**Table 2.** Adverse events (during Cycle 1 and 2)

| Category | First phase | | | | Second phase | |
|---|---|---|---|---|---|---|
| | Level 1 ($n = 6$) | | Level 2 ($n = 6$) | | RD[a] ($n = 25$) | |
| | All grades $n$ | Grade $\geq 3$ $n$ | All grades $n$ | Grade $\geq 3$ $n$ | All grades $n$ (%) | Grade $\geq 3$ $n$ (%) |
| Hematologic toxicities | | | | | | |
| Neutropenia | 2 | 1 | 3 | 3 | 10 (40) | 3 (12) |
| Leucopenia | 3 | 1 | 3 | 2 | 24 (96) | 2 (8) |
| Hemoglobin | 5 | 2 | 6 | 2 | 24 (96) | 3 (12) |
| Thrombocytopenia | 1 | 0 | 1 | 0 | 3 (12) | 0 |
| Non-hematologic toxicities | | | | | | |
| Bilirubin | 2 | 0 | 0 | 0 | 4 (16) | 0 |
| AST | 3 | 0 | 1 | 0 | 6 (24) | 0 |
| ALT | 3 | 0 | 1 | 0 | 4 (16) | 0 |
| Hyponatremia | 3 | 3 | 4 | 1 | 12 (48) | 4 (16) |
| Hypokalemia | 4 | 3 | 2 | 0 | 8 (32) | 3 (12) |
| Creatinine | 2 | 0 | 2 | 0 | 7 (28) | 0 |
| Anorexia | 6 | 4 | 5 | 2 | 19 (76) | 4 (16) |
| Nausea | 4 | 0 | 3 | 0 | 15 (6) | 0 |
| Vomiting | 4 | 0 | 2 | 0 | 11 (44) | 0 |
| Diarrhea | 3 | 0 | 3 | 0 | 9 (36) | 0 |
| Fatigue | 6 | 2 | 4 | 0 | 20 (80) | 2 (8) |
| Mucositis | 1 | 0 | 2 | 0 | 4 (16) | 0 |
| Neuropathy sensory | 1 | 0 | 2 | 0 | 7 (28) | 0 |
| Neuropathy motor | 0 | 0 | 0 | 0 | 1 (4) | 1 (4) |
| Allergic reaction | 0 | 0 | 0 | 0 | 0 | 0 |
| Febrile neutropenia | 0 | 0 | 0 | 2 | 0 | 0 |
| Infection | 0 | 0 | 0 | 1 | 4 (16) | 1 (4) |

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]The RD group ($n = 25$ patients) included six patients at Level 1 dose in the first phase.

and unacceptable toxicity ($n = 4$) consisting of Grade 2 sensory neuropathy ($n = 2$), Grade 3 motor neuropathy ($n = 1$) and Grade 3 perforation of the primary site ($n = 1$). Thirteen patients in the second phase received subsequent chemotherapy after FLTAX treatment.

Table 2 summarizes all toxicities observed during the protocol treatment. At the RD level, major Grade 3 or 4 toxicities were neutropenia, leucopenia, fatigue and anorexia.

### Treatment Efficacy

In the second phase, the ascites response was evaluated in 24 patients but not in 1 patient with peritoneal nodules. The overall ascites response rate was 44.0% (five patients CR, six patients PR). The ascites response rate in the 17 first-line patients in the second phase was 44.4%, and that of the 7 second-line patients in was 42.9%. At a median follow-up of 8.0 months, the median progression-free survival in the second phase was 4.2 months (Fig. 1): 6.2 months in first-line patients ($n = 18$) and 2.9 months in second-line patients ($n = 7$). Median overall survival in the second phase was 8.0 months (Fig. 2): 9.5 months in first-line patients ($n = 18$) and 5.6 months in second-line patients ($n = 7$).

## DISCUSSION

Our results suggest that FLTAX is a feasible and promising regimen for first-line treatment of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. The RD was determined as 500 mg/m$^2$ of 5-FU, 250 mg/m$^2$ of *l*-LV and 60 mg/m$^2$ of paclitaxel on Days 1, 8 and 15, every 28 days. At the RD level, the toxicity profile was acceptable and the completion rate of two cycles was

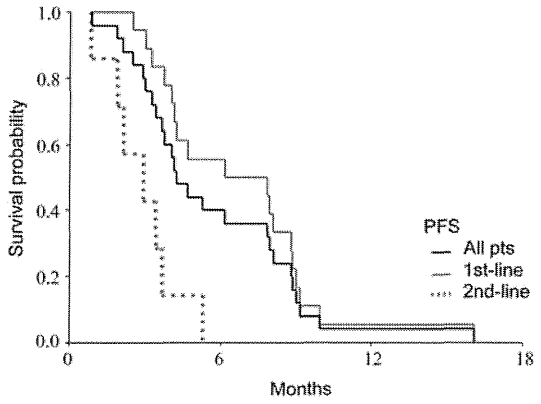


**Figure 1.** Progression-free survival in 25 patients at the recommended dose (RD) in the second phase of the study.

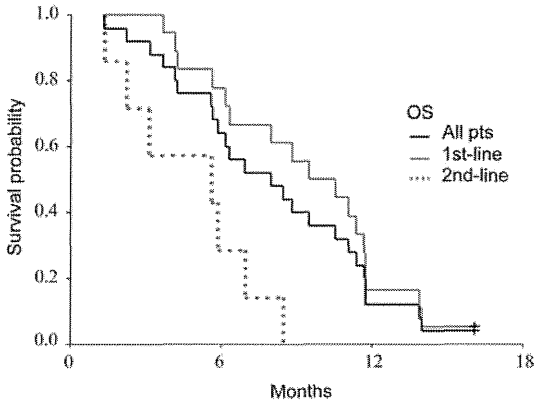


**Figure 2.** Overall survival in 25 patients at the RD in the second phase of the study. Tick marks indicate censored cases.

92%. Efficacy in the second phase of the study was promising; the response rate in ascites was 44%, the median progression-free survival was 4.2 months and median overall survival was 8.0 months.

Severe peritoneal metastasis causes severe clinical symptoms, such as abdominal fullness, vomiting, nausea, anorexia and abdominal pain, and it reflects rapid progression of the disease. Chemotherapy with greater therapeutic efficacy is needed as first-line treatment to promptly improve the symptoms and quality of life of patients. Furthermore, about 75% of patients with unresectable gastric cancer received second-line chemotherapy in some Phase III trials previously reported from Japan (1,5,12,13). However, only 40% of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake, who received 5-FU-based regimen as first-line chemotherapy, received second-line chemotherapy in our retrospective study (14). These data revealed that many patients with peritoneal disseminated gastric cancer and massive ascites or inadequate oral intake must have missed the opportunity to receive second-line chemotherapy because of rapid progression at the failure of first-line chemotherapy. Therefore, the use of a powerful combination regimen as first-line treatment is a promising strategy to improve the overall prognosis.

Bolus 5-FU/*l*-LV has been widely used in clinical practice for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake, who cannot receive standard treatment (oral fluoropyrimidines plus cisplatin) for general unresectable gastric cancer. Weekly paclitaxel was shown to significantly improve progression-free survival (hazard ratio, 0.57; 95% CI, 0.37–0.87; $P = 0.004$) when used as a second-line treatment in patients with peritoneal metastasis, except those with massive ascites (15). Therefore, a combination regimen of FLTAX would be more effective for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake because this combination regimen does not require the patient to be hydrated and includes no oral agents. FLTAX was already demonstrated to be an effective regimen in Phase I/II studies of general unresectable gastric cancer patients (6,7) and, therefore, we sought to evaluate the feasibility of FLTAX for the treatment of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake.

The median survival time in patients with peritoneal disseminated gastric cancer and massive ascites was much longer (8.0 months) with FLTAX treatment in our study than with MTX/5-FU (5.1 months) in a previous Phase II study (9). In retrospective studies, the median survival time of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake who received systemic chemotherapy was 4.6–5.0 months (14,16). Furthermore, the ascites response rate in this study (44%) was also higher than that of MTX/5-FU (35%) in the Phase II study described above. Such high therapeutic efficacy would improve severe clinical symptoms at the start of first-line chemotherapy, and lead more patients to receive second-line chemotherapy, thereby improving the prognosis. In fact, 77% of first-line patients at the RD level could receive second-line chemotherapy, and an overall survival time of 9.5 months was achieved in this study.

In conclusion, the FLTAX regimen of FLTAX (500/250/60 mg/m$^2$) is feasible as a first-line treatment for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. We intend to assess the FLTAX regimen relative to therapy with 5-FU/*l*-LV in a randomized trial of previously untreated patients with peritoneal disseminated gastric cancer and massive ascites or inadequate oral intake.

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## Conflict of interest statement

None declared.

