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ORIGINAL ARTICLE

Is neoadjuvant chemotherapy appropriate for patients with resectable liver metastases from colorectal cancer?

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Abstract

Purpose Neoadjuvant chemotherapy (NAC) for resectable liver metastasis from colorectal cancer (CRLM) is used widely, but its efficacy lacks clear evidence. This study aimed to clarify its worth and develop appropriate treatment strategies for CRLM.

Methods We analyzed, retrospectively, the clinicopathological factors and outcomes of 137 patients treated for resectable CRLM between 2006 and 2015, with upfront surgery (NAC^- group; $n=117$) or initial NAC treatment (NAC^+ group; $n=20$).

Results The time to surgical failure (TSF) and overall survival (OS) after initial treatment were significantly worse in the NAC^+ group than in the NAC^- group ($P=0.002$ and $P=0.032$, respectively). At hepatectomy, the NAC^+ group had a lower median prognostic nutrition index (PNI), higher rates of a positive Glasgow Prognostic Score ($P=0.002$) and more perioperative blood transfusions ($P=0.027$) than the NAC^- group. Moreover, the serum albumin ($P=0.006$), PNI ($P\leq0.001$) and lymphocyte-to-monocyte ratio ($P\leq0.001$) were significantly decreased and the GPS positive rate was increased from 15 to 35% in the NAC^+ group. The OS rates did not differ significantly according to the NAC response (5-year OS rates—CR/PR 67%, SD 60%, PD 38%).

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

Keywords Neoadjuvant chemotherapy · Resectable liver metastasis from colorectal cancer (CRLM) · Glasgow Prognostic Score

Introduction

Colorectal cancer (CRC) is the second most common malignancy in Japan. The liver is the most common metastatic site of advanced CRC and hepatectomy is considered the optimal and potentially curative treatment for colorectal liver metastasis (CRLM), with reported 5-year post-hepatectomy survival rates of 45–61% [1, 2]. However, the postoperative recurrence rate is approximately 75%, especially in the remnant liver [1]. On the other hand, combinations of 5-fluorouracil/folinic acid with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) plus molecular target agents have reportedly improved tumor response to > 50% resulting in improved median survival times of up to > 20 months, for unresectable or advanced recurrent CRLM [2]. In relation to neoadjuvant chemotherapy (NAC), Nordlinger et al. reported a phase III trial (EORTC 40983) that randomly assigned 364 patients with resectable CRLM to perioperative FOLFOX4 or to surgery alone, and showed a better progression-free survival (PFS) rate with perioperative NAC at 3 years [3]. However, no significant differences were found in the later-reported 3- or 5-year OS rates [4]. The authors concluded that perioperative NAC with FOLFOX-4 reduced the progression risk in eligible patients who also underwent resection, and that this strategy should be considered standard. Indeed, the oncology community has incorporated this practice worldwide. However, whether all patients with resectable CRLM benefit from NAC is unclear. The aim of this

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study was to clarify the effectiveness of NAC for resectable CRLM.

Patients and methods

Patients

Between April 2006 and March 2015, 169 patients underwent initial hepatectomy for CRLM at Osaka Medical College Hospital. Of these patients, 20 had received preoperative adjuvant chemotherapy (ACT) prior to being referred to our institution (NAC^+ group, $n=20$). The NAC^+ patients all had ≤4 tumors, the largest of which was ≤5 cm (H1 classification) at their initial visit. Of the remaining 149 patients, 117 also had ≤4 tumors, the largest of which was ≤5 cm (NAC^- group, $n=117$). Thirty-two patients who had ≥5 tumors, or tumors > 5 cm, were excluded from this analysis. This study thus included 137 patients, each of whom had ≤4 tumors, the largest of which was ≤5 cm, when the CRLM was detected and this state was defined as "resectable CRLM". There was no perioperative mortality. Each patient in this study who received NAC gave informed consent.

Surgical indications and procedure

In this series, hepatectomy for CRLM met the following two conditions: the primary CRC was curatively resected and metastases were located only in the liver. All patients underwent potentially curative hepatectomy with removal of gross tumors and negative macroscopic margins. In our experience, with respect to hepatic hilar lymph nodes, lymph node dissection was not performed routinely as node positivity in this region was strongly associated with extremely poor survival [5]. Synchronous (as opposed to metachronous) CRLM was defined as the presentation of liver metastasis at the time of CRC surgery and was detected in 42 patients (31%). These patients underwent either synchronous or metachronous hepatectomy, based mainly on their respective conditions and emergent needs. Non-anatomical hepatectomies were performed in principal, but in some cases, anatomical hepatectomy was carried out when this procedure offered advantages in operative time, blood loss, safety, or invasiveness. Hepatic resection followed the standard technique [6]. During resection, intraoperative ultrasonography was used to confirm surgical margins of 5–10 mm. In 80% of patients, the hepatic surgical margin was ≥5 mm.

