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ORIGINAL ARTICLE

A phase 2 study of adjuvant chemotherapy with 5-fluorouracil/leucovorin and oxaliplatin after lung metastasectomy for colorectal cancer (WJOG5810G)

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Abstract

Background: The clinical significance of adjuvant chemotherapy after lung metastasectomy for colorectal cancer remains unknown. This phase 2 study evaluated adjuvant chemotherapy with modified 5-fluorouracil/leucovorin and oxaliplatin (mFOLFOX6) after lung metastasectomy.

Methods: Eligibility criteria included colorectal adenocarcinoma, first curative resection of ≤4 lung metastases, and no prior chemotherapy. Treatment consisted of 12 cycles of mFOLFOX6. The primary endpoint was the 5-year overall survival (OS) rate, with the expectation of 50% (threshold, 35%) and a planned sample size of 100 (90% power; alpha error, 5%).

Results: Fifty-two patients were enrolled between July 2011 and July 2014; patient enrollment was closed prematurely because of slow accrual. Excluding four ineligible patients, the characteristics of the 48 patients in the efficacy analysis set were a median age of 62 years (range, 43–75 years), Eastern Cooperative Oncology Group performance status of 0 in 45 patients, prior resection of extrathoracic metastasis in four patients, and postoperative carcinoembryonic antigen within normal range in 43 patients; the status of lung metastasis was single in 34 patients, unilateral in 40 patients, and metachronous in 41 patients; and a disease-free interval between primary tumor resection and diagnosis of lung metastasis of <2 years in 33 patients. The 5-year OS rate was 85.2% (95% confidence interval [CI], 71.4%–92.6%), and the 5-year disease-free survival rate was 60.2% (95% CI, 44.9%–72.4%). Forty-one of the 52 patients (78.8%) in the safety analysis set completed 12 cycles of mFOLFOX6. Grade ≥3 adverse events were neutropenia (50.0%), fatigue (7.7%), peripheral sensory neuropathy (7.7%), and other (<5%).

Conclusions: Adjuvant chemotherapy with mFOLFOX6 is feasible, and may be effective after lung metastasectomy for colorectal cancer.

KEYWORDS
adjuvant chemotherapy, colorectal cancer, lung metastasectomy, modified 5-fluorouracil/leucovorin and oxaliplatin (mFOLFOX6), oligometastasis

INTRODUCTION

Approximately 1.1 million cases of colorectal cancer (CRC) are reported annually worldwide, and CRC is the second leading cause of death due to malignancy after lung cancer.[1,2] The prognosis of patients with unresectable metastatic CRC is poor, with a median survival time of approximately 30 months.[3–6] Surgical resection has been attempted in patients with resectable metastasis of CRC. Several reports indicate that liver metastasectomy for CRC, including initially unresectable liver metastasis that became resectable after systemic chemotherapy, resulted in 5-year overall survival (OS) rates ranging from 35% to 58%.[7–10] Although the clinical significance of lung metastasectomy (LM) for CRC has not been proven, one early-terminated randomized trial showed a hazard ratio of 0.82 (95% confidence interval [CI], 0.43–1.56)[11] as well as in its collaborative prospective cohort studies.[12–14] LM is recommended as the standard of care in European Society for Medical Oncology and National Comprehensive Cancer Network guidelines[15,16] on the basis of many retrospective analyses of LM reporting 5-year OS rates from 27% to 48%.[17–21] Thus, LM is recognized as an important treatment option for resectable lung metastasis from CRC.

Postoperative adjuvant chemotherapy (AC) is the standard of care for stage III colon cancer to prevent recurrence after primary tumor resection.[22] Two clinical trials have shown the benefits of post- or perioperative AC added to liver metastasectomy for CRC.[23,24] In contrast, AC after LM for CRC has not been investigated prospectively. One retrospective study reported that AC after LM for CRC prolonged disease-free survival (DFS) but not OS, and two other studies did not show a survival benefit.[25–27] Thus, the benefits of AC after LM for CRC are controversial. Therefore, we conducted a prospective phase 2 study of AC after LM for CRC.