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## Background

The median overall survival (OS) was about 2 years in several pivotal phase III studies of chemotherapy for unresectable or metastatic colorectal cancer, in which combination therapy with 3 anticancer drugs (oxaliplatin or irinotecan and fluoropyrimidine) and a molecular target drug administered as a first-line treatment showed efficacy, and these therapies are considered as the standard treatment [1–3].

In several phase III clinical studies performed before the introduction of any molecular target drug, oxaliplatin or irinotecan and fluoropyrimidine combination chemotherapy as a first-line treatment were compared with the sequential chemotherapy started with fluoropyrimidine treatment followed by oxaliplatin or irinotecan as the second-line treatment, and no significant difference was noted in the median OS in any of these clinical studies [4–6]. The response rate was higher in combination chemotherapy, whereas progression-free survival (PFS) of sequential chemotherapy was comparable. Regarding adverse events, toxicity was lower in sequential than in combination chemotherapy, attracting attention.

It has been found that cure or long-term survival may be achieved when curative resection of the liver is performed after a response to chemotherapy in patients with liver metastasis alone [7]. As a therapeutic strategy, it has been proposed to select combination chemotherapy for patients requiring an active approach in whom curative resection may be possible after responding to chemotherapy, and sequential chemotherapy for patients for whom stability of the disease condition is important rather than responses and also those without a tumor-associated symptom not requiring an aggressive approach [8].

On the other hand, many colorectal cancer patients are elderly, aged 65 years or older, in whom the incidence of complications is high and many are frail patients. The incidence of adverse events, particularly neutropenia, is high in combination chemotherapy in the elderly compared to that in the non-elderly, although the efficacy is similar [9–14]. The characteristics of adverse events induced by 5 types of anticancer drug effective for colorectal cancer are as follows: the incidence of anti-epidermal growth factor receptor (EGFR) antibody preparation-induced skin toxicity is high, oxaliplatin is likely to protract peripheral sensory neuropathy, irinotecan induces diarrhea, malaise and depilation, bone marrow toxicity of oxaliplatin and irinotecan is slightly high, whereas the incidences of gastrointestinal hemorrhage/perforation and thrombosis caused by an anti-vascular endothelial growth factor (VEGF) antibody preparation, bevacizumab, are very low, and the incidence of severe adverse events induced by fluoropyrimidine is lower than those induced by oxaliplatin and irinotecan. These characteristics suggest that the incidence of adverse events in chemotherapy combined bevacizumab with fluoropyrimidine may be lower than that in 3-drug combination therapy, making it more suitable as the first-line chemotherapy for frail patients, mainly the elderly.

The usefulness of chemotherapies combined bevacizumab with 5FU/LV or capecitabine has been shown in several clinical studies: these were administered to frail patients as a first-line treatment in the AVF2192g study [15] and as a sequential chemotherapy in the MAX study [16]. The median PFS times achieved by chemotherapy combined bevacizumab with fluoropyrimidine in these studies were 9.2 and 8.5 months, respectively, which were comparable to those achieved in pivotal phase III studies in which oxaliplatin or irinotecan was additionally combined (9.4 [1], 8.9 [2] and 9.6 months [3]).

In Japan, chemotherapy combined bevacizumab with S-1 achieved a favorable anti-tumor effect (response rate: 57%, PFS: 9.9 months) and caused low incidence of adverse events in frail patients aged 65 years or older in a phase II study (BASIC study), but the number of studies is still insufficient [17]. The efficacy and safety of chemotherapy combined bevacizumab with S-1 or 5FU/LV as a first-line for frail patients with unresectable or metastatic colorectal cancer were investigated based on the outcomes obtained at our hospital.

## Subjects and Methods

*Subjects*

Twenty-six patients diagnosed with unresectable or metastatic colorectal cancer at our hospital between October 2007 and December 2010 in whom treatment was started as chemotherapy combined bevacizumab with S-1 or 5FU/LV [modified Roswell Park Memorial Institute (RPMI) regimen] were retrospectively investigated. They were aged 65 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and met one or more of the following conditions: serum albumin <3.5 g/dl, past medical history of radiation of the abdominal region or pelvic cavity, and incompatibility with oxaliplatin and irinotecan. This is the same as the eligibility criteria of the AVF2192g study [15].

*Treatment Protocol*

In chemotherapy combined bevacizumab with S-1, the daily dose of S-1 was set as follows based on the body surface area (BSA): 80 mg/day for BSA <1.25 $m^2$, 100 mg/day for 1.25 $m^2$ ≤ BSA <

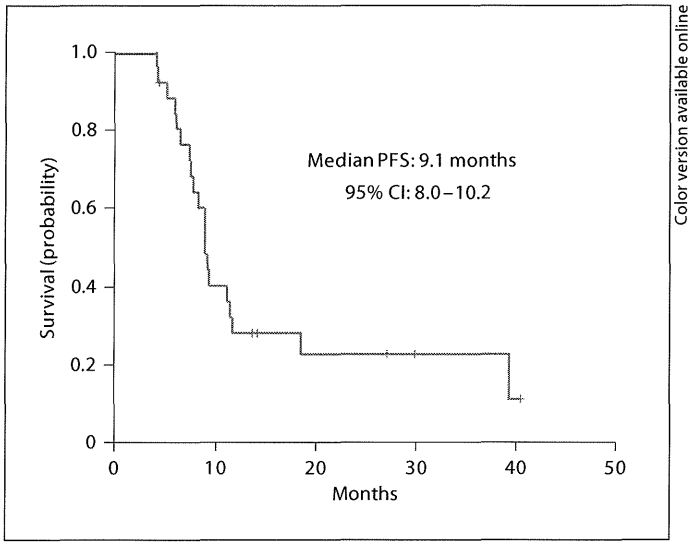


**Fig. 1.** Progression-free survival.

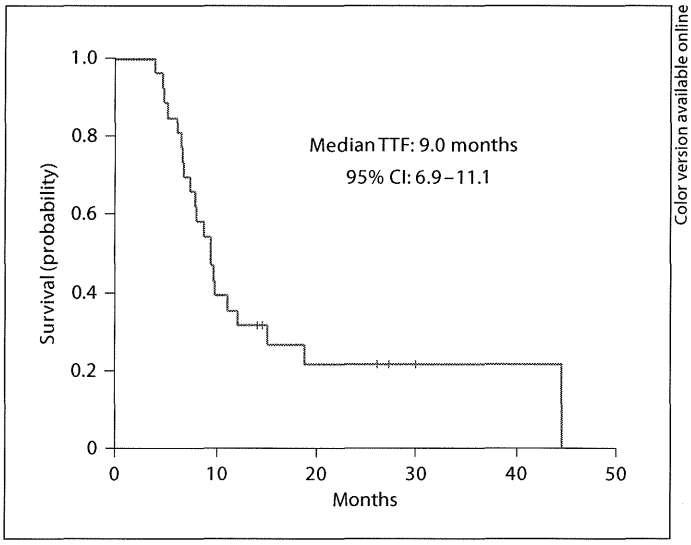


**Fig. 2.** Time to treatment failure.

1.5 $m^2$, and 120 mg/day for BSA ≥1.5 $m^2$. The drug was orally administered twice a day daily for 28 days, followed by a 14-day withdrawal. Bevacizumab was administered at 5 mg/kg by 30- to 90-min drip infusion on days 1, 15 and 29 (2-week intervals). One complete cycle was comprised of a total of 42 days.

In chemotherapy combined bevacizumab with 5FU/LV (modified RPMI regimen), 250 mg/$m^2$ of LV was administered by 2-hour drip infusion and 600 mg/$m^2$ of 5FU was administered by intravenous bolus injection on days 1, 8 and 15. Bevacizumab was administered at 5 mg/kg by 30- to 90-min drip infusion on days 1 and 15 (2-week interval). One complete cycle was comprised of 28 days.

*Assessment of Outcome*

Reponses were evaluated following the Response Evaluation Criteria in Solid Tumors version 1.0 before and after therapy in each patient. Complete response (CR) and partial response (PR) were confirmed when judged twice or more consecutively at a 4-week or longer interval.

PFS was defined as the time between the days on which consent for treatment initiation was obtained and disease progression was confirmed. When disease progression could not be confirmed, it was defined as the time until death. OS was defined as the time between the treatment initiation and death and, when death could not be confirmed, it was defined as the time until the final confirmation of survival. PFS and OS were analyzed employing the Kaplan-Meier method.

Adverse events were evaluated based on the worst grade observed during the treatment period following the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Protocol of this retrospective research approval was obtained from an institutional ethics committee at our hospital.