Patient follow-up

Patients were examined for CRLM recurrence using ultrasonography and contrast-enhanced computed tomography (CT) every 4–6 months and blood tests (including tumor markers such as carcinoembryonic antigen) every 2–3 months after discharge. When recurrence was suspected, patients underwent magnetic resonance imaging to check for new lesions in the remnant liver. Systemic recurrence was checked by fluorodeoxyglucose positron emission tomography or gallium scintigraphy. Chest and pelvic CTs were also performed every 6 months for local and pulmonary metastases or recurrence. Recurrence was diagnosed when at least two imaging studies confirmed new lesions showing typical features of CRC/CRLM, compared with the previous images. Recurrent CRLM was treated by repeat resection when applicable ($n=40$).

Chemotherapy

Patients elected whether to undergo NAC after having been told that the efficacy of ACT for CRLM was controversial. Twenty patients received NAC, with regimens of either 5-fluorouracil (5FU) + leucovorin (LV) + oxaliplatin (FOLFOX) ± molecular-targeted agent (bevacizumab, cetuximab or panitumumab ($n=14$); 5FU + LV + irinotecan (FOLFIRI) + bevacizumab ($n=1$); 5FU + LV + oxaliplatin + irinotecan (FOLFOXIRI) + bevacizumab ($n=1$); or tegafur/gimeracil/oteracil (TS-1) or capecitabin + oxaliplatin (SOX or XELOX; $n=4$). Responses to NAC (per RECIST 1.1) were defined as follows: complete/partial response (CR/PR): $n=7$; stable disease (SD): $n=5$; or progressive disease (PD) $n=8$. The median numbers of treatment cycles were 5 (range 4–12) for the CR/PR group, 9 (2–23) for the SD group, and 6.5 (6–24) for the PD group. Numbers of treatment cycles varied in this retrospective study as they were decided at the discretion of the physicians. Patients also decided whether to undergo postoperative ACT. Ultimately, 58 patients received ACT, including tegafur/uracil ± calcium folinate ($n=33$), FOLFOX ($n=15$), capecitabine + oxaliplatin ($n=6$), and FOLFIRI ($n=4$).

Clinicopathological analysis

Patient demographics and laboratory test results, including tumor marker levels, tumor characteristics, treatment, recurrence, and survival data, were analyzed to identify prognostic factors for the survival rate 5 years after initial curative hepatectomy for CRLM. Surgically resected specimens were studied macro- and microscopically to identify various tumor characteristics, including the size of the largest tumor, the number of tumors, morphology, extent of the tumors, and surgical margins. For microscopic analysis, resected specimens were fixed in 10% formaldehyde and sliced into 5-mm-thick sections, then into 5-μm-thick tissue sections, and stained with hematoxylin and eosin. Two pathologists then reviewed them for histological confirmation of the pathological diagnosis. In this study, surgical margin status

was defined by distance to the lesion closest to the liver's cut surface, and macroscopically classified as ≥ 1 mm or 0 mm.

Definitions

The Japanese Classification of Colorectal Carcinoma H-classifications are based on the number and maximum size of tumors (General Rules for Clinical and Pathologic Studies on Cancer of the Colon, Rectum and Anus, 7th Japanese edition, 2006;[7] 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). In this study, resectable CRLM was defined as the H1 status. The time to surgical failure (TSF) was defined as the time from the initial treatment until the first unresectable recurrence or death from any cause [8]. Overall survival (OS) was defined as the time from the initial treatment until death from any cause. The Glasgow Prognostic Score (GPS) was estimated by giving one point each to elevated C-reactive protein (CRP; > 1.0 mg/dl) and hypoalbuminemia (< 3.5 g/dl): Patients with neither had score of 0, those with either one had score of 1, and those with both had score of 2 [9]. The response of tumors was evaluated by the Response Evaluation Criteria for Solid Tumors (RECIST: v 1.1).