MATERIALS AND METHODS

Study design

This was a phase 2, multicenter, open-label, single-arm study (WJOG5810G). The study protocol was approved by the ethics review committee of each institution. All participating patients provided written informed consent before enrollment. This study was conducted in compliance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Studies, and was registered at the University Hospital Medical Information Network (000005693).

Patients

Eligibility criteria included age 20–75 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, preserved organ function, initial LM resulting in no residual disease including the primary tumor and extrathoracic lesions, adenocarcinoma pathologically confirmed as metastasis from CRC, four or fewer lung metastases in the resected specimens, no hilar or mediastinal lymph node metastasis if resected, 70 days or less after LM, and no prior systemic chemotherapy except for AC with fluoropyrimidine alone after resection of the primary tumor and/or extrathoracic lesions if it was completed more than 180 days before recurrence.

Procedure

Treatment consisted of modified FOLFOX6 (mFOLFOX6; a drip infusion of oxaliplatin [L-OHP] 85 mg/m^2 and L-leucovorin 200 mg/m^2, a bolus injection of 5-fluorouracil [5-FU] 400 mg/m^2, and continuous infusion of 5-FU 2400 mg/m^2) repeated every 2 weeks for 12 cycles, which was started within 14 days after registration. Criteria for dose reduction for each agent and dose delay were specified. The study treatment was discontinued under the following conditions: detection of recurrence, occurrence of an unacceptable severe adverse event, treatment delay of >36 days due to any adverse event, a third dose reduction of 5-FU required because of adverse events (although cessation of L-OHP due to neuropathy or allergic reactions was permitted), patient refusal to continue the study treatment, or the attending physician's decision to discontinue treatment for any reason. Laboratory tests and medical examinations were repeated at least once every 2 weeks during the treatment. Adverse events were evaluated according to Common Terminology Criteria for Adverse Events, version 4.0. Tumor marker levels were measured every 2 months for 1 year, every 4 months for 2–3 years, and once every 6 months for 4–5 years after enrollment. Computed tomography was repeated every 4 months for 3 years and every 6 months for 4–5 years after enrollment.

Endpoints

The primary endpoint was the 5-year OS rate, and the secondary endpoints included DFS, safety, and site of recurrence. OS was defined as the time from enrollment to death from any cause. DFS was defined as the time from the date of enrollment to the date of imaging examination detecting recurrence or death, whichever occurred earlier.

Statistical analysis

Efficacy endpoints were analyzed in the efficacy analysis set defined as eligible patients assessable for efficacy, excluding those with incomplete observations/follow-ups or major violations of the study treatment regarding dosage, administration schedule, or concomitant therapy. Safety endpoints were analyzed in the safety analysis set, which included patients who received at least one dose of the study drug. OS and DFS were estimated with the Kaplan–Meier method. The Greenwood formula was used to calculate the standard errors of survival function estimates. The incidence of each adverse event was calculated on the basis of the worst grade observed during the study treatment.

With the expectation of a 5-year OS rate of 50% with a threshold of 35%, 93 patients were required to preserve a power of 0.9 with a one-sided alpha error of 0.05, and the sample size was determined to be 100. Interim analyses were not performed. Central monitoring, based on case reports, was performed regularly. Statistical analyses were performed with SAS software (version 9.4).

RESULTS

Patients

Between July 2011 and July 2014, 52 patients were enrolled from 34 centers in Japan. Patient enrollment was closed prematurely because of slow accrual. Four patients were identified as ineligible after enrollment. The reasons for ineligibility were prior chemotherapy containing L-OHP in four patients (one patient had liver metastasis). All 48 eligible patients were assessed for efficacy, without major protocol violations. Finally, the safety and efficacy analysis sets comprised 52 and 48 patients, respectively. Table 1 shows the patient characteristics and tumor status of the efficacy analysis set. The median age was 62 years (range, 43–75 years); 45 patients (93.8%) had an ECOG performance status of 0, 32 patients (66.7%) had rectal cancer, and postoperative carcinoembryonic antigen (CEA) levels immediately before enrollment were within the normal range in 43 patients (91.5%). Thirty-seven patients (77.1%) had recurrent (metachronous) lung metastases after primary tumor resection, with a disease-free interval (DFI) between primary tumor resection and

TABLE 1 Patient characteristics in the efficacy analysis set (n = 48).