**Table 1.** Patient characteristics (n = 26)

| | |
|---|---|
| Median age (range) | 72 (66–84) |
| Gender (male/female) | 9/17 |
| ECOG performance status (0/1/2) | 8/17/1 |
| Primary site (colon/rectum) | 14/12 |
| Resection (yes/no) | 20/6 |
| Adjuvant chemotherapy (yes/no) | 8/18 |
| Number of metastatic site (1/2/3) | 17/9/0 |
| Metastasis | |
| Liver | 9 |
| Lung | 9 |
| Lymph node | 11 |
| Peritoneum | 5 |
| KRAS gene (wild/mutated/unknown) | 11/7/8 |
| S-1 + bevacizumab/5FU + bevacizumab | 17/9 |

## Results

The patient characteristics are shown in table 1. Median age was 72 years (range 66–84). ECOG performance status was 0, 1 and 2 in 8, 17 and 1 patient, respectively. The primary lesion was located in the colon in 14 patients and in the rectum in 12. Twenty patients were with resection of the primary lesion and 6 were without, 8 were with postoperative adjuvant chemotherapy and 18 were without. The number of metastasized organs was 1, 2 and 3 in 17, 9 and 0 patients, respectively. The liver, lung, lymph node and peritoneum was metastasized in 9, 9, 11 and 5 patients,

**Table 2.** Adverse Events by CTCAE v3.0

| Event | Grade | | | | | Any grade % | Grade >3 % |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | | |
| Neutropenia | 1 | 5 | 2 | 0 | 1 | 31 | 12 |
| Thrombocytopenia | 8 | 3 | 0 | 0 | 0 | 42 | 0 |
| Anemia | 14 | 5 | 1 | 0 | 0 | 77 | 4 |
| Nausea | 9 | 0 | 0 | 0 | 0 | 35 | 0 |
| Diarrhea | 6 | 2 | 1 | 0 | 0 | 35 | 4 |
| Fatigue | 13 | 0 | 0 | 0 | 0 | 50 | 0 |
| Stomatitis | 8 | 0 | 0 | 0 | 0 | 31 | 0 |
| Hand-foot syndrome | 10 | 2 | 0 | 0 | 0 | 46 | 0 |
| Hypertension | 3 | 2 | 3 | 0 | 0 | 31 | 12 |
| Proteinuria | 4 | 11 | 0 | 0 | 0 | 58 | 0 |
| Epistaxis | 9 | 0 | 0 | 0 | 0 | 35 | 0 |
| Cerebral hemorrhage | 0 | 0 | 1 | 0 | 0 | 4 | 4 |
| Thrombosis | 0 | 0 | 0 | 1 | 0 | 4 | 4 |

respectively. The KRAS gene was wild in 11, mutant in 7 and unknown in 8 patients, and treatment was chemotherapy combined bevacizumab with S-1 in 17 patients and chemotherapy combined bevacizumab with 5FU/LV in 9.

Regarding the efficacy, response was CR in 1, PR in 12, stable disease in 13, progressive disease in 0 and not evaluated 0 patients. The response rate was 50% and disease control rate was 100%. The median PFS was 9.1 months (95% CI 8.0–10.2; fig. 1). The median time to treatment failure was 9.0 months (95% CI 6.9–11.1; fig. 2), median OS was 28.9 months (95% CI 19.6–38.2) and median duration of follow-up was 20.7 months.

The mean relative dose intensity of chemotherapy combined bevacizumab with S-1 was: S-1 94.0% (range 66.5–100) and bevacizumab 62.0% (range 3.1–100), and that of with 5FU/LV was: 5FU 76.6% (range 68.6–91.3) and bevacizumab 71.7% (range 49.0–91.3).

The incidence of neutropenia at all grades was 31% and that of grade 3 or severer was 12%, the incidence of hypertension at all grades was also 31% and that of grade 3 or severer was 12%, showing low incidence, and those of other adverse events were also generally low. Grade 3 cerebral hemorrhage, grade 4 pulmonary embolus and grade 5 febrile neutropenia occurred each in 1 patient (table 2). First-line therapy was continued in 4 patients (15%), discontinuation of therapy occurred due to the following reasons: CR in 1 patient (4%), resection of liver metastasis in 1 (4%) or lung metastasis in 1 (4%), disease progression in 18 (69%) and adverse events in 3 (12%; cerebral hemorrhage, pulmonary embolus and FN). Excluding 7 patients under the first-line of therapy or course observation, 84% of patients received second-line chemotherapy: FOLFOX/XELOX was administered to 5 patients, FOLFIRI/IRI to 9 and 5FU/LV to 2.

## Discussion

We investigated the safety and efficacy of chemotherapy combined bevacizumab with fluoropyrimidine for elderly or frail patients with unresectable or metastatic colorectal cancer. The response rate was 50%, disease control rate was 100% and PFS was 9.1 months. These result suggest that such combined therapy might be useful for frail patients. However, this was a retrospective study performed at a single facility, not a prospective clinical study, and no statistical endpoint was established, showing the limitations of the study. Moreover, patient selection was biased and the OS observation period was short, indicating that the data are still immature.

Several clinical studies have reported the efficacy and safety of chemotherapy combined bevacizumab with fluoropyrimidine. In the AVF2192g randomized controlled phase II study involving frail patients, the primary endpoint, PFS, was 5.5 months in 5FU/LV therapy and 9.2 months in chemotherapy combined bevacizumab with 5FU/LV, suggesting the usefulness of combination with bevacizumab, and the therapy was tolerated with regard to safety [15]. Similarly, in the MAX study, which was a phase III study of chemotherapy combined bevacizumab with capecitabine, PFS was 5.7 months in capecitabine monotherapy and 8.5 months in chemotherapy combined bevacizumab with capecitabine, showing the usefulness of combination with bevacizumab [16]. In a phase II study of chemotherapy combined bevacizumab with capecitabine involving elderly patients, PFS was 10.8 months, suggesting high-level efficacy, and tolerability was also high [18]. In Japan, marked efficacy was also obtained in a phase II study (BASIC study) of chemotherapy combined bevacizumab with S-1 involving 65-year-old or older frail patients, in which PR was 57% and PFS was 9.9 months [17].

Regarding the efficacy, the common points of reports on chemotherapy combined bevacizumab with fluoropyrimidine are a slightly lower response rate than that of the standard combination therapy but comparable disease control rates and PFS. Based on these common findings, the standard combination therapy may be desirable for patients requiring tumor size reduction at the time of treatment initiation, but chemotherapy combined bevacizumab with fluoropyrimidine may be appropriate for patients for whom marked tumor size reduction is not nec-

essary but stabilization of the disease condition is, i.e. cases aiming at curative resection after tumor size reduction and treatment for those with no tumor-associated symptoms. It has been reported that the efficacy of combination therapy with oxaliplatin or irinotecan does not differ between elderly and young patients [9–14]. The efficacy of chemotherapy combined bevacizumab with fluoropyrimidine may also be similar in elderly and young patients because PFS in chemotherapy combined bevacizumab with capecitabine involving elderly patients in a phase II study was not markedly different from that in the MAX study, in which young patients were included [16, 18].

Regarding safety, the common points of reports on chemotherapy combined bevacizumab with fluoropyrimidine were a lower incidence of adverse events, particularly neutropenia, than that in clinical studies of the standard combination therapy, and the incidences of all grades and grade 3 or severer neutropenia were 31 and 12%, respectively [1–3]. The incidence of bone marrow toxicity, such as neutropenia, is high in combination therapies with oxaliplatin and irinotecan, particularly in elderly patients [11–16], and the induction of febrile neutropenia is of concern.

Many colorectal cancer patients are elderly, aged 65 years or older, and complications increase as patient age advances [19], meaning it can be difficult to apply chemotherapy to frail patients due to the increasing likelihood of complications. Since the patients in this study were also 65 years old or older, it included many frail patients. Regarding adverse events, the incidences of all grades and grade 3 or severer hypertension were 31 and 12%, respectively, which were higher than those in reported clinical studies. This may have been due the high age of the patients, rather than blood pressure elevation newly induced by bevacizumab.

One patient under chemotherapy combined bevacizumab with S-1 developed proteinuria in the 2nd cycle and bevacizumab administration was discontinued after day 15 in that cycle. Accordingly, the relative dose intensity of bevacizumab was 3% in this patient, but dose intensity of bevacizumab in chemotherapy combined bevacizumab with S-1 was high (81%) in the other 16 patients, and proteinuria in this patient was reversible. Therefore, the tolerability of the therapies was high, suggesting high-level safety. However, grade 3 cerebral hemorrhage, grade 4 pulmonary embolism and grade 5 febrile neutropenia occurred each in 1 patient. Performance status is likely to decrease earlier in elderly or frail patients than in young patients as adverse events develop, requiring treatment as early as possible in many cases. Thus, attention should be paid to the development of adverse events. In actual clinical practice, standard combination chemotherapy is started at a dose lower than the recommended dose because of safety concerns in relatively many cases, but the efficacy of chemotherapy administered at a reduced dose has not been clarified. It is possible that the efficacy of sequential chemotherapy without dose reduction is higher than standard combination chemotherapy with dose reduction.

