Efficacy of risk-stratified indicators for adjuvant chemotherapy with fluorouracil and oxaliplatin after hepatectomy for colorectal cancer liver metastasis Running title: Risk-stratified indication for doublet AC after hepatectomy for CRLM

Tetsuro Tominaga (tetsuro.tominaga@nagasaki-u.ac.jp)
Nagasaki University Graduate School of Biomedical Science
Keizaburo Maruyama
Nagasaki University Graduate School of Biomedical Science
Takashi Nonaka
Nagasaki University Graduate School of Biomedical Science
Masaaki Moriyama
Nagasaki University Graduate School of Biomedical Science
Shosaburo Oyama
Nagasaki University Graduate School of Biomedical Science
Mitsutoshi Ishii
Nagasaki University Graduate School of Biomedical Science
Terumitsu Sawai
Nagasaki University Graduate School of Biomedical Science
Takeshi Nagayasu
Nagasaki University Graduate School of Biomedical Science

Research Article

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Abstract

Background: The recurrence rate after hepatectomy for colorectal cancer liver metastasis (CRLM) is high, and there is no consensus regarding the effect of adjuvant chemotherapy (AC) using oxaliplatin (doublet AC) in these patients.

Methods: The present study included 91 patients who underwent hepatectomy for complete resection at our hospitals between 2008 and 2018. Based on whether or not they had undergone doublet AC, patients were divided into AC (n=35) and non-AC (n=56) groups. Recurrent risk was evaluated by Memorial Sloan Kettering Cancer Center clinical risk score (MSKCC-CRS).

Results: The number of females and median age were higher in the AC group (51.4% vs 25.0%, p=0.010 and 67 vs 61 years, p=0.012, respectively). Doublet AC was an independent prognostic factor for 5-year relapse-free survival (hazard ratio, 0.225; 95%CI, 0.097–0.522; p<0.001) and for 5-year overall survival (hazard ratio, 0.165; 95%CI, 0.057–0.476; p<0.001) in multivariate analysis. In patients with high risk of recurrence (MSKCC-CRS 3–5), 5-year relapse-free survival and 5-year overall survival was higher in the doublet AC group than in the non-AC group (p<0.01). In low-risk patients (MSKCC-CRS 0–2), 5-year relapse-free survival and 5-year overall survival were similar between the groups.

Conclusions: Doublet AC could have a positive effect on prognosis after curative resection of CRLM, especially in high-risk patients. Selection of patients and AC regimen should take into consideration the risk of recurrence.

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide [1]. The liver is the most common metastatic site, and at least 25%–50% of patients with CRC develop colorectal liver metastases (CRLM) during the course of their illness [2, 3]. Currently, surgery is the only treatment that offers a long-term prognosis for resectable CRLM [4, 5]. However, the recurrence rate after hepatectomy is high, ranging from 50% to 70% [6, 7].

In patients with Stage III CRC, adjuvant chemotherapy (AC) with combined 5-fluorouracil (5FU) and oxaliplatin (doublet AC) has been reported to provide oncological benefit, and 6 months of AC is the gold standard globally [8-10]. The recurrence rate is much higher in patients who undergo curative liver resection than in Stage III patients. Previous randomized controlled trials (RCTs) have examined the oncological benefit of AC after curative resection of CRLM [11-14]. Although relapsefree survival (RFS) was better in the AC group, overall survival (OS) was similar between AC and non-AC groups. This discrepancy might be due to differences in the inclusion criteria or among chemotherapy regimens. In addition, there is no consensus regarding the recommendation for AC after CRLM resection among leading guidelines [15-17].

The aim of this study is to examine the efficacy of doublet AC after curative hepatectomy in patients with CRLM. Furthermore, we identified the patient types in which doublet AC positively affected prognosis.

Materials And Methods

We performed a retrospective review of patients with CRC and liver metastases who had undergone hepatectomy for R0 resection at our hospitals between March 2008 and January 2018. The exclusion criteria were incomplete laboratory data, synchronous metastases at another site at the time of CRLM diagnosis, non-resective procedure (bypass or stoma), and emergency surgery. A final total of 91 patients were eligible for analysis. The study was reviewed and approved by the Clinical Research Review Board of Nagasaki University hospitals.