Parameter			
Age, median (range), years		62	(43–75)
Sex, No. (%)	Male	28	(58.3)
	Female	20	(41.7)
ECOG performance status, No. (%)	0	45	(93.7)
	1	3	(6.3)
Primary tumor location, No. (%)	Colon	16	(33.3)
	Rectum	32	(66.7)
N stage at primary surgery, No. (%)	0	30	(62.5)
	1–3	18	(27.5)
Prior adjuvant chemotherapy after primary tumor resection, No. (%)	None	31	(64.6)
	Fluoropyrimidine	17	(35.4)
Resection of extrathoracic metastasis, No. (%)	(–)	44	(91.7)
	(+)	4	(8.3)
Timing of diagnosis of lung metastasis, No. (%)	Synchronous	11	(22.9)
	Metachronous	37	(77.1)
Disease-free interval between primary tumor resection and diagnosis of lung metastasis, median (range), months		17	(0–88.8)
Disease-free interval between primary tumor resection and diagnosis of lung metastasis, years	<2	33	(68.7)
	≥2	15	(31.3)
Postoperative CEA, No. (%), ng/mL[a]	≤5	43	(91.5)
	>5	4	(8.3)
Postoperative CA 19-9, No. (%), U/mL[a]	≤37	45	(95.7)
	>37	2	(4.3)
Laterality of lung metastasis, No. (%)	Unilateral	38	(79.2)
	Bilateral	10	(20.8)
Lung metastases, median (range), No.		1	(1–4)
Lung metastases, No. (%)	1	34	(70.9)
	≥2	14	(29.1)
Mode of pulmonary resection, No. (%)	Wedge resection	32	(66.7)
	Anatomic[b]	16	(33.3)
Maximum size of lung metastasis, median (range), mm		10	(1–55)

Abbreviations: CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group.
[a]Missing in one patient.
[b]Segmentectomy or lobectomy.

diagnosis of lung metastasis of 17 months (range, 0–89 months) at median and >2 years in 15 patients (31.3%). Thirty-four patients (70.8%) had solitary lung metastasis, and 38 patients (79.2%) had unilateral metastasis. The median diameter of the largest lung metastasis pathologically was 10 mm (range, 1–55 mm).

Efficacy

All patients in the efficacy analysis set, except for one who was lost 2 years after enrollment, were followed up for at least 5 years. The 5-year OS rate was 85.2% (95% CI, 71.4%–92.6%; 90% CI, 74.2%–

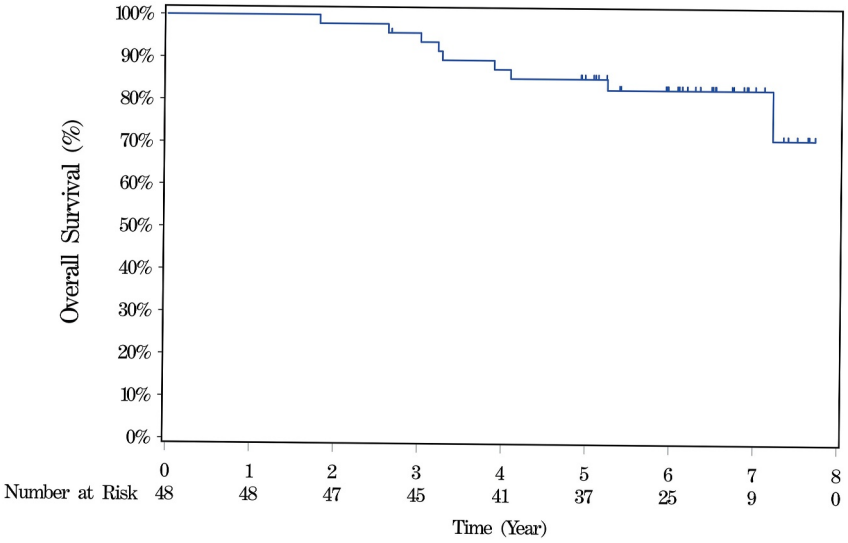

FIGURE 1 Overall survival after lung metastasectomy in the efficacy analysis set (n = 48).