Although there have been fewer reports of clinical studies on the usefulness of sequential chemotherapy using molecular target drugs, there was no significant difference in OS between sequential chemotherapy started with fluoropyrimidine monotherapy as the first-line treatment followed by oxaliplatin or irinotecan as the second-line or later treatment, and chemotherapy combined fluoropyrimidine with oxaliplatin or irinotecan as the first-line therapy in the FOCUS [4], CAIRO [5] and FFCD 2000–2005 studies [6], suggesting the usefulness of sequential chemotherapy.

In a study of chemotherapy combined fluoropyrimidine with anti-EGFR antibody involving untreated elderly patients, the response rate was 31.8% (95% CI 20.9–44.4) and PFS was 7.1 months, which is not superior to treatment with anti-EGFR antibody preparation alone, and the incidences of grade 3 or severer adverse events were high (skin toxicity 30%, hand-foot syndrome 22% and diarrhea 18.5%), showing that it is not a favorable relationship [20].

In conclusion, the first-line chemotherapy combined bevacizumab with fluoropyrimidine for unresectable or metastatic colorectal cancer frail patients in Japan was comparable to the safety and efficacy of combination therapy reported previously in Western countries. Because chemotherapy combined anti-VEGF antibody with fluoropyrimidine is lower than the other chemotherapy regimen regarding toxicity, further clinical studies may be necessary for such combined chemotherapy not only as a treatment more tolerable for frail patients than other drug therapies, but also as the first-line treatment of sequential chemotherapy.

## Disclosure Statement

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ORIGINAL ARTICLE

# Multicenter phase II study of modified FOLFOX6 as neoadjuvant chemotherapy for patients with unresectable liver-only metastases from colorectal cancer in Japan: ROOF study

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**Abstract**
*Background* Neoadjuvant chemotherapy for unresectable colorectal liver metastases can reduce tumor size, which sometimes leads to curative resection. The aim of the present study was to identify and describe patients with initially unresectable liver-only metastases from colorectal cancer who obtained sufficient chemotherapeutic benefit that eventually lead to the removal of the metastatic diseases in the liver.
*Methods* A phase II multicenter cooperative study was conducted in 38 medical institutions using modified FOLFOX6 (mFOLFOX6) as neoadjuvant chemotherapy from January 2008 to June 2009. Patients with liver-only metastases from colorectal cancer that was deemed not optimally resectable by liver surgeons received mFOLFOX6 as preoperative neoadjuvant chemotherapy for 6-8 cycles. Patients were reassessed for resectability after 6 cycles of mFOLFOX6. Surgery was carried out 3-6 weeks after chemotherapy. The primary endpoint was the rate of macroscopic curative surgery including liver resection.
*Results* 36 patients (23 male/13 female, ECOG performance status 0-1) were enrolled. The median age of the patients was 62.5 years; 78% (28 patients) had 5 or more metastatic tumors, and 50% (18 patients) had metastatic tumors over 5 cm diameter. The mFOLFOX6 regimen was

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safety administered resulting in 18 partial responses (50%), 12 stable disease, and 4 progressive disease. There was no grade 3/4 neurotoxicity. Fourteen patients (38.9%) underwent surgery (R0: 13; R1: 1). Of these, thirteen patients (36.1%) underwent R0 surgery.

*Conclusions* Our data suggest that mFOLFOX6 has a high response rate in patients with liver-only metastases from colorectal cancer, allowing for R0 resection of liver metastases in a proportion of patients initially not judged to be optimally resectable.

**Keywords** ROOF study · mFOLFOX6 · Colorectal cancer · Unresectable liver-only metastases · Liver resection

## Introduction

Colorectal cancer represents one of the most common cancers in Japan, and the liver is the most common site of metastases in patients with colorectal cancer. Liver metastases are a major cause of morbidity and mortality in this patient population. With the best supportive care, patients with liver metastases from colorectal cancer have a median survival time of 5–12 months [1–3]. Surgical resection of colorectal liver metastases is a potentially curative option, with a reported 5-year survival rate of 28–39% [4, 5]. However, about 80% of patients with colorectal liver metastases have unresectable diseases at the time of diagnosis, and long-term survival is not usually possible.

Historically, most of the patients with unresectable colorectal liver metastases have received palliative chemotherapy. However, a number of retrospective studies have reported the downsizing of colorectal liver metastases for rescue surgery following treatment with a combination of fluorouracil with irinotecan or with oxaliplatin, with the resection rate of 12.5–28% and 5-year survival rate of 33–50% after successful surgical resection [6, 7]. Resection of liver metastases can result in long-term survival in a subset of patients. A 5-year survival rate of 25–37% has been reported in a number of studies, with a median survival time of 24–42 months [8]. The improved efficacy of neoadjuvant chemotherapy has not only improved patient survival in a palliative setting, but has also offered a possibility of curative resection to previously unresectable patients with subsequent liver surgery after tumor downstaging by the chemotherapy. Adam et al. reported that liver resection could offer a possibility of long-term survival to patients with primarily unresectable metastases that were downstaged by chemotherapy. The survival rate was 33% at 5 years and 22% at 10 years, with a median survival of 39 months [5]. The use of neoadjuvant chemotherapy in patients with initially unresectable liver metastases has been explored in a prior study. Bismuth et al. [9] reported retrospectively on the potential for surgical resection in a group of patients receiving neoadjuvant chemotherapy with oxaliplatin, fluorouracil (5-FU), and leucovorin. The addition of oxaliplatin and irinotecan to 5FU in metastatic colorectal cancer (mCRC) has improved patient survival and the chance of downsizing initially unresectable mCRC, to allow curative-intent surgery. Albert et al. [10] reported a phase II study of FOLFOX4 in a group of patients with initially unresectable liver-only metastases from colorectal cancers through the North Central Center Treatment Group (NCCTG). Seventeen out of 42 patients (40%) underwent surgery after a median of 6 months of chemotherapy.

The aim of the present study was to identify and describe patients enrolled in this trial with initially unresectable liver-only metastases from colorectal cancer, who obtained sufficient chemotherapeutic benefit that eventually led to the removal of the metastatic diseases in the liver. This study was a phase II clinical trial of mFOLFOX6 in a group of patients with initially unresectable liver-only metastases from colorectal cancer. The primary endpoint of this study was to evaluate the resection rate of the patients who had been diagnosed with unresectable colorectal cancer metastasis, who turned out to be resectable after treatment with mFOLFOX6. Secondary endpoints included (1) R0 resection rate, (2) overall survival, (3) response rate to neoadjuvant chemotherapy, (4) percentage reduction of the tumor size after chemotherapy, (5) pathological response rate, (6) adverse event of neoadjuvant chemotherapy, (7) liver damage after mFOLFOX6 treatment and safety of hepatectomy after mFOLFOX6 neoadjuvant chemotherapy.

## Patients and methods

### Patient selection

Patients with liver-only metastases from colorectal cancer deemed unresectable by surgeons who were experienced in liver surgery were considered as potential candidates for the study. Unresectable liver metastases was defined as (1) $\geq$5 metastatic tumors and/or (2) a tumor >5 cm in maximum diameter or technically unresectable (inadequate future liver remnant even after surgery), such as tumors adjacent to major vascular structures that would preclude resection with tumor-free margins. At the time of study entry, patients were required to have imaging of the liver with computed tomography or magnetic resonance imaging, no evidence of extrahepatic disease and no previous history of chemotherapy with oxaliplatin or irinotecan. To

be eligible for enrolment, patients had to be aged between 20 and 75 years old, have histologically proven mCRC, adequate organ function (AST, ALT $\leq 3\times$ upper limit of normal, bilirubin $\leq 2\times$ upper limit of normal, and creatinine $\leq 1.2$ mg/dl), adequate bone marrow function, and an Eastern Cooperative Oncology Group performance status of 0–1. Patients were excluded from study entry if they had received prior therapy such as hepatectomy, radiotherapy, or MCT/RFA for liver metastases. A signed written informed consent was obtained from all patients before initiating therapy. Women who were pregnant or breast-feeding were also excluded from participation to the study. This trial was approved by the medical ethics committees of all participating institutions.

