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ORIGINAL ARTICLE

Neoadjuvant Chemotherapy Versus Upfront Surgery for Resectable Liver Metastases from Colorectal Cancer: a Multicenter, Propensity Score–Matched Cohort Study

Fumitoshi Hirokawa[1] · Masaki Ueno[2] · Takuya Nakai[3] · Masaki Kaibori[4] · Takeo Nomi[5] · Hiroya Iida[6] · Shogo Tanaka[7] · Koji Komeda[1] · Shinya Hayami[2] · Hisashi Kosaka[4] · Daisuke Hokuto[5] · Shoji Kubo[7] · Kazuhisa Uchiyama[1]

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Abstract

Background Adjuvant chemotherapy for resectable colorectal liver metastasis (CRLM) is widely used, but its efficacy lacks clear evidence. This retrospective cohort study investigated the effectiveness of neoadjuvant chemotherapy (NAC) compared to upfront surgery for CRLM.

Methods Data from patients with resectable CRLM were analyzed. Short-term outcomes and long-term prognosis were analyzed using propensity score matching. CRLM was stratified according to the H-classification (H1 and H2), and the effectiveness of adjuvant chemotherapy was analyzed in each group.

Results We analyzed 599 cases that were matched into an NAC group ($n=136$) and an upfront surgery group ($n=136$). The proportion of synchronous metastases, H2-classification, and postoperative chemotherapy rate did not differ between the groups. Overall survival (OS) after initial treatment was significantly worse in the NAC group than in the upfront surgery group ($P=0.029$). The 5-, 7-, and 10-year OS rates for H1 patients were significantly better in the upfront surgery group than in the NAC group (64%, 51%, and 44% vs. 50%, 31%, and 18%, respectively) ($P=0.004$).

Conclusion Patients with resectable CRLM should undergo upfront surgery, because NAC did not improve OS after initial treatment in these patients.

Keywords Neoadjuvant chemotherapy · Colorectal cancer · Liver · Metastasis · Hepatectomy

Abbreviations

CRLM	Colorectal liver metastasis
NAC	Neoadjuvant chemotherapy
OS	Overall survival

Introduction

Colorectal liver metastasis (CRLM) is a major cause of death worldwide, and the number of cases has significantly increased. Liver resection is the optimal and potentially curative treatment for CRLM, with reported 5-year posthepatectomy survival rates of 45–61%.[1, 2] However, the rate of

Synopsis: Unplanned NAC exacerbated rather than improved overall survival after initial treatment in resectable liver metastasis from colorectal cancer (CRLM).

✉ Fumitoshi Hirokawa
sur122@osaka-med.ac.jp

[1] Department of General and Gastroenterological Surgery, Osaka Medical and Pharmaceutical University, 2-7 Daigaku-machi, Takatsuki City, Osaka 569-8686, Japan

[2] Second Department of Surgery, Wakayama Medical University, Wakayama, Japan

[3] Department of Surgery, Faculty of Medicine, Kinki University, Osaka-Sayama, Japan

[4] Department of Surgery, Hirakata Hospital, Kansai Medical University, Hirakata, Osaka, Japan

[5] Department of Surgery, Nara Medical University, Kashihara, Japan

[6] Department of Surgery, Shiga University of Medical Science, Otsu, Japan

[7] Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan

postoperative recurrence is approximately 75%, commonly occurring in the remnant liver.[1]

In recent years, neoadjuvant chemotherapy (NAC) has been frequently administered for all carcinomas, including CRLM. NAC reduces micrometastases, downstages the tumor, and improves the tumor resection rate.[3, 4] It was introduced to prolong recurrence-free survival of patients with upfront resectable metastases and to achieve secondary resectability for borderline or nonresectable metastases.[3, 5, 6] However, NAC has some potential disadvantages: including a risk of tumor progression; local fibrosis; tissue adhesion; and toxicities like sinusoidal obstruction syndrome, nodular regenerative hyperplasia, and hematological toxicities.[7–9]

Previously, we reported that preoperative chemotherapy was ineffective for resectable CRLM of tumors small in number and diameter.[10] However, that report was based on a small sample at a single institution. Thus, we conducted a large retrospective cohort study using patient data from seven institutions to compare the use of NAC with upfront surgery for resectable CRLM.

Methods

Study Design and Subjects

In this retrospective cohort study, patients with CRLM who underwent liver resection at seven university hospitals from April 2007 to March 2013 were included. The study and the associated protocol are not registered with UMIN or ClinicalTrials.gov, although they received approval from the Ethics Committee of each institution (approval number: 2734; Osaka Medical College). After obtaining informed consent, patient data was collected from the patients' clinical report forms. Institutions performed more than 100 liver resections per year. The inclusion criteria were as follows: (1) curative resection of primary CRC, (2) liver metastases (located only in the liver) that can be resected as per macroscopic findings, and (3) liver metastases at the onset were judged to be resectable cases (not conversion cases). Synchronous CRLM was defined as the presentation of liver metastasis occurring within 3 months after CRC surgery. These patients underwent either simultaneous or staged hepatectomy according to their respective conditions and emergent needs. To obtain margins of 5–10 mm, surgical margins were carefully confirmed using ultrasonography during the resection procedure. We retrospectively collected demographic and clinicopathological data of consecutive patients, including the physical status, tumor marker levels, original tumor pathology, surgical duration, blood loss, liver tumor pathology, length of hospitalization, postoperative complications, relapse-free survival (RFS), and OS periods. The surgical margin was defined by the distance to the lesion closest to the cut surface of the liver, and it was macroscopically classified as ≥ 1 mm or 0 mm. The primary endpoint of this study was OS, while secondary endpoints were RFS and complications. Furthermore, we explored the influence of the response to NAC on the OS curves.