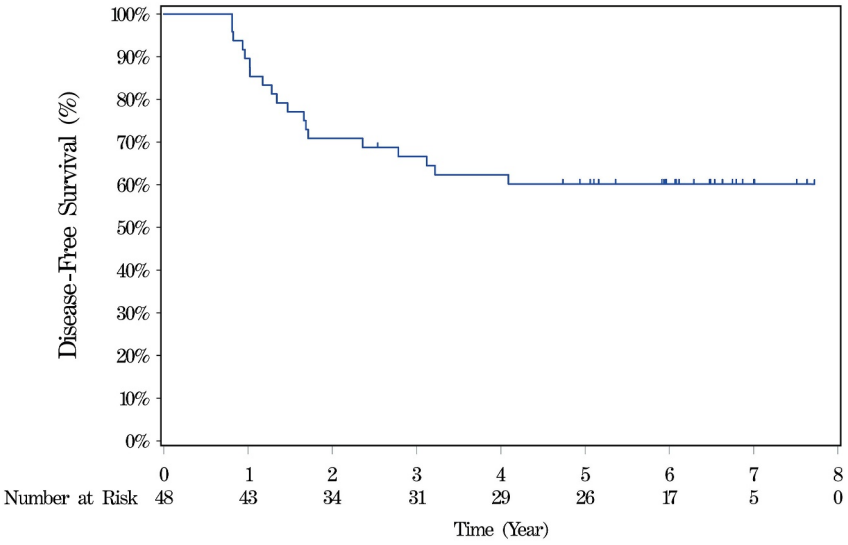

FIGURE 2 Disease-free survival after lung metastasectomy in the efficacy analysis set (n = 48).

91.8%) (Figure 1), and the 5-year DFS rate was 60.2% (95% CI, 44.9%–72.4%) (Figure 2). No recurrences were observed during treatment. Among 19 patients with recurrence, the sites of recurrence were the lungs in 13 patients, liver in three patients, and other in seven patients (double counting multiple recurrences).

Table 2 shows the subset analysis of OS. Although there was no subset showing a significant difference in OS, patients with older age, the primary tumor in the colon, postoperative CEA level higher than the normal range, bilateral lung metastasis, and number of lung metastases ≥3 showed substantially lower 5-year OS rates compared with the others. No recurrence was observed in patients with a DFI of ≥2 years (Figure S1).

Treatment exposure

Among the 52 patients in the safety analysis set, 41 (78.9%) completed the study treatment (12 cycles of mFOLFOX6). The reasons for discontinuation in the remaining 11 patients (21.1%) were related to adverse events: patient refusal in eight patients (peripheral

TABLE 2 Subset analysis of overall survival in the efficacy analysis set (n = 48).