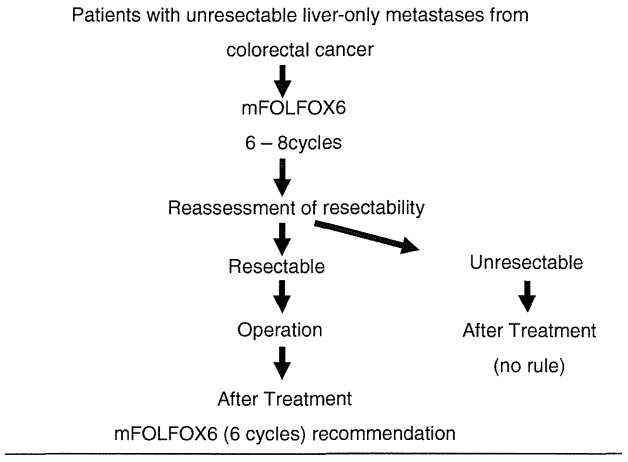
### Neoadjuvant chemotherapy

Patients received mFOLFOX6, which consisted of biweekly oxaliplatin 85 mg/m$^2$, followed sequentially by leucovorin 400 mg/m$^2$, bolus 5FU 400 mg/m$^2$, and then continuous-infusion 5FU 2400 mg/m$^2$ over 46 h for 6–8 cycles.

### Disease evaluation

Table 1 shows the profile of the Resection of metastatic colorectal cancer after Oxaliplatin, Fluorouracil, and leucovorin (ROOF) study. Patients with unresectable liver-only metastases from colorectal cancer were treated with 6–8 cycles of mFOLFOX6 as neoadjuvant chemotherapy. Tumor response was assessed every three cycles (6 weeks) with the same method as baseline, and was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Treatment was planned for 6–8 cycles.

**Table 1** The outline of the ROOF study of patients with unresectable liver-only metastases from colorectal cancer




Reassessments for resectability after neoadjuvant chemotherapy were made. Hepatic resection was attempted by investigators when technically positive and when potentially curative. If it was judged that the tumor turned out to be resectablewhen it had initially been determined unresectable, tumor resection was planned within 3–6 weeks from the last administration of preoperative chemotherapy. Six cycles of mFOLFOX6 as adjuvant postoperative chemotherapy is recommended after hepatectomy.

### Endpoints

The primary endpoint was the rate of patients with macroscopically curative surgery including liver resection. The definition of the patients who completed the treatment was those with unresectable liver-only metastases from colorectal cancer who were able to be treated with 6–8 cycles of mFOLFOX6 as neoadjuvant chemotherapy, with macroscopic R0 hepatectomy performed within 3–6 weeks of the last treatment cycles. If the excision of all the metastases was not possible, it was assumed that RFA or MCT in addition to hepatectomy was acceptable as the complete treatment.

Secondary endpoints included R0 resection rate, overall survival, response rate of neoadjuvant chemotherapy, percentage reduction after chemotherapy, pathological response rate, adverse event of neoadjuvant chemotherapy, and liver damage after mFOLFOX6 treatment and safety of hepatectomy.

### Statistical considerations

The sample size was calculated to be 32 in order to show an improvement in resection rate from 20 to 40% with the acceptance of a 5% type I error under a 80% statistical power. Taking ineligible patients into account, the sample size in this study was set at 35.

## Results

### Patients characteristics

A phase II multicenter cooperative study was conducted in 38 medical institutions using mFOLFOX6 as neoadjuvant chemotherapy from January 2008 to June 2009. 36 patients (23M/13F, ECOG PS 0-1) were enrolled. Eligible patient characteristics at the time of study entry are listed in Table 2. The median age of the patients was 62.5 years, 78% (28 patients) had 5 or more metastatic tumors, and 56% (20 patients) had metastatic tumors over 5 cm in diameter. In these cases, 15 patients (42%) had $\geq 5$

metastatic tumors and at least one tumor >5 cm in maximum diameter (H3) [11]. Moreover, 3 cases with liver metastases that were technically unresectable, with <5 metastatic tumors and a tumor <5 cm in maximum diameter (H1) [11], were noted (Table 2). H1, H2, and H3 of liver metastases are defined as in General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus: 7th Edition, 2009, by Japanese Society for Cancer of the Colon and Rectum [11]. The synchronicity of liver metastases was 32 synchronous (89%) and 4 metachronous (11%).

## Neoadjuvant treatment administration and adverse events

Thirty-one patients (86.1%) out of 36 enrolled patients completed treatment with 6–8 cycles of mFOLFOX6, with a median of 6 cycles of treatment (range 1–8 cycles).

For safety assessment, adverse events were graded according to National Cancer Institute Common Criteria version 2.0. With regard to the hematological toxicity, neutropenia was observed as grade 3 in 8 patients, and grade 4 in 3 patients (Table 3). As for non-hematological toxicity, there were 4 patients with grade 2 peripheral neuropathy. Grade 3/4 adverse events included nausea, vomiting, and stomatitis; there was one case (3%) with grade 3 (Table 3). No patient died from the mFOLFOX6 treatment. Six to eight cycles of mFOLFOX6 as neoadjuvant chemotherapy were administered safely in general.

**Table 2** Patient characteristics

| Characteristic | Cases | % |
|---|---|---|
| Age (years), median (range) | 62.5 (45–72) | |
| Sex | | |
| Male | 23 | 64 |
| Female | 13 | 36 |
| ECOG | | |
| PS 0 | 35 | 97 |
| PS 1 | 1 | 3 |
| Primary tumour site | | |
| Colon | 18 | 50 |
| Rectum | 18 | 50 |
| Reason for unresectability | | |
| ≥5 metastases | 28 | 78 |
| >5 cm | 20 | 56 |
| Technically non-resectable | 3 | 8 |
| Before treatment | | |
| Operation | 28 | 78 |
| No operation | 8 | 22 |
| Synchronicity of liver metastases | | |
| Synchronous | 32 | 89 |
| Metachronous | 4 | 11 |

There was only one case (7%) of perioperative complications, with MRSA infection, among 14 hepatectomies.

## Best response of neoadjuvant chemotherapy

The mFOLFOX6 regimen was safety administered, resulting in 18 partial responses (50%), 12 stable disease, and 4 progressive disease (Table 4). A high disease control rate of 83.3% (30/36) was also confirmed by this study.

## Resection rate

14 out of 36 patients (38.9%) underwent surgery with curative intent, in whom R0 resection was achieved in 13 out of 14 patients (R0: 13; R1: 1). Thirteen patients (36.1%) underwent R0 surgery after all. Of 36 patients enrolled with unresectable liver-only metastases from colorectal cancer, the number of patients who could be treated with 6–8 cycles of mFOLFOX6 treatment was 31 (86.1%). Five cases dropped out from the treatment in 1–5

**Table 3** Toxicity

| No. of patients ($n$ = 36) | | | | | |
|---|---|---|---|---|---|
| NCI-CTC grade: | 1 | 2 | 3 | 4 | 3/4 (%) |
| Hematotoxicity | | | | | |
| Leukopenia | 7 | 9 | 3 | 0 | 8 |
| Neutropenia | 2 | 4 | 8 | 3 | 31 |
| Thrombopenia | 20 | 5 | 0 | 0 | 0 |
| Anemia | 19 | 7 | 1 | 0 | 3 |
| Non-hematotoxicity | | | | | |
| Peripheral neuropathy | 16 | 4 | 0 | 0 | 0 |
| Nausea | 9 | 4 | 1 | 0 | 3 |
| Vomiting | 1 | 0 | 1 | 0 | 3 |
| Diarrhea | 4 | 1 | 0 | 0 | 0 |
| Appetite loss | 4 | 0 | 0 | 0 | 0 |
| Fatigue | 2 | 0 | 0 | 0 | 0 |
| Fever | 2 | 1 | 0 | 0 | 0 |
| Stomatitis | 3 | 2 | 1 | 0 | 3 |
| Dysgeusia | 3 | 1 | 0 | 0 | 0 |

**Table 4** Best response to neoadjuvant chemotherapy

| | Cases ($n$ = 36) | % |
|---|---|---|
| Complete response | 0 | 0 |
| Partial response | 18 | 50.0 |
| Stable disease | 12 | 33.3 |
| Progressive disease | 4 | 11.1 |
| Not evaluable | 2 | 5.6 |

cycles, although it was a study protocol that six cycles or more of chemotherapy were received. Those cases with poor compliance were not able to undergo hepatectomy.

Characteristics of patients undergoing hepatectomy

Fourteen patients (11 male/3 female, ECOG performance status 0) underwent attempted post-chemotherapeutic resection of liver-only unresectable metastases from colorectal cancer. Theedian age of the patients was 65.2 years; the synchronicity of liver metastases were 11 synchronous and 3 metachronous. H1, H2, and H3 degrees of liver metastases occurred in one case, 10 cases, and 3 cases, respectively [11]. The median number of cycles of neoadjuvant chemotherapy was 6.5.