Preoperative and Postoperative Management

Patients decided whether to undergo adjuvant chemotherapy after they were informed that the efficacy of adjuvant chemotherapy for CRLM is controversial. The patients were followed up every 3 months for up to 5 years after surgery. During the follow-up examinations, the patients' blood tests (including those for tumor markers such as carcinoembryonic antigen), and contrast-enhanced CT were performed. When recurrence was suspected by CT or blood tests, patients underwent magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (PET) to check for new lesions.

Recurrence was considered present when at least two imaging studies confirmed new lesions showing typical features of CRC/CRLM, relative to the findings on previous images. When applicable, repeat resection was performed for recurrent CRLM. If the recurrent metastases were not resectable, they were treated with chemotherapy where possible.

Definitions

Resectable liver metastases were not clearly defined, and it was determined by the liver surgeon at each institution. Participating institutions were high-volume centers for liver resection in Japan. Each liver surgeon had more than 15 years of experience and was certified as a hepatectomy specialist by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. The Japanese Classification of Colorectal Carcinoma H-classification is based on the number and maximum tumor size [11] as follows: H0, no liver metastasis; H1, number of metastases ≤ 4 and size of the largest tumor ≤ 5 cm; H2, other than H1 or H3; H3, number of metastases ≥ 5 and size of largest tumor > 5 cm. Onset time was defined as when the tumor was confirmed by CT or MRI. OS was defined as the time from the initial treatment to death from any cause, and RFS was defined as the time from the initial treatment to the initial CRC-related recurrence. Institutions followed a similar postoperative management protocol. Postoperative complications were graded according to the Clavien–Dindo classification, and those with a Clavien–Dindo grade of ≥ 3a were defined as major complications.[12] Biliary leakage and liver failure were defined according to the International Study Group of Liver Surgery criteria.[13, 14] Tumor response of NAC was evaluated using the Response Evaluation Criteria for Solid Tumors

(RECIST: v 1.1) and was not based on the observations of the pathologist.

Propensity Score Matching

Propensity score matching (PSM) is a method used to reduce the bias in patient selection between two treatment groups. In this study, 1:1 PSM was used between the patients who underwent upfront surgery and those who underwent NAC. PSM was performed on patients without missing data based on a logistic regression model with the odds as the dependent variable and age, H-classification at onset, CEA and CA19-9 level at onset, PT4 and LN metastases of primary tumor, and synchronous metastases as independent variables. The caliper size was set as 0.2 of the standard deviation of the logit of the estimated propensity score. Patients whose scores were found to be outside the caliper were excluded. Unmatched patients were excluded.

Statistical Analysis

Statistical analyses for primary and secondary endpoints were performed for matched-paired patients. OS was calculated from the date of initial treatment to the date of death from any cause or the last follow-up. RFS was calculated from the date of surgery to the date of confirmed recurrence or any cause of death. Survival curves were estimated using the Kaplan–Meier method, and between-group comparisons were performed using the log-rank test. Bonferroni's correction was used among the three groups. Fisher's exact test and a *t*-test were used to analyze categorical and continuous variables, respectively. For two-sided tests, a *P*-value of < 0.05 was considered statistically significant. For three-sided tests, a *P*-value of < 0.016 was considered statistically significant, using Bonferroni's correction for multiple comparisons. Analyses were performed using JMP pro 14.0.1 (SAS Institute, Cary, NC).

Results

Data for 613 patients were collected from the seven institutions. Fourteen patients were excluded, including seven who died from another disease, six with insufficient follow-up, and one with insufficient data. From the remaining 599 patients, 201 and 398 received NAC and upfront surgery, respectively. Propensity scoring was used to match the patients into a NAC group of 136 patients and an upfront surgery group of 136 patients (Fig. 1). The C-statistic for the goodness of fit was 0.800 in the PSM model. The median follow-up period was 47 months. The NAC regimens were as follows: (a) 5-fluorouracil (5FU) + leucovorin (LV) + oxaliplatin (FOLFOX) ± molecular-targeted agent (bevacizumab, cetuximab, or panitumumab) ($n = 110$), (b) 5FU + LV + irinotecan (FOLFIRI) + bevacizumab ($n = 13$), (c) 5FU + LV + oxaliplatin + irinotecan (FOLFOXIRI) + bevacizumab ($n = 15$), (d) tegafur/gimeracil/oteracil (TS-1) or capecitabin + oxaliplatin (SOX or XELOX) ($n = 61$), and (e) 5FU + LV ± molecular-targeted agent ($n = 2$). The number of treatment cycles was variable (median = 6; range = 2–20). The postoperative adjuvant chemotherapy regimens were as follows: (a) FOLFOX/ FOLFIRI ± molecular-targeted agent ($n = 75$), (b) FOLFIRI + bevacizumab ($n = 13$), (c) FOLFOXIRI + bevacizumab ($n = 15$), (d) SOX or XELOX ($n = 47$),