Statistical analysis

The 2003 edition of the International Union Against Cancer tumor-node-metastasis (TNM) classification was used for staging [10]. Survival rates were compared using the Kaplan–Meier method. Univariate analyses were done using the log-rank test and multivariate analyses were done using the Cox proportional hazards regression model. Statistical comparisons were made by Fisher's exact probability test. Changes in values before and after preoperative chemotherapy were analyzed by repeated-measures analysis of variation. All analyses were performed using the JMP version 11.0 software package (SAS Institute, Cary, NC, USA) on Mac OS X. $P < 0.05$ was considered significant.

Results

The median TSF after initial treatment was significantly shorter for the NAC$^+$ group (1.53 years) than for the NAC$^-$ group ($P = 0.002$; Fig. 1). The respective 3- and 5-year TSF rates were 39%, and 23% for the NAC$^+$ group and 66% and 62% for the NAC$^-$ group. On multivariate analysis, pT4 disease ($P = 0.034$) and lymph node metastasis in CRC ($P < 0.001$) were identified as risk factors for TSF (Table 1).

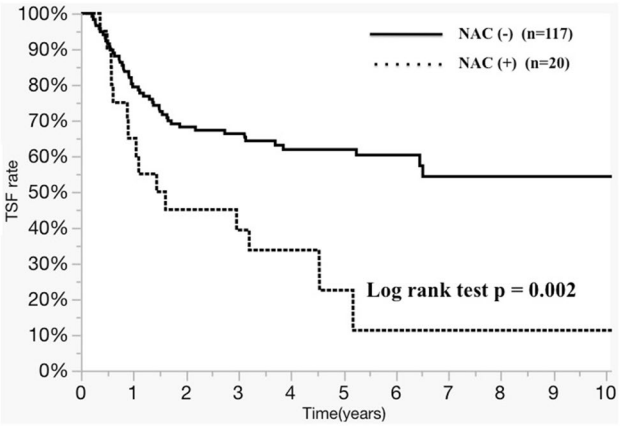

Fig. 1 Time to surgical failure (TSF) after initial treatment for resectable colorectal liver metastasis in the NAC$^+$ and NAC$^-$ groups. The TSF rate was significantly better in the NAC$^-$ group than in the NAC$^+$ group ($P = 0.002$). The respective 1-, 3-, 5-, and 7-year TSF rates were as follows: for NAC$^-$ ($n = 117$, thick line), 79%, 66%, 62%, and 54%; and for NAC$^+$($n = 20$, dotted line), 65%, 39%, 23%, and 11%. NAC, neoadjuvant chemotherapy

Overall survival after initial treatment was significantly worse in the NAC$^+$ group (5.56 years) than in the NAC$^-$ group (6.91 years; $P = 0.032$, Fig. 2). The respective 3- and 5-year OS rates after initial treatment were 59% and 53% in the NAC$^+$ group and 74% and 64% in the NAC$^-$ group. On univariate analysis, significant differences in OS rates were seen according to sex ($P = 0.041$), age ≥ 70 years ($P = 0.042$), low NLR (≤ 2.8, $P = 0.039$), low LMR (≤ 6.5, $P = 0.039$), rectal location of the CRC tumor ($P = 0.040$), depth of invasion in CRC (pT4, $P < 0.001$), and lymph node metastasis in CRC (pN1/2, $P = 0.035$). On multivariate analysis, pT4 ($P = 0.003$), lymph node metastasis ($P = 0.048$) in CRC, and a rectal primary lesion ($P = 0.008$) were significant independent prognostic factors (Table 2).

Table 3 summarizes the patients' clinicopathological characteristics at their hepatectomy. Depth of invasion (≤ pT3 vs. pT4), and lymph node metastasis (pN0 vs. pN1/2) in CRC did not differ significantly. However, on univariate analysis, the prognostic nutrition index (PNI) was significantly lower ($P = 0.004$), whereas the GPS positive rate ($P = 0.002$) and perioperative blood transfusion rate ($P = 0.027$) were significantly higher in the NAC$^+$ group than in the NAC$^-$ group. The postoperative ACT rates were 35% in the NAC$^+$ group and 44% in the NAC$^-$ group. On multivariate analysis, PNI, GPS, and perioperative blood transfusion did not differ significantly between the two groups.