There were 9 cases who underwent hepatectomy among 15 cases who had received six cycles of mFOLFOX6. All 3 cases who received seven cycles of mFOLFOX6 underwent hepatectomy. However, there were only 2 cases who became eligible for hepatectomy among 12 cases who had received up to eight cycles of mFOLFOX6. According to the protocol treatment of 8 cycles of mFOLFOX6, only one case was able to undergo hepatectomy after additional mFOLFOX6. Though the standard in the protocol by which the operation is performed was after 3 weeks and within 6 weeks from the final chemotherapy, there were four cases (29%) who actually underwent hepatectomy after 7 weeks due to convenience for the patient and the hospital or problems with liver function.

Surgical procedures were partial hepatectomy in 3 patients, hepatic segmentectomy in 2 patients, hepatic lobectomy in 2 patients, hepatic segmentectomy plus partial hepatectomy in 2 patients, hepatic lobectomy plus partial hepatectomy in 2 patients, hepatic extended lobectomy plus partial hepatectomy in 2 patients, and one hepatectomy including RFA.

Degree of liver metastasis (H factor)

General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus: 7th Edition, 2009, by Japanese Society for Cancer of the Colon and Rectum indicates an H factor regarding liver metastases [11]. H1 is defined as less than 4 liver metastases and below 5 cm in maximum diameter of liver metastases. On the other hand, H3 is defined as more than 5 liver metastases and over 5 cm in maximum diameter of liver metastases. H2 is defined as anything except H1 and H3. The response rates of H1, H2, and H3 were 66.7% (2 out of 3 H1 cases), 55.6% (10 out of 18 H2 cases), and 40.0% (6 out of 15 H3 cases), respectively. In all cases, the response rate was relatively high. There was no significant difference in response rate according to the H factor. There was only one case (33.3%) who underwent hepatectomy among the three H1 cases of patients who could not technically have liver metastases resected. There were ten cases (55.6%) who underwent hepatectomy among 18 H2 cases with marginally unresectable liver metastases. There were three cases (20.0%) who underwent hepatectomy among 15 H3cases. The rate of hepatectomy was the highest in H2. We were able to perform hepatectomy in one H1 case out of two with successful chemotherapy, and in seven H2 cases out of ten with successfulchemotherapy. Even though there were six H3 cases with successfulchemotherapy, we could perform hepatectomy in only one case. In other word, it is difficult to perform hepatectomy even if chemotherapy is successful in H3 cases.

## Discussion

Colorectal cancer is the third leading cause of cancer death, primarily attributed to metastatic disease rather than to the primary tumor in Japan. Surgery remains the only potentially curative treatment for metastatic disease. Less than 15% of patients with metastatic involvement are candidates for surgery. Some studies have continued to report good overall survival for patients undergoing surgical resection of their liver-only metastases from colorectal cancer [4, 12]. Chemotherapy as a first-line treatment for metastatic colorectal cancer has greatly improved within the last decade. In recent years, the survival of patients with advanced colorectal cancer has been improved, initially by the use of oxaliplatin- or irinotecan-based combination chemotherapy. Subsequently, it has been shown that the efficacy of cytotoxic chemotherapy can be enhanced by the addition of novel targeted agents, notably the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab and the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab.

Chemotherapeutic agents developed in colorectal cancer treatment, such as oxaliplatin associated with 5FU/LV, have demonstrated the ability to reduce tumor burden such that an important fraction of patients initially judged to be inoperable can be resected with curative intent [5, 12]. Delaunoit et al. [13] reported that post-chemotherapy surgical management of advanced colorectal cancer resulted in a 4.1% metastatic disease resection rate, and resection of metastatic disease after chemotherapy is possible in a small but important subset of patients with metastatic colorectal cancers, particularly after receiving an oxaliplatin-based chemotherapy regimen, with encouraging overall survival and time to progression observed in these highly selected patients. Tournigand et al. [14] found similar results for the secondary surgery rate in their trial, with a significant difference between patients treated with FOLFOX6 and

FOLFIRI (22 vs. 9%, $P = 0.02$). Response rate and resection rate is better for oxaliplatin-based chemotherapy such as FOLFOX. The resection rate has also been prospectively evaluated within phase II and III trials in patients with any-site mCRC, with relative risk of 33–66% and R0 resection rates of up to 22% reported, despite the unselected population [13–19] (Table 5).

Recently, an increasing number of reports on liver resection following intensive chemotherapy in patients with initially unresectable liver metastases have been published (Table 5). Prospective evaluation of conversion chemotherapy for the patients with liver-only, primarily unresectable disease has been undertaken in the phase II setting, with response rates of 48–71% and R0 resection rate of 12–40% in these selected populations [9, 10, 12, 15, 17, 20]. Alberts et al. [10] reported that twenty-five patients (60%) had tumor reduction and seventeen patients (40%) underwent surgery after a median of 6 months of FOLFOX4 chemotherapy in colorectal cancer patients with unresectable liver-only metastases (A North Central Cancer Treatment Group Phase II Study), which is consistent with other studies assessing the activity of FOLFOX4 as first-line therapy for liver-limited metastatic colorectal cancer [13]. The median overall survival from mCRC treated with 5-FU, oxaliplatin and irinotecan has reached over 20 months, whether given concomitantly [15] or sequentially [14], but, despite this, <5% of unresectable patients will live as long as 5 years with chemotherapy alone. In contrast, the reported 5-year survival rate of the highly selected group of patients with initial unresectable liver-only disease treated with conversion chemotherapy, then surgery, ranges from 33 to 50% [5, 6, 20, 21].

In retrospective analysis, a direct correlation between tumor response rate and resection rate has been shown in studies investigating patients with unresectable colorectal liver metastases [21]. A superior response rate has been reported with the FOLFOXIRI regimen (66 vs. 41% with FOLFIRI) which is not able to be used in the first-line setting, with a corresponding increase in R0 resection rate, reported as 36% in a subgroup of patients with liver-only metastatic disease [15]. An apparent increase in steatohepatitis and subsequently increased 90-day mortality after

**Table 5** Post-chemotherapy surgical management of advanced colorectal cancer

| Authors | Trial | Metastases | Regimen | *n* | Resectability rate (%) |
|---|---|---|---|---|---|
| Delaunoit et al. [13] | N9741 | | FOLFOX4 | 267 | 4.1 |
| Tournigand et al. [14] | GERCOR | | FOLFOX6 | 111 | 22 |
| Tournigand et al. [14] | GERCOR | | FOLFIRI | 109 | 9.0 |
| Falcone et al. [15] | GONO | | FOLFOXIRI | 122 | 15 |
| Falcone et al. [15] | GONO | | FOLFIRI | 122 | 6 |
| de Gramont et al. [16] | | | FOLFOX4 | 210 | 6.7 |
| Okines et al. [17] | First BEAT | | Oxaliplatin-based chemotherapy | 949 | 16.1 |
| Okines et al. [17] | First BEAT | | Irinotecan-based chemotherapy | 662 | 9.7 |
| Okines et al. [17] | NO16966 | | FOLFOX4/XELOX + bevacizumab | 699 | 8.4 |
| Okines et al. [17] | NO16966 | | FOLFOX4/XELOX | 701 | 6.1 |
| Van Cutsem et al. [18] | CRYSTAL | | FOLFIRI + cetuximab | 599 | 7.0 |
| Van Cutsem et al. [18] | CRYSTAL | | FOLFIRI | 599 | 3.7 |
| Bokemeyer et al. [19] | OPUS | | FOLFOX6 + cetuximab | 169 | 9.8 |
| Bokemeyer et al. [19] | OPUS | | FOLFOX4 | 168 | 4.1 |
| Bismuth et al. [9] | | Liver-only metastases | Oxaliplatin-based chemotherapy | 330 | 16 |
| Alberts et al. [10] | NCCTG | Liver-only metastases | FOLFOX4 | 44 | 40 |
| Adam et al. [12] | | Liver-only metastases | Oxaliplatin-based chemotherapy | 701 | 13.5 |
| Falcone et al. [15] | GONO | Liver-only metastases | FOLFOXIRI | 39 | 36 |
| Falcone et al. [15] | GONO | Liver-only metastases | FOLFIRI | 42 | 12 |
| Okines et al. [17] | First BEAT | Liver-only metastases | Oxaliplatin-based chemotherapy | 350 | 24.3 |
| Okines et al. [17] | First BEAT | Liver-only metastases | Irinotecan-based chemotherapy | 230 | 18.7 |
| Okines et al. [17] | NO16966 | Liver-only metastases | FOLFOX4/XELOX + bevacizumab | 211 | 12.3 |
| Okines et al. [17] | NO16966 | Liver-only metastases | FOLFOX4/XELOX | 207 | 11.8 |
| Folprecht et al. [20] | CELIM | Liver-only metastases | FOLFOX6 + cetuximab | 53 | 38 |
| Folprecht et al. [20] | CELIM | Liver-only metastases | FOLFIRI + cetuximab | 53 | 30 |
| Our paper | ROOF | Liver-only metastases | mFOLFOX6 | 36 | 38.9 |

liver resection has been reported with irinotecan given before liver surgery. Oxaliplatin is also known to affect the liver, causing sinusoidal dilatation in 19% of cases in the same series [22]. It is interesting to note that in a retrospective series of 105 patients treated with oxaliplatin-based chemotherapy with or without bevacizumab, the investigators reported a lower incidence and severity of sinusoidal dilatation in patients receiving bevacizumab ($P < 0.01$) [23]. Although the choice of chemotherapy regimen may be a key to maximizing resection rate with bevacizumab combinations, the choice to be made is unclear [17].