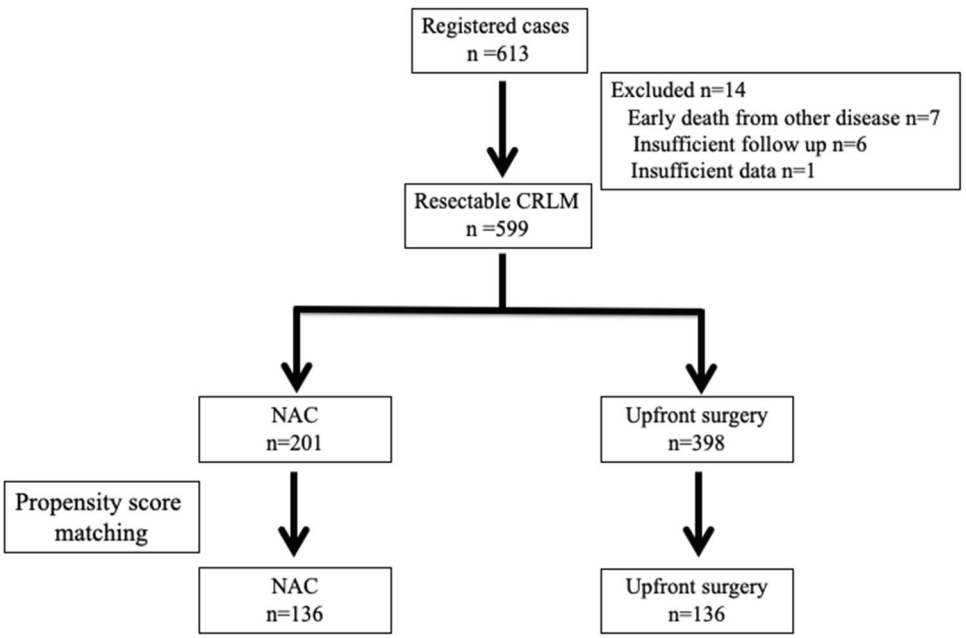

Fig. 1 Flow diagram of the study. A total of 613 patients were registered, and case matching was performed using the propensity score from five factors: age, H-classification (at onset), CEA (at onset), tumor number, and synchronous metastases, as prescribed in the protocol. Finally, there are 136 patients in the NAC group and 136 patients in the upfront surgery group. CRLM, liver metastasis from colorectal cancer; CEA, carcinoembryonic antigen; NAC, neoadjuvant chemotherapy

and (e) 5FU + LV ± molecular-targeted agent ($n = 32$). A hepatic surgical margin of ≥ 5 mm was achieved in 80% patients.

Table 1 summarizes the background and clinical characteristics of the overall cohort and matched cases. Before matching, the patient age was lower while the CEA level, proportion of synchronous metastases, liver tumor location, and rate of H2-classification were much higher in the NAC group. After matching, these parameters were more balanced. The median ages were 64 and 67 years

Table 1 Background and clinical characteristics of patients with colorectal cancer liver metastases (CRLM) before and after propensity score matching: upfront surgery vs. neoadjuvant chemotherapy (NAC)

	Overall cohort			After matching		
	NAC	Upfront surgery	*p*-value	NAC	Upfront surgery	*p*-value
Characteristic	($n = 201$)	($n = 398$)		($n = 136$)	($n = 136$)	
Background characteristics						
Age, years	63 (27–86)	69 (26–90)	< 0.001	65 (27–86)	66 (26–87)	0.682
Male/female*	126/75	240/158	0.595	85/51	83/53	0.901
Virus infection	5 (2%)	16 (4%)	0.481	5 (4%)	4 (3%)	1.000
Child–Pugh (grade B)	14 (7%)	18 (5%)	0.248	12 (9%)	11 (8%)	1.000
Diabetes mellitus	33 (16%)	73 (18%)	0.650	24 (18%)	21 (15%)	0.745
Time to start treatment (days)	45 (14–86)	48 (23–105)	0.065	49 (16–85)	43 (20–89)	0.834
Tumor-related factors: colorectum						
Location (right colon)	40 (20%)	102 (26%)	0.065	33 (24%)	33 (24%)	1.000
pT4	56 (28%)	96 (24%)	0.369	39 (29%)	34 (25%)	0.492
pN1	139 (69%)	255 (64%)	0.200	93 (68%)	91 (67%)	0.897
Tumor-related factors: liver						
Synchronous metastases	158 (79%)	160 (40%)	< 0.001	102 (75%)	102 (75%)	1.000
Location (bilateral)	96 (48%)	82 (21%)	< 0.001	51 (38%)	44 (33%)	0.446
Tumor number (single)	49 (24%)	256 (64%)	< 0.001	44 (32%)	44 (32%)	1.000
Tumor size (mm)	28 (8–165)	25 (5–148)	0.002	28 (8–165)	27 (5–148)	0.483
H-classification (H2)	83 (41%)	61 (15%)	< 0.001	42 (31%)	41 (30%)	1.000
CEA	20.0 (1–6380)	8.5 (1–4483)	< 0.001	15.5 (1–1548)	10.4 (1–3439)	0.089
CA19-9	24.7 (0.1–84,585)	21.0 (1–79,991)	0.063	19.0 (0.1–5654)	22.2 (1–79,991)	0.849
Surgical factors						
Major hepatectomy	37 (18%)	69 (17%)	1.000	22 (16%)	31 (23%)	0.221
Operative time (min)	329 (95–837)	253 (20–8 29)	< 0.001	315 (95–787)	288 (20–666)	0.032
Blood loss (ml)	483 (6–5130)	315 (5–8688)	< 0.001	488 (6–5130)	420 (10–5200)	0.210
Blood transfusion	52 (26%)	68 (17%)	0.023	38 (28%)	33 (24%)	0.581
The short-term outcomes						
Complications (CD ≥ 3a)	44 (22%)	54 (14%)	0.014	28 (21%)	22 (16%)	0.434
Liver failure	3 (1%)	1 (1%)	0.112	2 (1%)	1 (1%)	1.000
Bile leakage	9 (4%)	9 (2%)	0.138	6 (4%)	2 (1%)	0.282
Ascites	13 (6%)	14 (4%)	0.142	8 (6%)	7 (5%)	0.798
Abdominal abscess	7 (3%)	13 (3%)	1.000	3 (2%)	5 (4%)	0.723
Bleeding	1 (1%)	1 (1%)	1.000	1 (4%)	0 (0%)	1.000
Pulmonary complication	10 (5%)	7 (2%)	0.035	7 (5%)	4 (3%)	0.540
Others	9 (4%)	23 (6%)	0.569	7 (5%)	7 (5%)	1.000
Length of hospital stay (POD)	12 (5–197)	11 (4–173)	0.003	12 (7–197)	12 (6–173)	0.968
Postoperative chemotherapy	109 (54%)	190 (48%)	0.168	73 (54%)	78 (57%)	0.626