Parameter	Subset	No.	5-year overall survival rate (95% CI)		Hazard ratio[a] (95% CI)	
Age, years	<65[b]	29	89.4	(70.6–96.5)	3.03	(0.76–12.14)
	≥65	19	78.9	(53.2–91.5)		
	<70[b]	38	89.3	(73.8–95.8)	2.44	(0.58–10.20)
	≥70	10	70.0	(32.9–89.2)		
Sex	Male[b]	28	81.6	(61.3–91.9)	0.62	(0.15–2.49)
	Female	20	90.0	(65.6–97.4)		
Primary tumor location	Colon[b]	16	80.4	(50.6–93.2)	0.50	(0.13–1.87)
	Rectum	32	87.5	(70.0–95.1)		
N stage at primary surgery	0[b]	30	83.3	(64.5–92.7)	1.42	(0.38–5.29)
	1–3	18	88.2	(60.6–96.9)		
Prior adjuvant chemotherapy	(–)[b]	31	83.9	(65.5–92.9)	0.89	(0.22–3.57)
	(+)	17	87.5	(58.6–96.7)		
Prior resection of extrathoracic metastasis	(–)[b]	44	86.1	(71.7–93.5)	1.76	(0.22–14.35)
	(+)	4	75.0	(12.8–96.1)		
Timing of diagnosis of lung metastasis	Synchronous[b]	11	81.8	(44.7–95.1)	0.48	(0.11–2.01)
	Metachronous	37	86.2	(69.9–94.0)		
Disease-free interval, years	<1[b]	17	76.5	(48.8–90.4)	0.39	(0.10–1.45)
	≥1	31	90.0	(72.1–96.7)		
	<1.5[b]	25	80.0	(58.4–91.1)	0.51	(0.13–2.04)
	≥1.5	23	90.9	(68.3–97.6)		
	<2[b]	33	78.8	(60.6–89.3)	—	—
	≥2	15	100.0	—		
Postoperative CEA, ng/mL[c]	≤5[b]	43	88.1	(73.8–94.9)	3.49	(0.70–17.30)
	>5	4	50.0	(5.8–84.5)		
Postoperative CA 19-9, U/mL[c]	≤37[b]	45	84.2	(69.6–92.1)	—	—
	>37	2	100.0	(100–100)		
Laterality	Unilateral[b]	38	89.5	(74.3–95.9)	2.26	(0.56–9.07)
	Bilateral	10	67.5	(29.1–88.2)		
Lung metastases, No.	1[b]	34	88.2	(71.6–95.4)	1.47	(0.37–5.94)
	≥2	14	77.4	(44.9–92.1)		
	1 or 2[b]	41	90.2	(76.1–96.2)	5.08	(1.21–21.40)
	≥3	7	51.4	(11.8–81.3)		
Mode of resection	Wedge[b]	32	84.4	(66.5–93.2)	0.60	(0.12–2.93)
	Anatomic[d]	16	86.7	(56.4–96.5)		
Maximum size of lung metastasis, mm	<10[b]	21	85.7	(62.0–95.2)	1.04	(0.28–3.89)
	≥10	27	84.7	(64.3–94.0)		

Abbreviations: CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval.

[a]Hazard ratio comparing lower with upper subsets.

[b]Reference for calculating a hazard ratio.

[c]Missing in one patient.

[d]Segmentectomy or lobectomy.

sensory neuropathy in three, frequent hospital visits associated with treatment cycle delay due to neutropenia in two, thrombosis in one, fatigue in one, and anxiety from adverse events in one) and physician judgment in three patients (encephalopathy associated with hyperammonemia in one, treatment cycle delay due to liver dysfunction in one, and ileus in one).

The treatment cycle was delayed at least once in 46 patients (88.4%), most frequently due to neutropenia. A one-level dose reduction of 5-FU or L-OHP was required in 23 patients (44.2%), and a two-level dose reduction was required in nine patients (17.3%); neutropenia and peripheral sensory neuropathy were the most frequent reasons for dose reduction. The median dose intensities (relative dose intensities) of L-OHP, bolus 5-FU, and continuous 5-FU were 27.7 mg/m^2/week (65.3%), 161.5 mg/m^2/week (80.7%), and 999.0 mg/m^2/week (83.3%), respectively.

Safety

A summary of the adverse events in the safety analysis set is presented in Table 3. Adverse events of grade ≥3 with an incidence of ≥5% were neutropenia (50.0%), fatigue (7.7%), and peripheral sensory neuropathy (7.7%). Treatment-related death was not observed.

Postrecurrence treatment

Among the 23 patients with recurrence in the efficacy analysis set, repeated metastasectomy was performed in 16 patients (69.6%) (intrathoracic surgery in 13, liver resection in two, other in two, and double counting multiple surgeries in one), and chemotherapy containing L-OHP was reused in 10 patients (43.2%). The 5-year OS rate of the 23 patients was 63.2% (95% CI, 37.9%–80.4%).

DISCUSSION

Most previous studies on postoperative AC after LM for CRC have been retrospective,[25–28] and these retrospective analyses were inconsistent regarding subjects such as the number of lung metastases, postoperative AC, and postoperative surveillance, whereas more than half of the patients had rectal cancer as the primary

TABLE 3 Incidences of adverse events in the safety analysis set (n = 52).