Patients

The patients were divided into two groups according to whether or not they had received AC after hepatectomy (AC group, n = 35; non-AC group, n = 56). To compare clinical features between the groups, the following data were collected: sex, age at surgery, tumor location, pathological T factor of primary cancer, pathological N factor of primary cancer, synchronous or metachronous metastasis, operative procedure, number of liver metastases, presence or absence of neoadjuvant treatment, Memorial Sloan Kettering Cancer Center clinical risk score (MSKCC-CRS), preoperative CEA level (ng/mL), and postoperative complications. Tumor location was classified as colon (cecum to rectosigmoid colon) or rectum. Synchronous liver metastasis was defined as a disease-free survival interval <12 months, and metachronous liver metastasis was defined as a disease free survival interval >12 months. Postoperative complications were defined as those that occurred within 30 days of the primary surgery. Patients with Clavien–Dindo (CD) grade 2 or higher complications were included in the complication group. Some patients did not receive postoperative chemotherapy, based on the decision of the attending physician, the patients' wishes, advanced age, poor performance status, or poor general condition due to postoperative complications.

Adjuvant chemotherapy

Adjuvant chemotherapy was started at 8 weeks after liver resection and continued for 6 months (12 courses of FOLFOX, 8 courses of XELOX, 8 courses of capecitabine). The fluorouracil-based regimens included FOLFOX (5FU, leucovorin plus oxaliplatin, 2-week interval), XELOX (capecitabin plus oxaliplatin, 3-week interval), and capecitabin monotherapy (4-week interval). We defined doublet AC as fluorouracil plus oxaliplatin regimens, single AC as only fluorouracil regimens.

Scoring and assessment

We used the WHO toxicity criteria to classify adverse events due to treatment. Patient follow-up was performed every 3 months for 5 years, and included clinical examination, laboratory tests (CEA, CA19-9), and thoracoabdominal CT. Risk of recurrence after R0 resection of CRLM was evaluated by MSKCC-CRS (18). The scoring system comprises the following: a) node-positive primary cancer, b) largest metastasis >50 mm, c) multiple liver metastases, d) preoperative CEA level >200 ng/mL, and e) synchronous metastases. Patients were subdivided into six subgroups based on risk factor score (MSKCC-CRS 0–5): the low-risk group included those with scores 0–2, and the highrisk group included those with scores 3–5.

Statistical analysis

Statistical analysis was performed using JMP software (SAS Institute Inc., Cary, NC). Data are presented as the median value and the range. Differences in categorical variables were compared using Fisher's exact test or the chi-squared test, as appropriate. Differences in continuous variables were analyzed with the Mann–Whitney U-test. RFS and OS were calculated using the Kaplan–Meier method. Differences between groups were tested for significance using the log-rank test. Multivariate analysis using a Cox hazards model was used to identify independent risk factors for RFS and OS. Clinical variables with a p value <0.20 in univariate analysis were included in multivariate analysis. All p values <0.05 were considered significant.

Results

Table 1 lists the clinicopathological characteristics of the 91 patients. The study population included 32 male and 59 female patients, with a median age of 65 (range, 31–87) years. Median body mass index was 21 (range, 13–34) kg/m2. Tumor location was the colon in 50 patients (54.9%). The pathological T status of primary cancer was T1 in 4 (4.4%), T2 in 18 (19.8%), T3 in 42 (46.2%), and T4 in 19 (20.1%); 63 patients (69.2%) had pathological node-positive primary cancer; and 55 patients (60.4%) had synchronous CRLM. Preoperative CEA level was 8.5 (range, 1.5–176.5 ng/mL). Fortythree patients (47.3%) had multiple liver metastases and 38 patients (41.7%) received neoadjuvant chemotherapy. The number of MSKCC-CRS high-risk patients was 53 (58.3%). Partial resection was performed in 52 patients (57.1%). Eighteen patients (19.8%) had postoperative complications of severity CD >2. Of the 91 patients, 35 (38.5%) received AC, of whom 16 received a single-agent regimen and 19 received a doublet regimen. In the patients who received a single agent regimen, 68.7% completed the full course and 18.7% suffered severe adverse effects (Grades 3, 4). In the patients who received doublet AC, 31.6% completed the full course and 78.9% suffered severe adverse effects.