Data are presented as the no. (%) or as the median with the range, unless otherwise specified

*Number of patients

H-classification—H1: ≤ 4 metastases, largest tumor ≤ 5 cm, H3: ≥ 5 metastases, largest tumor > 5 cm; H2: other than H1, H3

CA19-9 carbohydrate antigen 19–9, *CEA* carcinoembryonic antigen, *CD* Clavien–Dindo classification, *POD* postoperative day, *TSF* time to surgical failure

while the CEA levels were 15.5 and 10.4, respectively. The proportion of synchronous metastases (both 79%) and rate of H2-classification (NAC: 33%; upfront surgery: 31%) showed no between-group differences.

Before matching, the surgical duration, blood loss, blood transfusion, and residual tumor rate were much higher in the NAC group. After matching, these parameters were more balanced. The median blood loss was 488 and 420 ml, blood transfusion rate was 30% and 22%, respectively. The surgical duration was longer in the NAC group (315 min) than in the upfront surgery group (288 min). Moreover, postoperative complications (Clavien–Dindo Classification, ≥ grade 3a; NAC: 21%; upfront surgery: 16%), length of hospitalization (NAC: 12 days; upfront surgery: 12 days), and postoperative chemotherapy (NAC: 53%; upfront surgery: 52%) showed no differences after matching.

Recurrence rates are summarized in Table 2. After matching, the recurrence site and treatment showed no differences between groups. However, the rate of recurrence within 1 year after surgery was much higher in the NAC group (61%) than in the upfront surgery group (43%; $P=0.005$).

Before matching, RFS and OS after the initial treatment were significantly better in the upfront surgery group than in the NAC group ($P=0.041$ and $P<0.001$, respectively; Fig. 2). After matching, RFS after the initial treatment did not differ while OS was significantly better in the upfront surgery group (82.3 months) than in the NAC group (57.5 months; $P=0.029$, Fig. 3). The respective 5-, 7-, and 10-year OS rates after the initial treatment were 60%, 49%, and 40%, respectively, in the upfront surgery group and 47%, 31%, and 25%, respectively, in the NAC group. Next, we explored curves of RFS and OS after the initial treatment according to the H-classification after matching, primarily because the definition of resectable CRLM was unclear in this study, and because the H1-classification could be easily determined at all institutions.

RFS for H1 patients after the initial treatment did not differ in both groups; however, in H2 patients, RFS was significantly better in the NAC group (18.2 months) than in the upfront surgery group (7.5 months; $P=0.003$, Fig. 4).

The 5-, 7-, and 10-year OS rates for H1 patients were significantly better in the upfront surgery group than in the NAC group (64%, 51%, and 44% vs. 50%, 31%, and 18%, respectively; $P=0.004$). For H2 patients, OS did not differ between the two groups (Fig. 5). Furthermore, we explored the influence of the response to NAC on the OS curves and found that the tumor response itself had a major influence on OS; however, patients with a partial response and complete response did not show a better prognosis than that of patients who underwent upfront surgery (Fig. 6).

Discussion

Liver resection is the optimal treatment for colorectal cancer liver metastases (CRLM) in many countries. On the other hand, chemotherapy has dramatically improved in recent times, and the Guidelines of the National Comprehensive Cancer Network [15] and European Society for Medical Oncology (ESMO) [16] have recommended perioperative adjuvant chemotherapy for CRLM since the phase III EORTC 40,983 trial.[3] However, the same group later reported that OS was not better in FOLFOX patients than in surgery-alone patients at the 5-year follow-up [17], and other articles have also reported some adverse events as a result of NAC.[18, 19] On the other hand, even patients who are easy to resect often perform NAC, and the question has arisen whether NAC is useful for patients who are easy to resect. As mentioned above, evidence of the effectiveness of perioperative

Table 2 Recurrence pattern of colorectal cancer liver metastases (CRLMs) before and after propensity score matching: upfront surgery vs. neoadjuvant chemotherapy (NAC)

	Overall cohort			After matching		
	NAC	Upfront surgery	*p*-value	NAC	Upfront surgery	*p*-value
Characteristic	(*n* = 201)	(*n* = 398)		(*n* = 136)	(*n* = 136)	
Time to recurrence						
≤ 1 year after operation	126 (63%)	159 (40%)	< 0.001	83 (61%)	58 (43%)	0.004
Site of recurrence						
Liver only	73 (36%)	108 (27%)	0.024	49 (36%)	49 (36%)	1.000
Lung only	31 (15%)	54 (14%)	0.538	21 (16%)	12 (9%)	0.137
Others	21 (10%)	49 (11%)	1.000	12 (9%)	12 (9%)	1.000
Multiple	43 (21%)	68 (19%)	0.514	31 (23%)	31 (23%)	1.000
Treatment of recurrence						
Resection	59 (29%)	126 (32%)	0.576	40 (30%)	43 (32%)	0.792
Chemotherapy	114 (57%)	278 (70%)	0.002	56 (41%)	52 (39%)	0.710
BSC	8 (4%)	26 (7%)	0.262	6 (4%)	8 (6%)	0.785

Data are presented as the no. (%) or as the median with the range, unless otherwise specified