Changes in inflammation-based prognostic indices in the NAC$^+$ group included significant decrease in albumin ($P = 0.006$), PNI ($P \leq 0.001$), and the lymphocyte-to-monocyte ratio (LMR; $P \leq 0.001$), but the

Table 1 Univariate and multivariate analyses of clinicopathological factors in relation to TSF in resectable CRLM after initial treatment

Factors/number	5-year survival rate (%)	Univariate analysis	Multivariate analysis	Odds ratio	CI
Patients' background characteristics					
NLR					
≤2.8/(*n* = 93)	64	0.006			
>2.8/(*n* = 51)	41				
Tumor-related factors: colorectal					
T factor					
pT4/(*n* = 24)	28	< 0.001	0.034	3.56	1.05–3.56
≤pT3/(*n* = 112)	62				
N factor					
≥pN1/(*n* = 83)	43	< 0.001	< 0.001	5.09	1.41–5.09
pN0/(*n* = 54)	77				
Tumor-related factors: liver					
CEA					
Positive/(*n* = 88)	51	0.026			
Negative/(*n* = 48)	68				
CA19-9					
Positive/(*n* = 38)	43	0.035			
Negative/(*n* = 97)	62				
Blood transfusion					
Yes/(*n* = 16)	29	0.009			
No/(*n* = 121)	60				

CA19-9 carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *NLR* neutrophil-to-lymphocyte ratio, *TSF* time to surgical failure

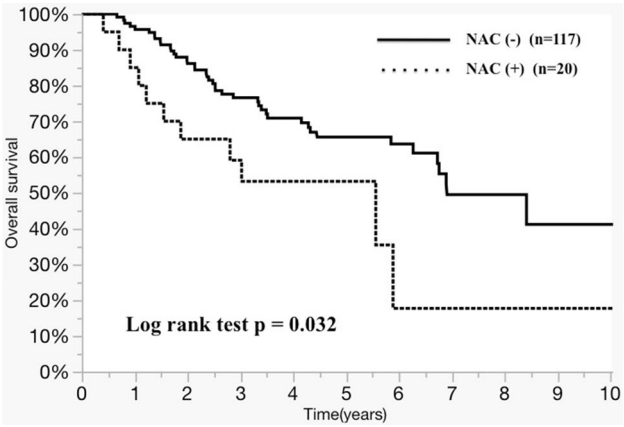

Fig. 2 Overall survival (OS) after initial treatment for resectable colorectal liver metastasis in the NAC^+ and NAC^- groups. The OS rate was significantly better in the NAC^- group than in the NAC^+ group ($P = 0.032$). The respective 1-, 3-, 5-, and 7-year OS rates were as follows: for NAC^- ($n = 117$, thick line), 97%, 77%, 66%, and 49%; and for NAC^+($n = 20$, dotted line), 85%, 59%, 53%, and 18%. NAC, neoadjuvant chemotherapy

neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) were not significantly changed (Table 4). The GPS positive rate increased from 15 to 35%. Overall survival also did not differ significantly according to the NAC response (5-year NAC^+ OS rates: CR/PR 67%, SD 60%; PD 38%; Fig. 3).

Discussion

The present retrospective study indicates that NAC potentially worsens the outcomes of patients with CLRM after initial treatment compared with upfront surgery. The possible reasons for this include potential liver damage or poor nutritional status caused by NAC, loss of optimal surgical timing, and disease progression related to NAC inefficacy. Following the phase III EORTC 40983 trial [3], the Guidelines of the National Comprehensive Cancer Network [11] and European Society for Medical Oncology (ESMO) [12] recommended perioperative ACT for CRLM. However, the same group later reported that OS was not better in a FOLFOX group than in a surgery-alone group (HR 0.87, 95% CI 0.66–1.14, $P = 0.303$) at 5-year follow-up,[4] and other articles have also reported some adverse events by NAC [13, 14]. The effectiveness of ACT is still controversial. In fact, surgical-only and postoperative chemotherapy treatments were added to the ESMO guideline of 2016, in addition to perioperative chemotherapy for resectable CRLM [15]. Although patients who undergo

Table 2 Univariate and multivariate analyses of clinicopathological factors in relation to overall survival in resectable CRLM after initial treatment