There are fewer safety concerns with the addition of the EGFR monoclonal antibody, cetuximab, to neoadjuvant chemotherapy. The CELIM study compared two treatment arms both containing cetuximab combined with FOLFIRI or FOLFOX6. After eight cycles, in technically unresectable disease, treatment was continued for four further cycles. In that study, the response rates of FOLFIRI plus cetuximab and FOLFOX6 plus cetuximab reached 57 and 68%, respectively. R0 resection rates of FOLFIRI plus cetuximab and FOLFOX6 plus cetuximab were 30 and 38%, respectively [20].

In our prospective study, we evaluated the efficacy of a combination regimen, 6–8 cycles of mFOLFOX6, in the neoadjuvant treatment of patients with unresectable liver metastases. The present study confirmed the well-known efficacy of mFOLFOX6, with a relatively high response rate of 50% and R0 resection rate of 36.1%. Our data indicate that neoadjuvant chemotherapy is effective mainly for patients with H2, which is defined as more than 5 liver metastases or over 5 cm in maximum diameter of liver metastases considered suitable for surgery after neoadjuvant chemotherapy. The crucial endpoint of neoadjuvant treatment is the achievement of a high R0 resection rate. Strategies that result in higher response rates can lead to high R0 rates.

The optimal regimen for patients with potentially resectable diseases is yet to be defined, but a strong correlation between response to chemotherapy and subsequent resection rate has been described [6]. Therefore, the goal of current medical treatment for unresectable metastatic colorectal cancer is to improve tumor response to maximize the rates of potentially curative resection. As mentioned above, randomized studies have recently shown that the addition of cetuximab to first-line chemotherapy (FOLFOX or FOLFIRI) significantly improves efficacy in patients without activating mutations of the *KRAS* gene in their tumors [18–20]. The use of novel agents such as cetuximab may also provide additional benefit for the R0 resection rate of colorectal liver metastases. Further studies need to address the optimum neoadjuvant combination treatment for patients with initially unresectable liver metastases and standardized criteria for determining respectability. Finally, we suggest that mFOLFOX6 has a high response rate in patients with liver-only metastases from colorectal cancer, allowing for R0 resection of liver metastases in a proportion of patients initially not judged to be optimally resectable.

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**Conflict of interest** No author has any conflict of interest.

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Research Article Open Access

# Dynamic Registration Method with Balancing for Prognostic Factors in Observational Studies

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## Abstract

Randomized controlled trials are the most scientifically informative studies for evaluating treatment effects. However, we need to conduct observational studies to evaluate unallocatable factors such as genotype, preference, or lifestyle. In observational studies, subject characteristics among the comparison groups might be imbalanced due to non-random allocation. We proposed a dynamic registration method to improve comparability among comparison groups with no allocation. The dynamic registration method is a registration method based on the minimization method, which decides whether or not to register a subject based on the background information of subjects already recruited and the new subject. Simulation studies were conducted to examine the performance of this method in improving comparability among comparison groups. Simulation studies showed that the dynamic registration method improves the comparability among comparison groups. The dynamic registration method can be used to enhance the quality of observational studies for unallocatable factors.

**Keywords:** Dynamic registration; Minimization method; Observational study; Simulation studies

## Introduction

To conduct clinical trials ethically and scientifically, we need to consider various issues at the time of protocol planning. One of the most important elements of the design is the method of treatment allocation. Random allocation of treatments is conducted to evaluate the treatment effect in the most optimal way. However, random allocation has a risk of imbalancing important prognostic factors between the treatment groups, particularly in smaller trials. In clinical trials, imbalances in important prognostic factors degrade the quality of the clinical trial and reduce the statistical efficiency even if the imbalanced factors are adjusted in the statistical analysis [1]. In view of these considerations, various allocation methods have been proposed to avoid chance imbalances [1]. In particular, the methods proposed by Taves [2] and by Pocock and Simon [3], and their modifications are widely known as the minimization method and frequently used in clinical trials. The minimization method can be classified as a dynamic allocation method, as the allocation depends on the prognostic factors of subjects already recruited. The minimization method has been recommended as an effective method for treatment allocation in randomized trials [4,5].

Randomized Controlled Trials (RCTs) are the most scientifically informative studies in the evaluation of treatment effects. However, if one aims to compare patient groups with respect to unallocatable factors such as genotype, preference, and lifestyle, randomization cannot be used. In such cases, since conducting RCTs is difficult, observational studies without random allocation are often conducted.

Recently, a number of genetic polymorphisms have been reported to affect pharmacokinetics and pharmacodynamics of drugs. This field in pharmacology, pharmacogenomics, is rapidly developing, and its outcomes, as sensitive genetic biomarkers for drug safety and efficacy, have been already applied to development and proper usage of drugs. An anticancer drug irinotecan (CPT-11) is metabolized to form active SN-38, which is further conjugated and detoxified by UDP-glucuronosyltransferase (UGT) 1A1 enzyme. Genetic polymorphisms of the UGT1A1 would affect an interindividual variation of the toxicity by CPT-11 *via* the alternation of bioavailability of SN-38 [6,7]. Since concerns have been expressed about severe toxicity, such as diarrhea and neutropenia, for treatment with CPT-11, we planned a prospective observational study to investigate whether a patient with the variant UGT1A1 genotypes would be at higher risk for severe toxicity by CPT-11 in Japanese cancer patients. In this observational study, the frequency of the severe toxicity will be compared among the UGT1A1 genotype groups treated with CPT-11-containing regimens.

RCTs generally evaluate efficacy rather than effectiveness, as there are many restrictions that limit generalizability under restricted conditions. On the other hand, observational studies can evaluate effectiveness under the conditions of real clinical practice [8]. In observational studies, however, unequal distribution of prognostic factors among compared groups causes confounding bias. Although evaluation of the compared factors in observational studies requires adjustment for confounding factors through statistical analyses, if the distributions of the prognostic factors greatly differ among comparison groups, this adjustment is difficult. Methods to adjust for confounding factors have included stratification, regression models such as Cox proportional hazards model, and propensity score methods [9]. However, when the distributions of the prognostic factors hardly overlap among compared groups, the results from statistical analyses should be interpreted carefully [10]. Therefore, even in observational studies, procedure to improve the comparability among comparison

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groups as much as possible before starting the study might be important and enhance the quality of the study. The matched case-control approach is considered as a method for this purpose. However, especially in the case where the number of controls is large relative to the number of cases, this approach requires large resources and costs since this approach needs follow up of all registered subjects until matching pairs are formed.

In this paper, we propose a dynamic registration method which dynamically judges subject registration using the minimization method to reduce resources and costs in conjunction with improvement in comparability for prognostic variables between two groups in the observational studies. We examined the performance of the dynamic registration method for improvement of comparability between two groups through simulation studies.

## Methods

### Proposed dynamic registration

The proposed dynamic allocation method is a prospective registration method which does not register a new subject if it would be difficult to maintain the balance in prognostic factors among groups consisting of unallocatable factors such as subject preferences, habits, and genes if the subject were registered. Note that subjects who are not registered are put in a tentative registration pool as candidates for registration. To apply the dynamic registration method, first, we need to decide the prognostic factors related to the outcome before starting the study. Next, we set the registration probabilities so that the best possible balance was obtained between the comparison groups based on prognostic-factor information of subjects already recruited and a candidate for registration. The registration probability is the probability of registration given for the candidate. The registration probability will be high if registration of the subject would improve the balance in prognostic factors between groups. In contrast, the registration probability will be low and registration of the subject will be difficult if it would adversely affect the balance. The registration procedure is shown in Figure 1.

### Procedure of dynamic registration

The minimization method used in randomized controlled trials was independently proposed by Taves [2] and Pocock and Simon [3], but the method proposed by Taves is often used due to its practical convenience [4]. The dynamic registration method proposed in this study was developed based on Taves' minimization method from a practical viewpoint. We will explain the procedure of the dynamic registration method based on examples (Table 1) presented by Scott et al. [4].