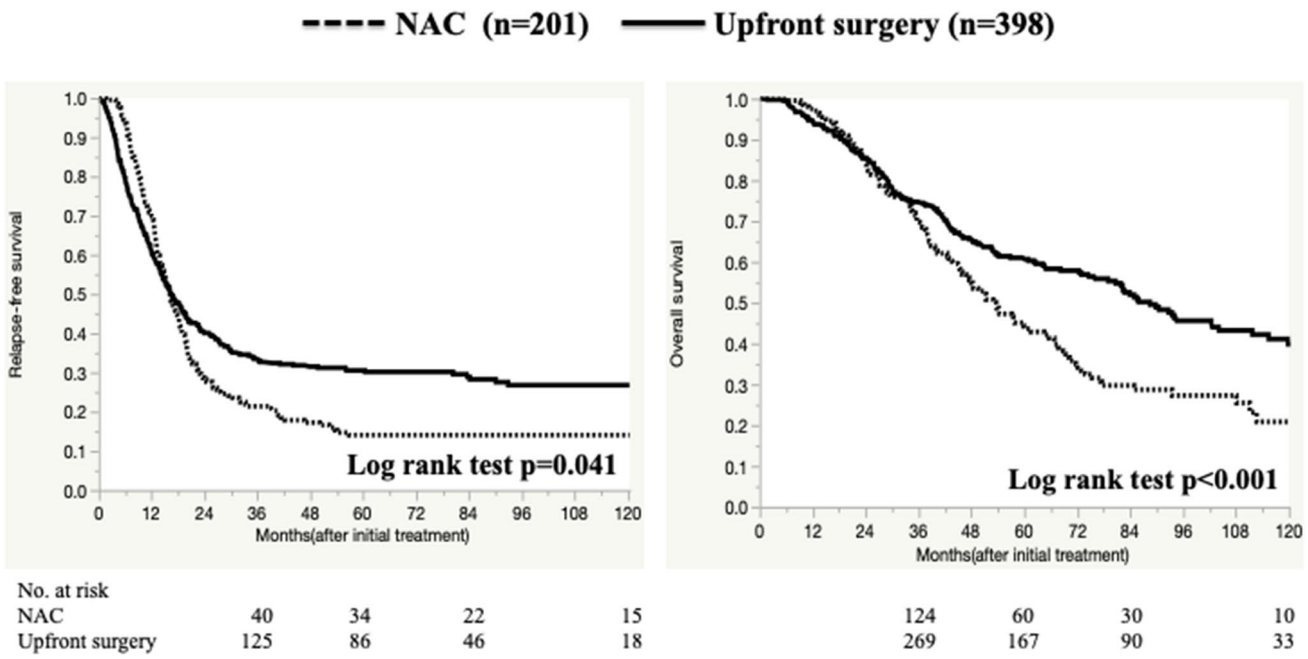

Fig. 2 Relapse-free survival (RFS) and overall survival (OS) after initial treatment for resectable colorectal liver metastases in neoadjuvant chemotherapy (NAC) and upfront surgery groups. The RFS rate is significantly better in the upfront surgery group ($P=0.041$). The respective 1-, 3-, and 5-year RFS rates are as follows: upfront surgery ($n=398$, thick line), 61%, 33%, and 31%, respectively; NAC ($n=201$, dotted line), 70%, 21%, and 14%, respectively. The OS rate is significantly better in the upfront surgery group ($P<0.001$). The respective 5-, 7-, and 10-year OS rates are as follows: upfront surgery ($n=398$, thick line), 61%, 52%, and 40%, respectively; NAC ($n=201$, dotted line), 44%, 30%, and 21%, respectively