Adverse event	G1, %	G2, %	G3, %	G4, %	G3–G4, %
WBC count decreased	21.2	55.8	3.8	0	3.8
Neutrophil count decreased	7.7	28.8	34.6	15.4	50.0
Anemia	17.3	7.7	0	0	0
Platelet count decreased	36.5	15.4	0	0	0
AST increased	67.3	9.6	1.9	0	1.9
ALT increased	48.1	9.6	1.9	0	1.9
Bilirubin increased	15.4	3.8	0	0	0
Creatinine increased	15.4	0	0	0	0
Nausea	50.0	19.2	0	—	0
Vomiting	11.5	5.8	0	0	0
Anorexia	38.5	23.1	3.8	0	3.8
Diarrhea	21.2	5.8	3.8	0	3.8
Mucositis oral	34.6	9.6	0	0	0
Palmar-plantar erythrodysesthesia syndrome	9.6	1.9	1.9	—	1.9
Peripheral sensory neuropathy	40.4	44.2	7.7	0	7.7
Fatigue	36.5	19.2	7.7	—	7.7
Fever	9.6	0	0	0	0
Febrile neutropenia	—	—	1.9	0	1.9
Infections	1.9	1.9	1.9	0	1.9
Allergic reaction	5.8	9.6	1.9	0	1.9
Alopecia	34.6	0	—	—	—

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; G, grade according to Common Terminology Criteria for Adverse Events, version 4.0; WBC, white blood cell.

tumor site consistently. To our knowledge, this is the first study to evaluate the treatment outcomes of AC after LM for CRC.

Unfortunately, the planned number of patient enrollments was not reached. However, the 5-year OS rate, the primary endpoint of this study, was 85.2%, which was associated with a lower limit of 90% CI (corresponding to a one-sided alpha error of 5%) of 74.2%, which was higher than the prespecified threshold of 35%. This implies that our null hypothesis was rejected statistically, regardless of the premature study termination. Although the threshold of the primary endpoint prespecified as 35% in this study seemed low compared to a 5-year OS rate of 54.1% in the recent meta-analysis of LM[29] reported after initiating this study in 2011, it was determined by referring to the 5-year OS rate of 38.3% in a Japanese multicenter retrospective study reported in 2004.[30] Notably, both the 5-year OS and DFS rates in this study were better than those reported in recent studies on LM for CRC.[31]

Some reasons for these favorable results can be considered besides the efficacy of AC with mFOLFOX6, such as selection bias and postrecurrence treatment. Regarding selection bias, the number of metastases is one of the prognostic factors after LM.[31,32] The eligibility criteria limited the number of lung metastases to ≤4, which resulted in the proportion of patients with a single lung metastasis being 70%, which was very similar to that of 74% in a recent Japanese retrospective study with more than 700 patients.[31] Moreover, the proportion of patients with ≥3 lung metastases of 14.6% was also similar to that of 10%–20% in retrospective studies with more than 100 patients.[31,33–35] It is considered that the participants of this study might represent a clinically practical approach of LM for CRC in terms of their number. Furthermore, in a previous retrospective study, a DFI of ≥2 years, the absence of extrathoracic lesions, a normal preoperative CEA level, and the number of lung metastases of <3 were identified as favorable prognostic factors.[31–33] The proportion of patients with extrathoracic metastatic lesions was low, 8.3% in this study, whereas it was 24% in a previous Japanese study.[31] In addition, the proportion of patients with a postoperative CEA level of >5 ng/mL was also low, 8.3% (the preoperative CEA level was not collected). In contrast, the proportion of patients with a DFI of <2 years being 68.7% in this study was higher than the 59% reported in a previous study.[31] Therefore, it is difficult to estimate how much these differences in patient characteristics might have contributed to the favorable results in this study.

Regarding the efficacy of AC, DFS makes for a better cross-trial comparison of the efficacy of AC than OS, although DFS may be influenced by patient background to some extent. The 5-year DFS rate of 60.2% in this study appears to be higher than the 50.6% observed in patients classified into the low-risk group with all four favorable prognostic factors in a previous Japanese report.[31] In that report, fewer than half of the patients received AC after LM, including fluoropyrimidine alone (32%), L-OHP–containing regimens (11%), irinotecan-containing regimens (4%), and other (1%). Although a retrospective study did not show a survival benefit of AC with oral fluoropyrimidine alone in majority of patients after LM,[27] the favorable results of DFS in this study suggest that AC with mFOLFOX6 may be effective after LM for CRC.

