the same team and was based on the response of lesions to chemotherapy and the likelihood of achieving R0 resection. Response to chemotherapy was assessed after three cycles (6 weeks) of treatment, and repeated one more time after six cycles (12 weeks) of treatment. Responses to chemotherapy were determined using World Health Organization criteria: an objective response was defined as either a CR (disappearance of all known disease) or a partial response (PR; ≥50% reduction in the size of the lesion from baseline). Following the assessment of response to chemotherapy, suitability for liver resection was determined. Toxicity was assessed by a combined oncologist/surgeon team, according to National Cancer Institute Common Toxicity Criteria, before each dose administration, at the operability assessment, and before the chemotherapy was re-started after intervention.

### Statistical analysis

The main objective of this study was to assess the response rate of FOLFIRI chemotherapy in multiple colorectal liver metastases. On the basis of three phase II clinical trials using the FOLFIRI regimen for colorectal liver metastasis, the estimated response rate was 46.8% [7,11,12]. A response rate of 45% (P0) was considered as the minimum activity level of interest, while a response rate of 60% (P1) was promising. According to the two-stage phase II study of Simon's Optimal Design, 44 patients were calculated with β power of 80% and α error level of 0.05. Clinical response rates, resectability rates, and toxicity were calculated with 95% confidence interval.

## RESULTS

Between May 2007 and September 2010, 44 patients were accrued. The characteristics of the 44 were summarized in Table 1. They consisted of 33 men and 11 women aging from 34 to 83 years (median, 62 years). Forty-two patients (95.6%) had more than clinical T3 stage and 39 patients (88.6%) had clinical N positive stage. The numbers of liver metastasis were as follows: 2 in 7 patients (15.9%), 3 in 9 patients (20.5%), 4 in 8 patients (18.2%), and 5 or more in 20 patients (45.4%). Imaging showed 161 liver metastases before chemotherapy in the 44 patients in the study. Of these, 128 had lesions smaller than 5 cm, 30 had lesions larger than 5 cm, and 3 were not identified.

Of the 44 included patients, 27 patients (61.4%) had objective

**Table 1.** Patient characteristics

| Characteristic | Value |
|---|---|
| Age (yr) | 62 (34–83) |
| Sex | |
| Male | 33 (75.0) |
| Female | 11 (25.0) |
| Primary tumor site | |
| Colon | 24 (54.5) |
| Rectum | 20 (45.5) |
| ECOG performance status | |
| 0 | 23 (52.3) |
| 1–2 | 21 (47.7) |
| Clinical T stage | |
| T1–T2 | 2 (4.4) |
| T3–T4 | 42 (95.6) |
| Clinical N stage | |
| Negative | 5 (11.4) |
| Positive | 39 (88.6) |
| No. of liver metastasis | |
| 2 | 7 (15.9) |
| 3 | 9 (20.5) |
| 4 | 8 (18.2) |
| ≥5 | 20 (45.4) |
| Largest length of liver metastasis (cm) | |
| <5 | 128 (79.5) |
| ≥5 | 30 (18.6) |
| Missing value | 3 (1.9) |

Values are presented as median (range) or number (%).
ECOG, Eastern Cooperative Oncology Group.

**Table 2.** Response to chemotherapy

| Response | No. of patients (%) |
|---|---|
| Complete response | 1 (2.3) |
| Partial response | 26 (59.1) |
| Stable disease | 13 (29.5) |
| Progressive disease | 4 (9.1) |

Objective response = complete response + partial response

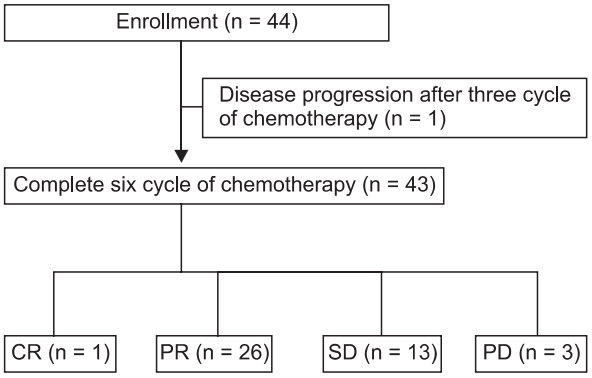


**Fig. 2.** Flowchart. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

**Table 3.** Treatment summary and R0 resection

| | No. of patients (%) |
|---|---|
| Patients who completed 6 cycles of chemotherapy | 43 (97.7) |
| Received chemotherapy with dose modification | 4 (9.0) |
| Overall radical resection rate (R0) | 10 (22.7) |
| Reason why R0 resection was NOT performed (n = 34) | |
| Unresectability of liver metastasis | 19 (55.9) |
| Disease progression | 4 (11.8) |
| Patients' refusal | 7 (20.6) |
| Microscopically positive resection margin (R1 resection) | 1 (2.9) |
| Macroscopically remnant disease (R2 resection) | 2 (5.9) |
| No visible lesion | 1 (2.9) |