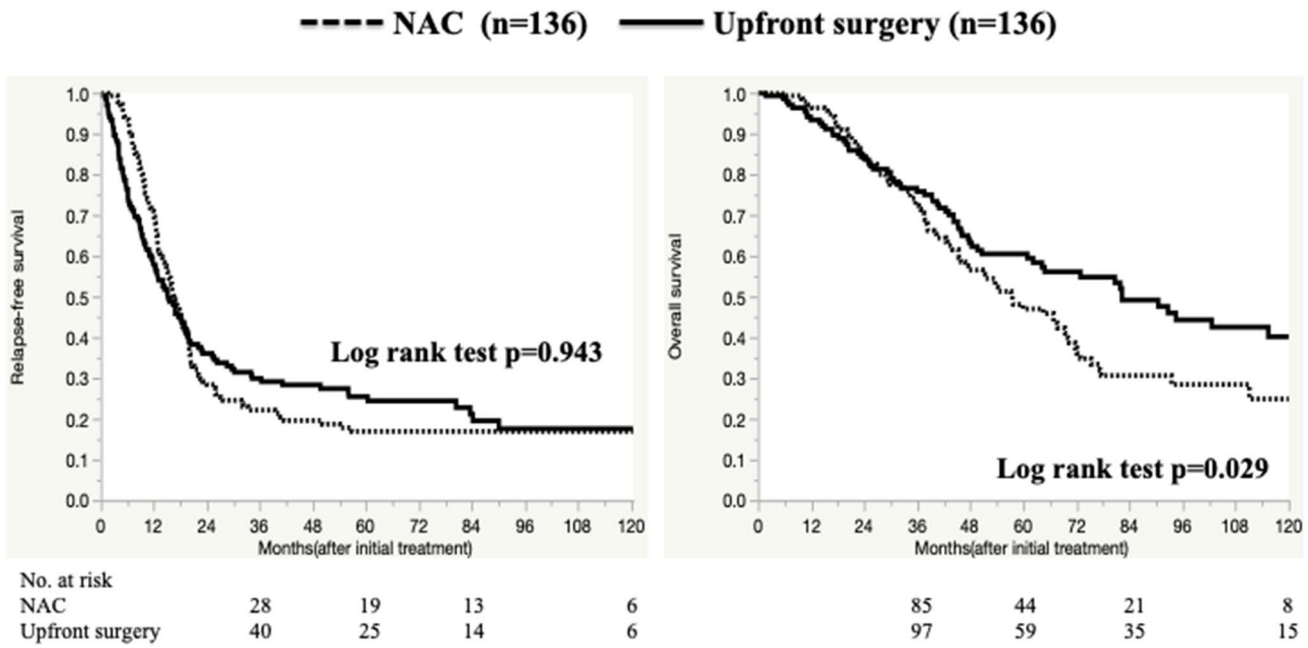

Fig. 3 Relapse-free survival (RFS) and overall survival (OS) after initial treatment for resectable colorectal liver metastases in neoadjuvant chemotherapy (NAC) and upfront surgery groups after matching. The RFS rate in the upfront surgery group is similar to that in the NAC group ($P=0.943$). The respective 1-, 3-, and 5-year RFS rates are as follows: upfront surgery ($n=136$, thick line), 58%, 30%, and 25%, respectively; NAC ($n=136$, dotted line), 70%, 22%, and 17%, respectively. The OS rate is significantly better in the upfront surgery group ($P=0.029$). The respective 5-, 7-, and 10-year OS rates are as follows: upfront surgery ($n=136$, thick line), 60%, 49%, and 40%, respectively; NAC ($n=136$, dotted line), 47%, 31%, and 25%, respectively

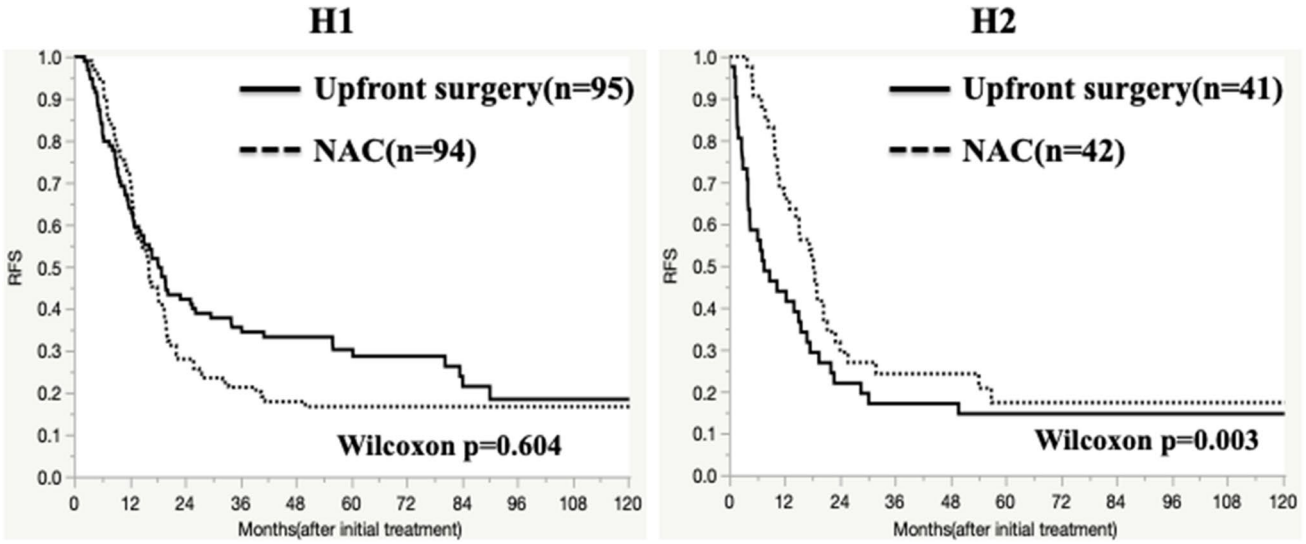

Fig. 4 Relapse-free survival (RFS) after initial treatment for resectable colorectal liver metastases according to H-classification in neoadjuvant chemotherapy (NAC) and upfront surgery groups after matching. The RFS rate in the upfront surgery group is similar to that in the NAC group ($P=0.604$). The respective 1-, 3-, and 5-year RFS rates are as follows: upfront surgery ($n=95$, thick line), 64%, 36%, and 30%, respectively; NAC ($n=94$, dotted line), 64%, 36%, and 30%, respectively. The RFS rate is significantly better in the NAC patients with H2-classification than in the upfront surgery patients with H2-classification ($P=0.003$). The respective 1-, 3-, and 5-year RFS rates are as follows: upfront surgery ($n=41$, thick line), 44%, 17%, and 15%, respectively; NAC ($n=42$, dotted line), 66%, 24%, and 17%, respectively