However, the survival benefits of AC after resection of distant metastases of CRC remain unclear. Perioperative chemotherapy with FOLFOX showed significant improvement in DFS but not OS.[23] Moreover, in the JCOG0603 study evaluating the efficacy of AC with FOLFOX after liver metastasectomy for CRC, FOLFOX demonstrated superiority for DFS over surgery alone[24] but OS of the surgery-alone group tended to be better than that of the FOLFOX group. Thus, recent research indicates that recurrence-free survival is an inadequate surrogate endpoint for OS after liver metastasectomy for CRC.[36] Nevertheless, the favorable outcomes of both the 5-year OS rate of 85.2% and 5-year DFS rate of 60.2% in this study are considered to support the treatment strategy of LM followed by AC, and encourage a future phase 3 trial of perioperative chemotherapy for LM.

Regarding treatment after recurrence, which might also have contributed to the favorable OS in this study, the 19 patients with recurrence achieved a 5-year OS rate of 63.2%, for whom repeated metastasectomies for recurrent disease were performed in approximately 70%. It was reported that repeated LM for CRC showed a 5-year OS rate of 75.3%.[37] Furthermore, L-OHP was reused after recurrence in approximately 40% of the recurrent patients in this study because only one patient experienced recurrence within 6 months, which suggests that L-OHP might be effective for recurrent disease. These results highlight the effectiveness of multidisciplinary treatment even after recurrence.

The safety profile of mFOLFOX6 in this study was consistent with that in previous reports. Regarding the feasibility of AC with FOLFOX after LM, 41 patients (78.8%) completed the planned treatment in this study. In the MOSAIC trial,[22] which demonstrated the superiority of FOLFOX over 5-FU alone as AC after primary tumor resection of colon cancer, the completion rate of 12 cycles was 74.7%. In the IDEA trial,[38] which compared the duration of AC containing L-OHP for pathological stage III colon cancer between 6 and 3 months, the median dose intensities of L-OHP and 5-FU were 78.9% and 89.9% in patients receiving FOLFOX for 6 months, and these were 65.3% and 83.3% in this study, respectively. It is considered that there were no significant differences in the safety and feasibility of AC with mFOLFOX6 after LM compared with after primary tumor resection of colon cancer.

This study had some limitations. First, the study was prematurely terminated. However, this study has some value because of its prospective nature, with a long follow-up period confirming 5-year survival. Second, patients who had previously used L-OHP were excluded from this study. Because AC containing L-OHP is the standard of care after resection of primary colon cancer, the efficacy of AC with mFOLFOX6 may be reduced in patients who develop recurrence in the lung after AC containing L-OHP. Third, because this was a small, single-arm study, the significance of AC should be confirmed in a randomized

trial. This study provides a rationale for future phase 3 trials. Finally, biomarker analyses such as for *RAS*, *BRAF*, microsatellite instability, and circulating tumor DNA were not conducted. Recently, the *KRAS* mutation has been reported to be an important prognostic predictor of OS and relapse-free survival in patients with CRC undergoing LM.[39] In addition, information regarding primary site, right versus left sided, which have different biology, was not obtained in this study. However, biomarkers for AC have not yet been established. Biomarkers for determining whether to receive AC and for selecting an optimal chemotherapy regimen for each patient are important issues to be clarified in the future for LM for CRC.

In conclusion, adjuvant mFOLFOX6 chemotherapy is feasible, and may be effective after LM for CRC.