Table 2 summarizes the clinical characteristics of the AC and non-AC groups. The proportion of female patients was higher (51.4% vs 25.0%, p=0.010) and median age (67 vs 61 years, p=0.012) was greater in the AC group. Tumor location, pathological T and N factors, timing of liver metastasis, preoperative CEA level, number of liver metastases, presence or absence of neoadjuvant chemotherapy, operative procedure, and postoperative complications were similar between the groups.

Table 3 lists the results of univariate and multivariate analyses for predictors of RFS. Synchronous metastasis (hazard ratio, 0.483; 95%CI, 0.246–0.845; p=0.010) and doublet AC (hazard ratio, 0.225; 95%CI, 0.097–0.522; p<0.001) were independent favorable prognostic factors in univariate and multivariate analysis.

Table 4 lists the results of univariate and multivariate analyses for predictors of OS. Univariate analysis showed that doublet AC was significantly associated with OS (p=0.001). Multivariate analysis indicated the following as independent predictors of OS: number of liver metastases (hazard ratio, 2.767; 95%CI, 1.154–6.634; p=0.022), 5FU monotherapy (hazard ratio, 0.337; 95%CI, 0.142–0.801; p=0.013), and doublet regimen (hazard ratio, 0.165; 95%CI, 0.057–0.476; p<0.001).

The median survival time (MST) of all participants was 45 months. Five-year RFS was significantly higher in patients who received doublet AC compared with the non-AC group (62.3% vs 20.8%, p<0.05) (Fig. 1a). Five-year OS was significantly higher in patients who received doublet AC and single AC (5FU) compared with the non-AC group (81.9%, 60.5% vs 31.2%, p<0.05) (Fig. 1b). Among the MSKCC-CRS high-risk patients, 5-year RFS was significantly higher in the doublet AC group than in the single AC and non-AC groups (70.0% vs 22.2%, 18.9%; p<0.01) (Fig. 1c). Five-year OS was significantly higher in the doublet AC and single AC groups compared with the non-AC group (88.8%, 50.7% vs 30.7%, p<0.05) (Fig. 1d). In the MSKCC-CRS low-risk patients, 5-year RFS and OS were similar among the groups (Fig. 1e, 1f).

Discussion

This study examined the efficacy of doublet AC after curative hepatectomy in patients with CRC, and identified the patient types in which doublet AC had a positive effect on prognosis. Multivariate analysis predicting RFS and OS revealed the doublet regimen as an independent prognostic factor. Among patients with a high risk of recurrence (MSKCC-CRS 3–5), 5-year RFS and OS were higher in patients who received doublet AC compared with surgery alone. In low-risk patients (MSKCC-CRS 0–2), however, 5-year RFS and OS were similar between the groups.

Several guidelines have recommended AC using doublet AC of 5FU plus oxaliplatin for improving long-term outcomes in pathological stage III patients [18]. In contrast, there is no consensus regarding the effectiveness of doublet AC for patients who have undergone curative liver resection, and who have a much higher recurrence rate compared with Stage III patients. The FFCD9002 trial studied 173 patients who underwent complete resection of liver metastases from CRC [19]. Their evaluation of long-term outcomes between patients who had surgery alone (n=87) and those treated with 5FU and folinic acid (n=86) revealed significantly higher 5-year disease-free survival (DFS) in the AC group compared with the surgery-alone group (33.5% vs 26.7%, p=0.028). However, 5-year OS was similar between the groups (51.1% vs 41.1%, p=0.13). Hasegawa et al. examined oncological outcomes between patients in a surgery-alone group and an AC (tegafur-uracil//leucovorin) group [20]. Also in the FFCD9002 trial, OS was similar between the groups, but RFS at 3 years was higher in the AC group (38.6%) than in the surgery-alone group (32.3%).

A recent RCT (JCOG0603) reported that doublet AC (mFOLFOX6) was superior to surgery alone in CRC patients who underwent complete resection of liver metastases (21). Five-year DFS was 38.7% for hepatectomy alone compared with 71.2% for hepatectomy followed by AC (p=0.006), and 5-year OS was similar between the groups (83.1% vs 71.2%). In contrast to previous studies, oxaliplatin was used for AC in JCOG0603; however, 5-year DFS did not correlate with OS for liver metastatic CRC.