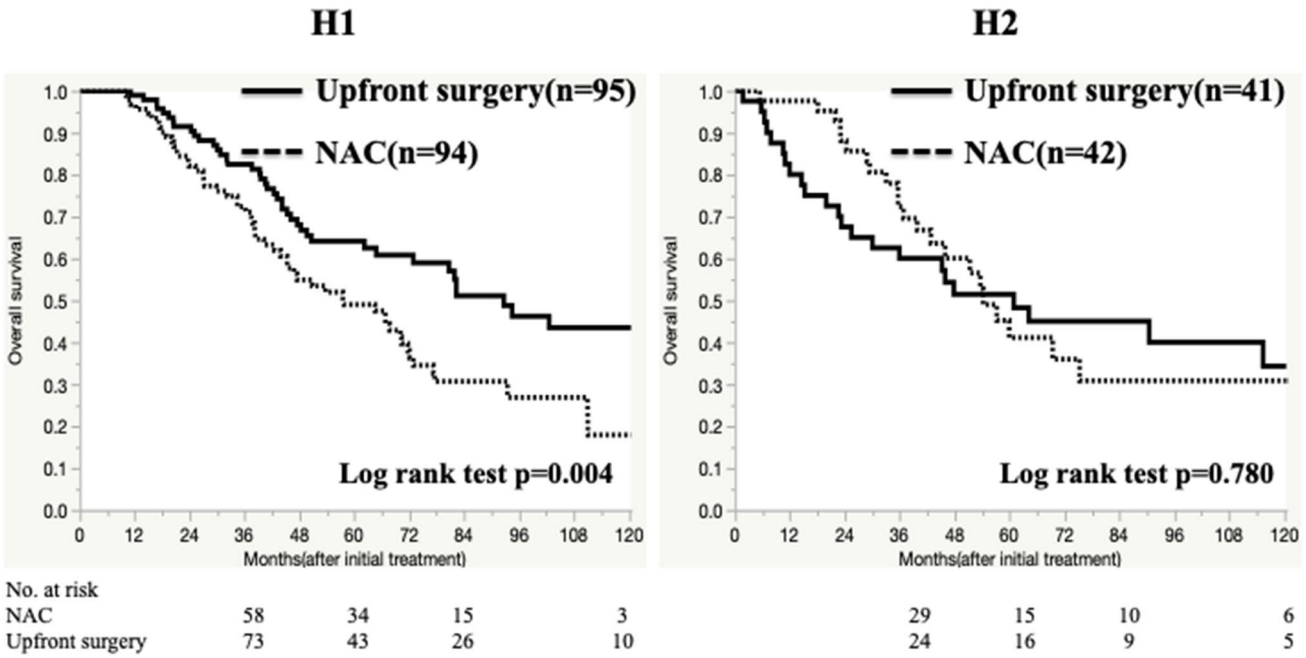

Fig. 5 Overall survival (OS) after initial treatment for resectable colorectal liver metastases according to H-classification in neoadjuvant chemotherapy (NAC) and upfront surgery groups after matching. The OS rate is significantly better in the upfront surgery patients with H1-classification than in NAC patients with H1-classification ($P=0.004$). The respective 5-, 7-, and 10-year OS rates are as follows: upfront surgery ($n=95$, thick line), 64%, 51%, and 44%, respectively; NAC ($n=94$, dotted line), 50%, 31%, and 18%, respectively. The OS rate in the upfront surgery group is similar to that in the NAC group ($P=0.780$). The respective 5-, 7-, and 10-year OS rates are as follows: upfront surgery ($n=41$, thick line), 51%, 45%, and 34%, respectively; NAC ($n=42$, dotted line), 41%, 31%, and 31%, respectively

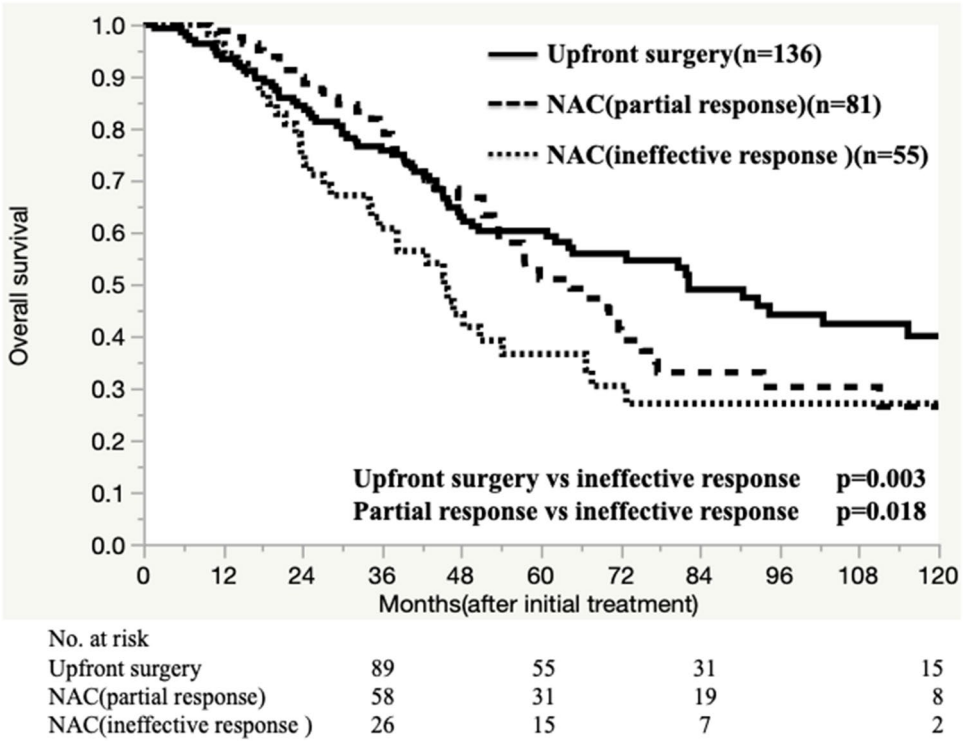

Fig. 6 Overall survival (OS) after initial treatment for resectable colorectal liver metastases according to tumor response and resection after matching. The OS rate is significantly better in partial responses, and the upfront surgery group than patients showing an ineffective response ($P=0.018$, $P=0.003$). There are no significant OS differences between partial response and upfront surgery. The respective 5-, 7-, and 10-year OS rates are as follows: upfront surgery ($n=136$, thick line), 63%, 52%, and 45%, respectively; partial response ($n=81$, thick dotted line), 51%, 36%, and 26%, respectively; ineffective response ($n=55$, thin dotted line), 36%, 25%, and 25%, respectively. * ineffective response, SD and/or PD patients; partial response, CR and/or PR patients. NAC, neoadjuvant chemotherapy. PD, progressive disease. SD, stable disease. PR, partial response. CR, complete response

adjuvant chemotherapy for CRLM is insufficient, and this study focused on neoadjuvant chemotherapy (NAC) for CRLM.