AUTHOR CONTRIBUTIONS

Nozomu Machida: Conceptualization, writing–original draft, investigation, project administration, and writing–review and editing. **Takehiro Okumura**: Conceptualization, investigation, project administration, and writing–review and editing. **Narikazu Boku**: Conceptualization, investigation, project administration, writing–original draft, and writing–review and editing. **Junji Kishimoto**: Conceptualization, data curation, formal analysis, and writing–review and editing. **Tomohiro Nishina**: Investigation and writing–review and editing. **Koichi Suyama**: Investigation and writing–review and editing. **Yasuhisa Ohde**: Conceptualization, investigation, and writing–review and editing. **Katsunori Shinozaki**: Investigation and writing–review and editing. **Hideo Baba**: Investigation and writing–review and editing. **Shinya Tokunaga**: Investigation and writing–review and editing. **Hisato Kawakami**: Investigation and writing–review and editing. **Takashi Tsuda**: Investigation and writing–review and editing. **Masahito Kotaka**: Investigation and writing–review and editing. **Hiroyuki Okuda**: Investigation and writing–review and editing. **Hisateru Yasui**: Investigation and writing–review and editing. **Kentaro Yamazaki**: Conceptualization, investigation, and writing–review and editing. **Shuichi Hironaka**: Investigation and writing–review and editing. **Kei Muro**: Conceptualization, investigation, project administration, and writing–review and editing. **Ichinosuke Hyodo**: Conceptualization, investigation, writing–original draft, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

Nozomu Machida has received honoraria from Bristol-Myers Squibb, Ono Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, Merck Sharp & Dohme, Daiichi Sankyo, Astellas Pharma, Yakult Honsha, Merck Biopharma, and Takeda Pharmaceutical. Narikazu Boku has received honoraria from Bristol-Myers Squibb, Ono Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, and Eli Lilly. Tomohiro Nishina has received honoraria from Bristol-Myers Squibb, Ono Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, Daiichi Sankyo, Astellas Pharma, and Merck Sharp & Dohme. Yasuhisa Ohde has received honoraria from AstraZeneca. Hisato Kawakami has received grants from Eisai, Bristol-Myers Squibb, Taiho Pharmaceutical, Astellas Pharma, Daiichi Sankyo, Chugai Pharmaceutical, and Kobayashi Pharmaceutical; royalties from Medical & Biological Laboratories; consulting fees from Daiichi Sankyo, Astellas Pharma, and AbbVie GK; and honoraria from Bristol-Myers Squibb, Bayer Pharma, Eli Lilly, Merck Sharp & Dohme, Ono Pharmaceutical, Chugai Pharmaceutical, Daiichi Sankyo, Merck Biopharma, Takeda Pharmaceutical, Yakult Honsha, Teijin Pharma, Taiho Pharmaceutical, Otsuka Pharmaceutical, Nippon Kayaku, GlaxoSmithKline, Amgen, and Novartis. Masahito Kotaka has received honoraria from Chugai Pharmaceutical, Yakult Honsha, Takeda Pharmaceutical, Taiho Pharmaceutical, and Eli Lilly. Kentaro Yamazaki has received honoraria from Chugai Pharmaceutical, Takeda Pharmaceutical, Yakult Honsha, Taiho Pharmaceutical, Daiichi Sankyo, Merck Biopharma, Eli Lilly, Bristol-Myers Squibb, Ono Pharmaceutical, and Merck Sharp & Dohme. Shuichi Hironaka has received honoraria from Ono Pharmaceutical, Eli Lilly, Chugai Pharmaceutical, Bayer, Taiho Pharmaceutical, Novartis, Astellas Pharma, Daiichi Sankyo, Servier, Merck Sharp & Dohme, Bristol-Myers Squibb, Merck Biopharma, Takeda Pharmaceutical, AstraZeneca, BeiGene, and Yakult Honsha. Kei Muro has received grants from Amgen, Ono Pharmaceutical, Astellas Pharma, Sanofi, Taiho Pharmaceutical, PRA Health Sciences, PAREXEL International, Novartis, Chugai Pharmaceutical, and Merck Sharp & Dohme; consulting fees from Amgen, AstraZeneca, Ono Pharmaceutical, Astellas Pharma, and Chugai Pharmaceutical; honoraria from Ono Pharmaceutical, Taiho Pharmaceutical, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Takeda Pharmaceutical, and Daiichi Sankyo; and participated on advisory boards for Astellas Pharma, Amgen, AstraZeneca, and Takeda Pharmaceutical. Ichinosuke Hyodo participated on data and safety monitoring boards and advisory boards for Taiho Pharmaceutical, Chugai Pharmaceutical, Asahi Kasei Pharma, Daiichi Sankyo, Eisai, and Ono Pharmaceutical. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data from this study are not available because informed consent for publication of the data was not obtained from the enrolled patients.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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