One explanation for the discrepancies in effect of AC for RFS and OS is the low completion rate of AC after hepatectomy. Indeed, it might be difficult for patients to tolerate systemic chemotherapy after hepatectomy, because hepatectomy is usually more invasive compared with colectomy. Regarding AC using 5FU monotherapy, previous studies have reported completion rates ranging from 54.9% to 66.7% (19, 20, 22). The incidence of grade 3 or 4 adverse events ranged from 12.2% to 24.7%, and dose reduction was 12%–25%. In contrast, for doublet AC using 5FU plus oxaliplatin, the incidence of Grade 3 and 4 events has been reported as 63% and 11%, respectively, with a dose reduction rate of 77%, delayed cycle rate of 95%, and total 6 months completion rate of 55% [21]. In the present study, the grade 3 or 4 adverse effect rate and the dose reduction rate were 18.7% and 56.2%, respectively, for single AC; and 78.9% and 89.5%, respectively, for doublet AC. Overall, the present 6-month completion rate was 68.7% for single AC and 31.6% for doublet AC, in agreement with results reported previously [21].

Another possible explanation for the discrepancies in effect of AC for RFS and OS is that hepatectomy alone may have been curative in some cases. Indeed, the JCOG0603 trial reported an imbalance between the surgery-alone group and the surgery followed by doublet AC group, with 7% more R0-1 resections in the surgery-alone group [22]. In a study of CRC patients who underwent initial hepatectomy for CRLM by Hirokawa et al., multivariate analysis revealed pT4, lymph node metastasis, and H2-classifiction as predictors of poor prognosis [23]. They subdivided CRLM patients into low-score (score 0–1) and high-score (score 2–3) groups, and concluded that AC did not improve OS or DFS in patients who had no more than two risk factors.

Pan et al. reported risk-stratified indicators for AC after hepatectomy for CRLM using MSKCC-CRS (24). AC markedly improved the 3-year OS rate in high-risk patients with MSKCC-CRS score 3–5, but provided no additional benefit in those with MSKCC-CRS 0–2. Among the present high-risk patients (MSKCC-CRS 3–5), 5-year RFS and OS was higher for doublet AC than for surgery alone; however, in low-risk patients (MSKCC-CRS 0–2), 5-year RFS and OS were similar among the groups, in agreement with the study of Pan et al. [24]. Of note, that study reported AC as an independent prognostic factor for OS only in high-risk patients, whereas the present study revealed doublet AC as an independent preferable prognostic factor in the overall patient cohort [24]. This discrepancy might be explained by the greater number of MSKCC-CRS high-risk patients (58.3%) in our cohort compared with the previous study (28.0%). As mentioned above, patients who undergo doublet AC after hepatectomy usually experience severe side effects, which may have caused a prolonged reduction in quality of life. Appropriate patient selection that takes the risk of recurrence into consideration is crucial for AC after hepatectomy of CRLM.

There were several limitations in the present study. First, the study was retrospective in design, with a small number of patients. Second, the choice of whether or not to undergo AC and the choice of regimen was at the discretion of the surgeon, without clear selection criteria. Third, the appropriate duration of doublet AC after hepatectomy remains controversial. In stage III CRC, 6 months of doublet AC has been recommended for high-risk patients (pT4 and/or N2); however, 3 months of AC has been considered sufficient for low-risk patients [25]. In the present study, only 31.6% of patients completed 6 months of doublet AC, but >70% of patients completed at least 3 months of treatment, which might have had a positive effect on long-term outcomes. Further studies are required to clarify these issues.

Conclusion

Adjuvant chemotherapy using oxaliplatin could positively influence prognosis after curative resection of CRLM, particularly in high-risk patients. It is important to select appropriate patients and decide the AC regimen with consideration to the risk of recurrence.

Declarations

Funding

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Conflict of interest

All authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This research study was conducted retrospectively from data obtained for clinical purposes, and was reviewed and approved by the Clinical Research Review Board of Nagasaki University Hospital. The approve number is 16062715-5.

Consent

Informed consent was obtained as part of routine care from all individual participants included in the study.

Author Contributions

Keizaburo Maruyama and Tetsuro Tominaga mainly designed the study and analyzed the data. Takashi Nonaka, Shosaburo Oyama, Masaaki Moriyama, and Mitsutoshi Ishii performed surgery. Terumitsu Sawai and Takeshi Nagayasu supervised this study.