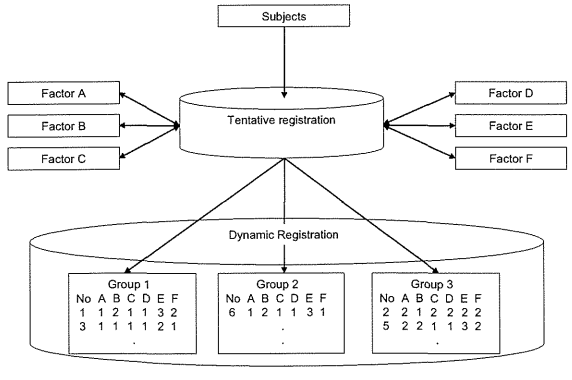



**Figure 1:** Flow chart of dynamic registration.

As shown in Table 1, a total of 16 subjects, 8 in each group, have already been registered in this example. A 17th subject (male, aged 38 and with a high risk factor) has been tentatively registered as a candidate for registration. Whether or not this subject will be registered is decided based on whether the overall balance in prognostic factors can be maintained. The balance between groups is evaluated by comparing the total values of the levels of prognostic factors that correspond to the background of the candidate for registration between groups. If the total becomes nearly equal between groups, it signifies that the overall balance between groups will improve. As shown in Table 1, in this example the 17th subject will be registered as it will improve the overall balance in prognostic factors between groups.

### Measures for balance between comparison groups

Let $N_k$, and $N$ be the planned number of subjects for group $k$ ($k$=1, 2) and the total number of subjects in all groups. Let $n_k$ and $n$ be the number of subjects in group $k$, immediately before a new subject is tentatively registered and the number of subjects in all groups is totaled. Then, when the number of subjects with level $j$ ($j$ =1, 2,..., $Q_i$) of factor $i$ ($i$ =1, 2,..., $P$) in group $k$ is expressed as $n_{ijk}$, the proportion of level $j$ of factor $i$ in group $k$ becomes $n_{ijk}/n_k$. The balance of the distribution of factors between groups is evaluated by the difference in the proportion $n_{ijk}/n_k$ for all $i$ and $j$ between groups.

We consider $S_k = \sum_{i,j=r_i} n_{ijk}$, which is the total number of subjects corresponding to the same level of each factor as a candidate for registration for all factors, as a measure to evaluate the imbalance in the distribution of factors between groups. Here, $r_i$ is the level of factor $i$ of the candidate for registration. When the candidate belongs to group $k_s$, a balance in the distribution of factors might be maintained between group $k_s$ and group $k$ within a certain range by registering this candidate in the case of $S_{k_s} \le \frac{N_{k_s}}{N_k} \cdot S_k$. When the planned number of subjects is the same between groups, the condition is $S_{k_s} \le S_k$.

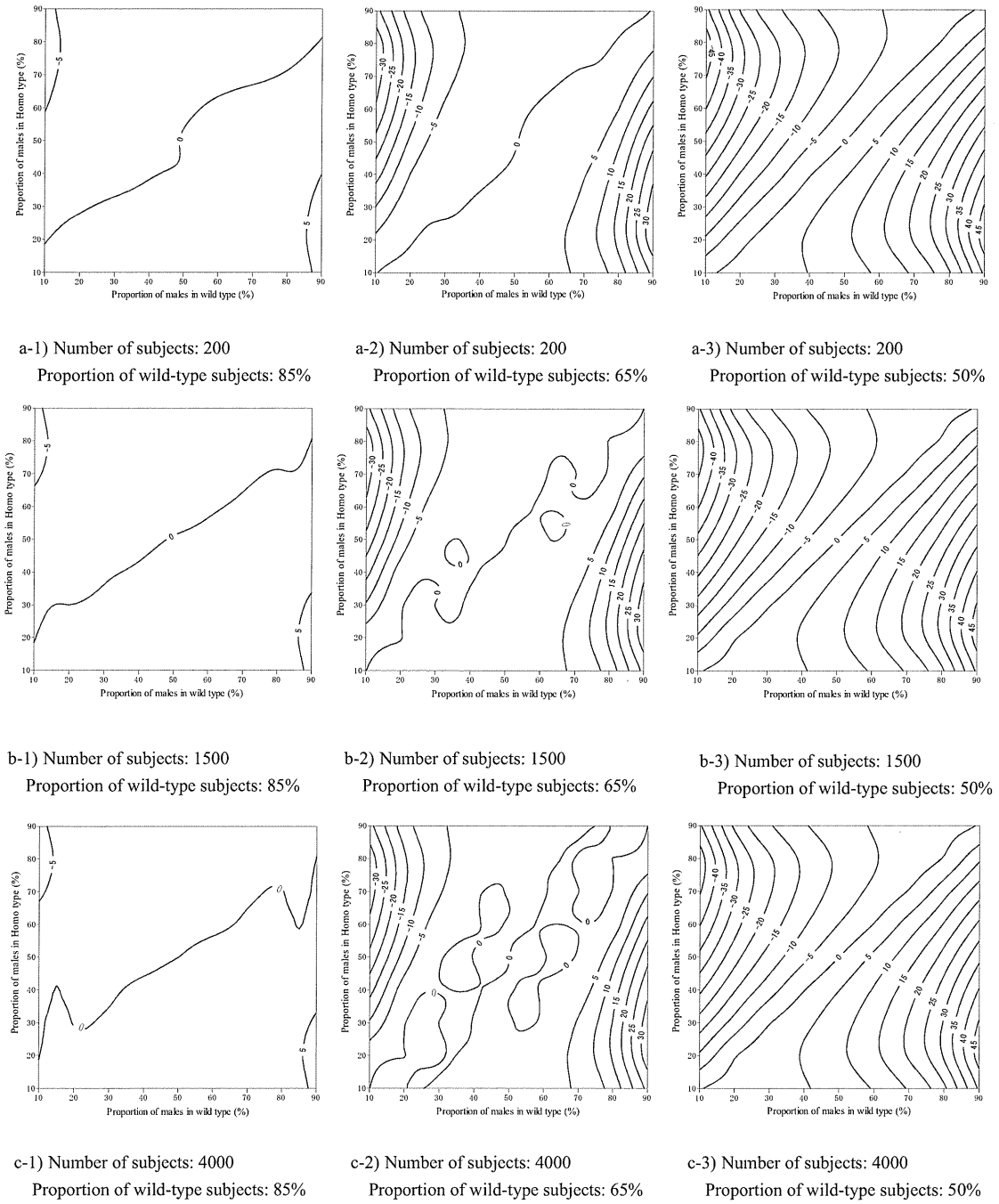
## Decision of subject registration

Next, we set the registration probability of a candidate for registration based on each group's $S_k$ ($k$ = 1, 2). We consider group

| Prognostic factor | Group 1 | Group 2 |
|---|---|---|
| Sex | | |
| Male | 3 | 5 |
| Female | 5 | 3 |
| Age band | | |
| 21-30 | 4 | 4 |
| 31-40 | 2 | 3 |
| 41-50 | 2 | 1 |
| Risk factor | | |
| High | 4 | 5 |
| Low | 4 | 3 |

If the 17th subject has factors Male, 31-40, High in Group 1:
Total in group 1, 3+2+4=9.
Total in group 2, 5+3+5=13.
17th subject is registered because 9≤13

**Table 1:** An example of how the dynamic registration works in a setting of an observational study.




a-1) Number of subjects: 200
Proportion of wild-type subjects: 85%

a-2) Number of subjects: 200
Proportion of wild-type subjects: 65%

a-3) Number of subjects: 200
Proportion of wild-type subjects: 50%

b-1) Number of subjects: 1500
Proportion of wild-type subjects: 85%

b-2) Number of subjects: 1500
Proportion of wild-type subjects: 65%

b-3) Number of subjects: 1500
Proportion of wild-type subjects: 50%

c-1) Number of subjects: 4000
Proportion of wild-type subjects: 85%

c-2) Number of subjects: 4000
Proportion of wild-type subjects: 65%

c-3) Number of subjects: 4000
Proportion of wild-type subjects: 50%

**Figure 2:** Contour line plots of mean of the proportion difference in wild-type and homo-type males in the simulations, with the probability (%) of a male of the wild type on the x-axis and the probability (%) of a male of the homo type on the y-axis.

$k$ = 2 as a reference group without the dynamic registration (100% registration) so as not to unnecessarily increase the number of subjects not registered. The logic for registration of a candidate in group 1 is described as follows.

If $a_1 S_1 \leq \frac{N_1}{N_2} S_2$ then $P$ {registration of subject in group 1}= $p_1$

Else if $a_2 S_1 \leq \frac{N_1}{N_2} S_2$ then $P$\{registration of subject in group 1\} = $p_2$

:

Else if $a_{L-1} S_1 \leq \frac{N_1}{N_2} S_2$ then $P$\{registration of subject in group 1\} = $p_L$-1

Else then $P$\{registration of subject in group 1\}= $p_L$