In this study, propensity score (PS) matching was performed to ensure that background patient data were uniform, because the treatment strategy for CRLM seems to vary widely. Four factors, namely age, H-classification (at onset), CEA (at onset), and synchronous metastases, were used as described in the protocol. Patient background was ideally balanced in the groups by matching; therefore, the comparison of NAC and upfront surgery patients was considered reliable.

NAC did not worsen RFS; however, it potentially worsened OS—the primary endpoint of this study—in patients with CRLM compared to that in upfront surgery patients. So why did the OS get worse in the NAC group?

The reason for selecting NAC rather than upfront surgery is generally a more advanced tumor, including the presence of tumors in bilateral lobes of the liver, large number of lesions, simultaneous metastases, and high levels of tumor markers. To eliminate that bias as much as possible, PS matching was performed as mentioned above; however, we cannot deny the possibility of a bias. We speculate that the reason for the significantly worse survival rate in the NAC group is the delay in surgery. For some patients, because of unplanned NAC, it is possible that chemotherapy was continued at the patient's request rather than undergoing liver resection when chemotherapy had reduced the tumor it was undertaken when the tumor had regrown. Indeed, resections following a response to chemotherapy and the tumor response itself have a major influence on the OS.[20] However, the survival rate in the chemotherapy response group (NAC; partial response) was not higher than that in the upfront surgery group (Fig. 5). Determining the most appropriate time for liver resection is difficult during the management of CRLM. Mentha et al.[21] stated that resection of liver metastases before primary resection improves prognosis in progressive synchronous liver metastases. Even in resectable CRLM, if the resection is performed when chemotherapy is most effective, the result may be better; however, its judgment is difficult.

Another reason is that NAC has been reported to reduce albumin, prognostic nutrition index (PNI), and lymphocyte to monocyte ratio (LMR) [10], and it may be because the

resection was performed with worsening the general condition by NAC.

NAC appears to improve the prognosis of other types of cancers, even if these are deemed resectable; as such, the use of NAC as a treatment option is increasing.[22–26] However, in the case of CRLM, which is radically different from the cases in the above-mentioned studies, if liver metastases can be completely resected, resection is a curative treatment no matter how many times it occurs. Furthermore, although patients who undergo hepatectomy for CRLM show a relapse rate of about 75% [1], as mentioned above, their prognosis remains favorable if the recurrent lesion is resectable.[27, 28] In this study, there were no differences in terms of recurrence site, and treatment in the two groups. However, recurrence occurred frequently within the first year after surgery in the NAC group; this clearly shows that preoperative chemotherapy is ineffective.

From this study, we believe that it is effective to perform upfront surgery at that time the CRLM is deemed resectable.

There is no generally accepted definition of unresectable CRLM, except for postoperative determination of inadequate remaining functional liver tissue. Patients considered to have an unresectable CRLM in one center might be considered to have resectable CRLM in another center. The likelihood of a major discrepancy was 7% according to the blinded surgical review based on imaging information.[6] In Japan, the H-classification, which is classified according to the number and size of liver metastases, has been used to estimate the prognosis of CRLM, and H1 is considered an oncologically favorable CRLM. Hence, we did not define resectability clearly; however, we considered H1 an oncologically favorable CRLM in this study. We stratified CRLM into H1 and H2 groups according to the H-classification and investigated RFS and OS. Regarding RFS, there was no difference in the H1 group, but in the H2 group, where the tumor was more advanced, the NAC group was significantly better. However, as in other reports, there was no difference in the OS. We speculated the reason RFS is good but not reflected in OS is owing to the strong effect of resection treatment on CRLM; therefore, unlike recurrence in other diseases, resection treatment might be effective in these recurrent lesions. On the other hand, RFS in the H1 group did not differ between the two groups, but a significant improvement in OS was observed in the upfront surgery group. The reason for the difference in OS when there is no difference in RFS is as described above, but if another reason is added, when patients who experienced serious side effects due to chemotherapy had unresectable recurrence, chemotherapy may be refused even if therapy is needed, which may have affected the OS. In addition, the early survival curve of the upfront surgery group in H2 was poor, reflecting the RFS results described above. As is well known, H2 patients are in a more advanced state, and this may be because resection treatment is performed for patients who are expected to have a potentially early recurrence or an early unresectable recurrence in the upfront surgery group. Thus, it is possible that NAC is less effective in patients with tumors that are easily resectable, such as in H1, where upfront surgery is recommended, but in patients with more advanced tumors, such as H2, NAC may be effective in terms of patient selection to avoid unnecessary surgery.

This study had several limitations. First, this was a retrospective analysis of surgical cases; therefore, for example, the prognosis of patients who underwent NAC but refused surgery due to disease progression or those who wished to continue chemotherapy chemistry is unknown.

Second, the frequency of administration, regimen, and timing of liver resection were not standardized. Therefore, further studies with larger samples might be necessary to validate the findings of the study. Possible bias was reduced as much as possible using propensity score matching. Thus, we believe that this study offers the highest level of evidence currently available regarding the clinical outcomes of patients with resectable CRLM.

Conclusion

In this study, OS rates were significantly poorer in preoperative chemotherapy patients than those in upfront surgery patients. We recommend that patients with resectable CRLM, especially those in the H1-classification, undergo upfront surgery, as the efficacy of unplanned NAC for these patients remains unclear based on the results of this large cohort study. However, further study is necessary regarding the treatment of patients who are H2 classified.

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Declarations

Ethics Approval This cohort study and the associated protocol are not registered with UMIN or ClinicalTrials.gov but were approved by the Ethics Committee of each institution (approval number: 2734; Osaka Medical College).

Conflict of Interest The authors declare no competing interest.

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