References

1. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al (2020) Cancer statistics, 2020. CA Cancer J Clin 70:145-164.
2. Pantel K, Brakenhoff RH (2004) Dissecting the metastatic cascade. Nat Rev Cancer. 4:448–456.
3. Adam R, Vinet E (2004) Regional treatment of metastasis: surgery of colorectal liver metastases. Ann Oncol 15 Suppl 4: iv103-iv106.
4. Ito K, Govindarajan A, Ito H, Fong Y (2010) Surgical treatment of hepatic colorectal metastasis: evolving role in the setting of improving systemic therapies and ablative treatments in the 21st century. Cancer J 16: 103-110.
5. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230: 309-318.
6. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al (2004) Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 239:818-825.
7. Beppu T, Sakamoto Y, Hasegawa K, Honda G, Tanaka K, Kotera Y, et al (2012) A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese 14 Society of Hepato-Biliary-Pancreatic Surgery. Journal of hepato-biliary-pancreatic sciences. 19:72-84.
8. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 350:2343-2351.
9. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, et al (2007) Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 25:2198-2204.
10. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al (2011) Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 29:1465-1471.
11. Ychou M, Hohenberger W, Thezenas S, Navarro M, Maurel J, Bokemeyer C, et al (2009) A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol. 20:1964-1970.

12. Lorenz M, Müller HH, Schramm H, Gassel HJ, Rau HG, Ridwelski K, et al (1998) Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen). Ann Surg. 228:756-762.
13. Rudroff C, Altendorf-Hoffmann A, Stangl R, Scheele J (1999) Prospective randomised trial on adjuvant hepatic-artery infusion chemotherapy after R0 resection of colorectal liver metastases. Langenbecks Arch Surg. 384:243-249.
14. Schulze T, Kemmner W, Weitz J, Wernecke KD, Schirrmacher V, Schlag PM (2009) Efficiency of adjuvant active specific immunization with Newcastle disease virus modified tumor cells in colorectal cancer patients following resection of liver metastases: results of a prospective randomized trial. Cancer Immunol Immunother. 58:61-69.
15. Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, et al (2018) Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. International journal of clinical oncology. 23:1-34.
16. Benson AB, 3rd, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, et al (2017) Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network : JNCCN. 15:370-398.
17. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 27:1386-1422.
18. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 233:309-318.
19. Portier G, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, et al (2006) Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 24:4976-4982.
20. Hasegawa K, Saiura A, Takayama T, Miyagawa S, Yamamoto J, Ijichi M, et al (2016) Adjuvant Oral Uracil-Tegafur with Leucovorin for Colorectal Cancer Liver Metastases: A Randomized Controlled Trial. PloS one. 11:e0162400.
21. Kanemitsu Y, Shimizu Y, Mizusawa J, Inaba Y, Hamaguchi T, Shida D, et al (2021) Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 39:3789-3799.
22. Uehara K, Maeda A, Sakamoto E, Hiramatsu K, Takeuchi E, Sakaguchi K, et al (2013) Phase II trial of adjuvant chemotherapy with S-1 for colorectal liver metastasis. Ann Surg Oncol. 20:475-481.
23. Hirokawa F, Hayashi M, Miyamoto Y, Asakuma M, Shimizu T, Komeda K, et al (2014) Reconsideration of the indications for adjuvant chemotherapy for liver metastases from colorectal cancer after initial

hepatectomy. Ann Surg Oncol. 21:139-146.

24. Pan Z, Peng J, Lin J, Chen G, Wu X, Lu Z, et al (2018) Is there a survival benefit from adjuvant chemotherapy for patients with liver oligometastases from colorectal cancer after curative resection? Cancer communications (London, England). 38:29.
25. Margalit O, Boursi B, Rakez M, Thierry A, Yothers G, Wolmark N, et al (2021) Benefit of Oxaliplatin in Stage III Colon Cancer According to IDEA Risk Groups: Findings from the ACCENT Database of 4934 Patients. Clinical colorectal cancer. 20:130-136

Tables

Table 1

Patient characteristics

	All patients (*n*=91) (%)
Sex	
Male	32 (35.2%)
Female	59 (64.8%)
Age, y (range)	65 (31–87)
Body mass index, kg/m^2	21 (13–34)
Tumor location	
Colon	50 (54.9%)
Rectum	41 (45.1%)
Pathological T factor of primary cancer	
1	4 (4.4%)
2	18 (19.8%)
3	42 (46.2%)
4	19 (20.1%)
Pathological N factor of primary cancer	
Negative	28 (30.8%)
Positive	63 (69.2%)
Synchronous metastasis	55 (60.4%)
Preoperative CEA levels (ng/mL)	8.5 (1.5–176.5)
Number of liver metastases	
1	48 (52.7%)
2	27 (29.7%)
3	7 (7.7%)
>3	9 (9.9%)
Neoadjuvant chemotherapy	38 (41.7)
FOLFOX	32 (35.1)
XELOX	3 (3.3)
5FU monotherapy	3 (3.3)