**Table 4.** Common adverse effect (NCI CTC ver. 2.0) (n = 44)

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Anemia | 8 (18.0) | 12 (27.2) | 2 (4.5) | 0 (0) |
| Neutropenia | 4 (9.0) | 6 (13.6) | 6 (13.6) | 4 (9.0) |
| Neutropenic fever | 0 (0) | 0 (0) | 3 (6.8) | 0 (0) |
| Mucositis | 1 (2.3) | 0 (0) | 1 (2.3) | 0 (0) |
| Nausea or vomiting | 26 (59.1) | 10 (22.7) | 1 (2.3) | 0 (0) |
| Diarrhea | 3 (6.8) | 1 (2.3) | 3 (6.8) | 0 (0) |

Values are presented as number (%).
NCI CTC, National Cancer Institute Common Terminology Criteria.

response (1 CR and 26 PR), and 4 patients (9.1%) had PD. Among patients with PD, aggravation of liver metastases was found in 3 cases and lung metastases were in 1 case (Table 2).

Forty-three patients (97.7%) completed six cycles of chemotherapy. The remaining one patient had to change the chemotherapeutic regimen because PD was noted after three cycles of chemotherapy (Fig. 2). Of the 44 patients enrolled, 10 patients (22.7%) underwent curative surgery (R0 resection) and 34 patients did not receive R0 resection. The reason for no R0 resection is described in Table 3.

Toxicities during chemotherapy were usually mild and tolerable. Grades 3 to 4 hematological toxicity consisted of anemia in 2 patients (4.5%) and neutropenia in 10 patients

(22.6%). Grade 3 neutropenic fever was observed in 3 patients (13.6%). Grade 3 mucositis, nausea or vomiting, and diarrhea occurred in one, one, and three patients, respectively (Table 4). Dose modification of irinotecan and FU was necessary in 4 patients (9.0%) who showed grade 4 neutropenia.

## DISCUSSION

Systemic chemotherapy base of 5-fluorouracil with leucovorin has been considered standard regimen for colorectal cancer. However, its response rate is relatively low. A recently available chemotherapeutic regimen of 5-FU with irinotecan or oxaliplatin significantly improved oncologic outcomes in terms of progression-free survival, overall survival, and response rates [7,13-15]. Response rates were almost two times higher in 5-FU combined with irinotecan or oxaliplatin than 5-FU alone. These remarkable response rates led to evaluating the efficacy of neoadjuvant chemotherapy for colorectal liver metastases [9,13]. The efficacy of neoadjuvant chemotherapy for unresectable liver metastases has expanded its indication to patients with resectable colorectal liver metastases. Phase II studies using oxaliplatin- or irinotecan-based regimens have suggested efficacy and feasibility of neoadjuvant chemotherapy for resectable colorectal liver metastases [16,17]. A recent randomized controlled phase III trial, EORTC (European Organization for Research and Treatment of Cancer) intergroup trial 40983, demonstrated that increased 3-year progression-free survival rates in perioperative chemotherapy group as compared with surgery alone group in patients with resectable colorectal liver metastases occurred [18]. In our study, objective response rate was 61.4%. This response rate was relatively high compared to similar clinical trials using FOLFIRI regimen [7,11,12]. However, neoadjuvant chemotherapy has several disadvantages. First, administration of preoperative chemotherapy may be associated with liver injury causing increased perioperative morbidity and mortality [19-21]. Combination of 5-FU and LV can develop hepatic steatosis [19]. Oxaliplatin-based regimens can increase the risk of vascular abnormalities in the liver [20,21]. Administration of irinotecan-based chemotherapy has been associated with steatosis and steatohepatitis [22,23]. Second, some liver metastases may disappear on radiologic imaging after neoadjuvant chemotherapy and these lesions may not be treatable. Benoist et al. [24] reviewed 66 liver metastases that had disappeared on CT scan. This study showed that 55 of 66 resolved liver metastases (83%) revealed residual cancer or early recurrence *in situ*. Therefore, they concluded that CR on CT scan did not mean cured. Another disadvantage of neoadjuvant chemotherapy is that some metastases become unresectable if they do not respond to chemotherapy. In the EORTC intergroup phase III study 40983, disease progression was identified in 12 out of 182 patients (7%) during systemic chemotherapy [18]. Thus, early decision of surgical resection should be considered if disease progression is identified in patients with neoadjuvant chemotherapy. In this study, neoadjuvant chemotherapy was indicated in patients with more than two liver metastases regardless of resectability, and resection or continuous chemotherapy using changed chemotherapeutic regimen was designed for disease progression.