Factors/number	5-year survival rate (%)	Univariate analysis	Multivariate analysis	Odds ratio	CI
Patients' background characteristics					
Gender					
Male/($n=83$)	57	0.041			
Female/($n=54$)	75				
Age					
≥70/($n=54$)	51	0.042			
<70/($n=83$)	73				
NLR					
≤2.8/($n=93$)	53	0.039			
>2.8/($n=41$)	68				
LMR					
≥6.5/($n=35$)	76	0.048			
<6.5/($n=99$)	59				
Tumor-related factors: colorectal					
Location					
Rectum/($n=58$)	56	0.040	0.008	2.27	1.00–4.23
Colon/($n=79$)	69				
T factor					
pT4/($n=24$)	32	<0.001	0.003	3.27	1.51–6.98
≤pT3/($n=112$)	70				
N factor					
≥pN1/($n=83$)	56	0.035	0.048	1.87	1.00–3.63
pN0/($n=54$)	74				

CA19-9 carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *LMR* lymphocyte-to-monocyte ratio, *NLR* neutrophil-to-lymphocyte ratio

hepatectomy for CRLM have a relapse rate of about 75%, these patients who undergo further surgical treatment can have good prognoses if the recurrent lesion is resectable and is removed [16, 17]. For this reason, we used the TSF (as proposed by Oba et al. [8]) instead of disease-free survival (DFS) as an index in this study.

The present study associated NAC with significantly worse TSF and OS rates than seen with upfront surgery for resectable CRLM, rather than no significant difference. However, liver resection at the time progression disease (PD) is detected can result in poor prognosis [18]. Furthermore, we compared the TSF and OS in the NAC^- and NAC^+ groups without PD patients and found that the TSF was worse in the NAC^+ group than in the NAC^- group, but that the OS was similar in the two groups (supplementary figure). To investigate the cause, we compared the patients' backgrounds, but found no significant differences in tumor size, original tumor status, or postoperative ACT between the groups. However, the NAC^+ group had worse nutrition (as indicated by PNI) and a higher perioperative blood transfusion rate than the NAC^- group, which probably adversely influenced the TSF and OS in the NAC^+ group.

A range of systemic inflammatory response indices: NLR [19, 20], PLR [21, 22], LMR [23, 24], GPS [9, 25, 26], and PNI, correlate with the prognosis associated with various malignancies. The PNI was initially designed to assess the immunological and nutritional aspects of patients who undewent gastrointestinal surgery, and uses the serum albumin level (Alb) and total lymphocyte count as indicators of nutritional status [27, 28]. The PNI was recently shown to be a prognostic marker of malignancy, regardless of the origin site [29]. Another inflammation-based indicator of nutritional disorder is GPS, which is based on Alb and CRP [9]. Nakagawa et al. recently reported preoperative mGPS to be a predictor of the postoperative survival of patients undergoing curative resection for CRLM [30].

Some studies associated perioperative blood transfusion with worse CRLM survival outcomes on univariate analysis [31, 32], but others did not [33, 34]. Hallet et al. reported that perioperative blood transfusion is independently associated with shorter OS and DFS following hepatectomy for CRLM on multivariate analysis. Interventions to minimize and rationalize the use of blood transfusions in hepatectomy are warranted to mitigate this detrimental effect on long-term outcomes [35].

Table 3 Background and clinical characteristics of the patients with resectable colorectal cancer liver metastases (CRLM) who received neoadjuvant chemotherapy at the onset of treatment vs. those who did not

Factors	NAC(+), ($n=20$)	NAC(−), ($n=117$)	Uni, *P* value	Multi, *P* value
Background characteristics				
Gender (male/female)[a]	13/7	70/47	0.806	
Age (years)	67 (28–76)	68 (38–89)	0.655	
Diabetes mellitus[b]	3 (15%)	15 (13%)	0.728	
Tumor-related factors: colorectal				
Location (colon/rectum)[a]	11/9	49/68	0.811	
pT4[b]	4 (20%)	20 (17%)	0.755	
pN1[b]	13 (65%)	70 (60%)	0.806	
Tumor-related factors: liver				
Synchronous metastasis[b]	6 (43%)	36 (30%)	0.370	
Time after colectomy (days)	220 (0–735)	257 (0–2979)	0.353	
CEA	12.3 (1–310)	7 (1–38584)	0.218	
CA19-9	16.8 (0.3–30819)	18.9 (0.1–2753)	0.973	
PNI	43.3 (30.9–53.5)	49.0 (33.8–61.7)	0.004	0.136
NLR	2.3 (0.6–12.3)	2.2 (0.9–6.4)	0.796	
LMR	3.5 (0.7–9.2)	4.8 (1.5–17.7)	0.196	
PLR	180 (92–786)	167 (57–657)	0.196	
mGPS (positive)	9 (44%)	14 (12%)	0.002	0.051
Tumor size (cm)	2.6 (1–9)	2.5 (1–5)	0.859	
Tumor number (Single)[b]	10 (50%)	83 (71%)	0.074	
Surgical factors				
Major hepatectomy[b]	4 (29%)	25 (21%)	0.504	
Surgical time (min)	240 (60–725)	240(95–765)	0.846	
Surgical bleeding (ml)	250(40–2920)	170 (10–5770)	0.082	
Blood transfusion[c]	6 (30%)	12 (10%)	0.027	0.100
Curability (R0)	14 (70%)	103 (88%)	0.078	
Adjuvant chemotherapy	7 (35%)	51 (44%)	0.626	
Extrahepatic recurrence	10 (50%)	46 (39%)	0.462	