MSKCC-CRS	
0–2	38 (41.7)
3–5	53 (58.3)
Operative procedure	
Partial resection	52 (57.1)
Segmentectomy or lobectomy	49 (42.9)
Post-operative complications, CD≥2	18 (19.8%)
AC, yes	35 (38.5%)
AC regimen	
Single AC (5FU)	16
Completed full course of 5FU	11 (68.7)
Adverse effects (≥Grade 3)	3 (18.7)
Dose reduction	9 (56.2)
Doublet AC (5FU plus oxaliplatin)	19
Completed full course of 5FU+Oxaliplatin	6 (31.6)
Adverse effects (≥ Grade 3)	15 (78.9)
Dose reduction	17 (89.5)

Data are presented as the numbers of patients or medians (range).

CEA, carcinoembryonic antigen; 5FU, fluorouracil; MSKCC-CRS, Memorial Sloan Kettering Cancer Center clinical risk score; CD, Clavien–Dindo classification; AC, adjuvant chemotherapy.

Table 2

Comparison of clinical characteristics between the AC and non-AC groups

	AC (+) (*n*=35) (%)	AC (−) (*n*=56) (%)	*p* values
Sex			0.010
Male	17 (48.6%)	42 (75.0%)	
Female	18 (51.4%)	14 (25.0%)	
Age, y (range)	67 (36–87)	61 (31–76)	0.012
Tumor location			0.594
Colon	18 (51.4%)	32 (57.1%)	
Rectum	17 (48.6%)	24 (42.9%)	
Pathological T factor of primary cancer			0.294
1	1 (2.9%)	3 (5.4%)	
2	10 (28.6%)	8 (14.3%)	
3	16 (45.7%)	26 (46.4%)	
4	5 (14.8%)	14 (25.0%)	
Pathological N factor of primary cancer			0.309
Negative	12 (34.3%)	16 (28.6%)	
Positive	23 (65.7%)	36 (71.4%)	
Timing of liver metastasis			0.090
Synchronous metastasis	25 (71.4%)	30 (53.8%)	
Metachronous metastasis	10 (28.6%)	26 (46.2%)	
Preoperative CEA levels (ng/mL), median (range)	6.7 (1.6–176.5)	9.8 (1.5–68.6)	0.777
Number of liver metastases			0.731
1	20 (57.1%)	28 (50.0%)	
2	8 (22.9%)	19 (33.9%)	
3	3 (8.6%)	4 (7.1%)	
>3	4 (11.4%)	5 (8.9%)	
Neoadjuvant chemotherapy	18 (51.4)	20 (35.7)	0.190
FOLFOX	16 (45.7)	16 (28.6)	
XELOX	0 (0)	3 (5.3)	

5FU monotherapy	2 (5.7)	1 (1.8)	
MSKCC-CRS			0.177
0–2	9 (25.7)	23 (41.1)	
3–5	26 (74.3)	33 (58.9)	
Operative procedure			1.000
Partial resection	20 (57.1%)	32 (57.1%)	
Segmentectomy or lobectomy	15 (42.9%)	24 (42.9%)	
Post-operative complications, CD≥2	7 (20.0%)	8 (14.3%)	0.474

Differences in categorical variables were compared using Fisher's exact test or the chi-squared test, as appropriate. Differences in continuous variables were analyzed with the Mann–Whitney *U*-test.

AC, adjuvant chemotherapy; CEA, carcinoembryonic antigen; 5FU, fluorouracil; MSKCC-CRS, Memorial Sloan Kettering Cancer Center clinical risk score; CD, Clavien–Dindo classification.