The rate of R0 resection of 22.7% is one of the highest results among the studies using neoadjuvant chemotherapy for colorectal liver metastases. Moreover, a relatively high rate of objective response (61.4%) was demonstrated in our study. These results might be attributed to the effectiveness of FOLFIRI regimen for colorectal liver metastases and the inclusion of some patients who had initially resectable disease. The superiority of the FOLFIRI regimen was demonstrated in the BICC-C (bolus, infusional, or capecitabine with camptostar-celecoxib) study [25]. In the BICC-study, three different irinotecan-containing regimens (FOLFIRI, irinotecan plus bolus FU/LV, and irinotecan plus oral capecitabine) were compared in the first-line treatment of metastatic colorectal cancer. The median progression-free survival for FOLFIRI was 7.6 months as opposed to 5.9 months for irinotecan plus bolus FU/LV (P = 0.004) and 5.8 months for irinotecan plus oral capecitabine (P = 0.015). In contrast, studies comparing FOLFIRI with FOLFOX in patients with metastatic colorectal cancer showed similar efficacy [14,26]. Therefore, the addition of targeted agents to FOLFIRI or FOLFOX has been focused on the efficacy in the metastatic colorectal cancer currently. The efficacy of first-line treatment with cetuximab plus FOLFIRI has been evaluated in clinical trials in patients with epidermal growth factor receptor-expressing metastatic colorectal cancer. The CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) trial was a landmark phase III study to make a head-to-head comparison of the efficacy of cetuximab plus FOLFIRI and FOLFIRI alone for metastatic colorectal cancer [27]. In the subgroup of patients with *KRAS* wild type tumors, cetuximab plus FOLFIRI demonstrated more favorable oncologic outcomes than FOLFIRI alone with regard to both median progression-free survival (9.9 months vs. 8.7 months; hazard ration [HR], 0.68; 95% confidence interval [CI], 0.5 to 0.94) and overall survival (24.9 months vs. 21.0 months; HR, 0.84; 95% CI, 0.64 to 1.11). Moreover, cetuximab plus FOLFIRI group had a higher response rate than FOLFIRI alone (59.3% vs. 43.2%; odds ratio, 1.91; 95% CI, 1.24 to 2.93). The overall objective response rate was 46.9% in cetuximab plus FOLFIRI and 38.7% in FOLFIRI alone, respectively (P = 0.004). The

higher objective response rate of our study compared to that of the CRYSTAL trial was due to the inclusion of some patients who had initially resectable disease as mentioned above.

The addition of bevacizumab to irinotecan-based chemotherapy in patients with metastatic colorectal cancer showed improved oncologic outcomes in first-line therapy according to the Hurwitz trial [28]. Hurwitz et al. [28] showed improved median duration of survival (20.3 months vs. 15.6 months, $P < 0.001$) and median duration of progression-free survival (10.6 months vs. 6.2 months, $P < 0.001$) in the bevacizumab plus irinotecan, bolus fluorouracil, and leucovorin (IFL) group than IFL alone. Bevacizumab plus FOLFIRI has been considered an upfront treatment strategy for stage IV colorectal cancer although no randomized controlled trial comparing FOLFIRI and FOLFIRI plus bevacizumab was conducted to confirm the Hurwitz trial results.

Our study showed that most of the patients (91%) completed the chemotherapy without dose modification. The toxicities of neoadjuvant chemotherapy were mild and manageable, and there was no mortality related to chemotherapy. The most frequent grade 3 or 4 toxicities were neutopenia (22.6%), neutropenic fever (6.8%), diarrhea (6.8%). anemia (4.5%), mucositis (2.3%), and nausea or vomiting (2.3%). These frequencies of grade 3 or 4 toxicities were reported similarly in other studies with the FOLFIRI regimen [29,30].

In conclusion, possibility of R0 resection, high rate of objective response, and tolerable toxicities after neoadjuvant chemotherapy for multiple colorectal liver metastases regardless of resectability, look promising in this study. However, early decision of surgical resection or changed chemotherapeutic regimen should be considered if disease progression is identified.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGEMENTS

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