Table 3

Univariate and multivariate analysis for predictors of relapse-free survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age ≥70 years	1.236	0.724–2.108	0.436			
Sex (male vs female)	0.996	0.584–1.698	0.990			
Primary tumor (rectum vs colon)	1.219	0.730–2.034	0.447			
Metachronous vs synchronous	0.723	0.426–0.927	0.042	0.483	0.246–0.845	0.010
Liver surgery (lobectomy vs partial resection)	0.917	0.547–1.532	0.744			
Number of liver metastases (≥3)	1.776	0.805–3.910	0.154	1.861	0.848–4.150	0.128
CEA ≥5 ng/mL	1.042	0.611–1.777	0.878			
Neoadjuvant chemotherapy	1.708	1.432–2.902	0.345			
Postoperative complications (yes vs no)	1.325	0.702–2.502	0.384			
Adjuvant chemotherapy, absent	1.00			1.00		
Single AC	0.876	0.443–1.731	0.704	0.539	0.265–1.097	0.088
Doublet AC	0.352	0.159–0.779	0.009	0.225	0.097–0.522	<0.001

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen.

Table 4

Univariate and multivariate analysis for predictors of overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age ≥70 years	1.477	0.812–2.769	0.195			
Sex (male vs female)	1.192	0.655–2.168	0.564			
Primary tumor (rectum vs colon)	1.502	0.858–2.627	0.153	1.398	0.784–2.448	0.250
Metachronous vs synchronous	0.873	0.495–1.539	0.640			
Liver surgery (lobectomy vs partial resection)	0.978	0.554–1.727	0.941			
Number of liver metastases (≥3)	2.155	0.962–4.835	0.062	2.767	1.154–6.634	0.022
CEA ≥5 ng/mL	1.198	0.665–2.157	0.547			
Neoadjuvant chemotherapy	1.220	0.783–2.445	0.263			
Postoperative complications (yes vs no)	1.636	0.852–3.142	0.139	1.110	0.566–2.177	0.761
Adjuvant chemotherapy, absent	1.00			1.00		
Single AC	0.655	0.295–1.462	0.303	0.337	0.142–0.801	0.013
Doublet AC	0.890	0.066–0.534	0.001	0.165	0.057–0.476	<0.001
HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen.						

Figures

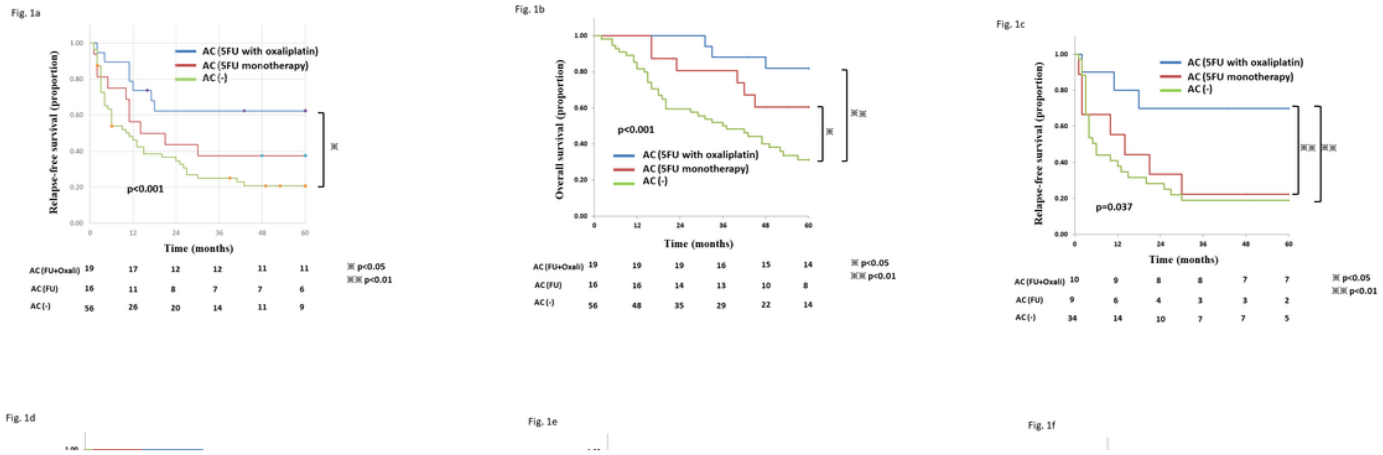

Figure 1

Survival curves for 5-year relapse-free survival (a: all patients; c: high-risk patients; and e: low-risk patients) and for 5-year overall survival (b: all patients; d: highrisk patients; and f: low-risk patients) AC, adjuvant chemotherapy; 5FU, fluorouracil