Median with range, unless specified

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, *LMR* lymphocyte-to-monocyte ratio, *mGPS* modified Glasgow prognostic score, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *PNI* prognostic nutrition index

[a]Number of patients

[b]Data are no. (%) of patients

[c]In the perioperative period

We also compared changes in values of inflammation-based prognostic indices in pre- and post- chemotherapy before hepatectomy. Albumin, PNI, and LMR were significantly decreased by NAC, whereas the GPS positive rate increased from pre- to post- NAC. We assume that NAC compromises the nutrition and inflammation status preoperatively, and consequently increases the need for perioperative blood transfusion, although the preoperative NLR, LMR and PLR did not differ significantly between the NAC^+ and NAC^- groups, and only LMR varied significantly from pre-chemotherapy to post-chemotherapy. These factors should be investigated in a larger cohort and in a randomized control trial.

Another possible reason for the significantly worse survival rate of the NAC^+ group is the loss of optimal surgery timing. For some patients, NAC reflected the patient's hope and the physician's intention for a cure. Thus, rather than undergoing hepatectomy when chemotherapy had reduced the tumor, the patient underwent hepatectomy during the tumor regrowth.

The PD rates were slightly higher in the present study than in previous studies because we counted tumors that had initially shrunk after the NAC but had then grown larger than their pre-NAC size by the time of surgery. Finally, although better tolerance of anticancer agents is considered an advantage of preoperative chemotherapy over postoperative

Table 4 The change in inflammation-based prognostic indices in patients who received preoperative chemotherapy

	Pre-chemotherapy	Pre-hepatectomy	*P*
Alb			
CR/PR (*n* = 7)	4.0 (3.8–4.6)	3.7 (3.3–4.7)	0.006
SD (*n* = 5)	4.3 (3.7–4.5)	3.9 (2.8–4.7)	
PD (*n* = 8)	4.3 (3.4–4.7)	4.0 (2.5–4.5)	
PNI			
CR/PR (*n* = 7)	53.2 (48.7–73.7)	43.4 (41.1–52.4)	< 0.001
SD (*n* = 5)	62.8 (50.5–70.1)	47.1 (33.9–53.5)	
PD (*n* = 8)	55.6 (43–66.7)	40.5 (30.6–53.5)	
NLR			
CR/PR (*n* = 7)	2.0 (1.1–3.6)	2.5 (0.9–3.1)	0.392
SD (*n* = 5)	2.1 (1.6–4.4)	2.0 (0.6–5.4)	
PD (*n* = 8)	2.5 (1.4–5.0)	2.9 (1.8–9.8)	
LMR			
CR/PR (*n* = 7)	5.9 (4.5–7.1)	4.6 (2.6–6.7)	< 0.001
SD (*n* = 5)	4.8 (3.4–10.2)	3.6 (0.6–8.1)	
PD (*n* = 8)	5.0 (1.3–7.1)	3.6 (1.4–9.2)	
PLR			
CR/PR (*n* = 7)	162 (78–362)	177 (101–246)	0.818
SD (*n* = 5)	166 (105–413)	123 (92–276)	
PD (*n* = 8)	348 (159–355)	205 (132–276)	
mGPS positive rate	3/20 (15%)	7/20 (35%)	

CR complete response, *LMR* lymphocyte-to-monocyte ratio, *mGPS* modified Glasgow prognostic score, *NLR* neutrophil-to-lymphocyte ratio, *PD* progressive disease, *PLR* platelet-to-lymphocyte ratio, *PNI* prognostic nutrition index, *PR* partial response, *SD* stable disease

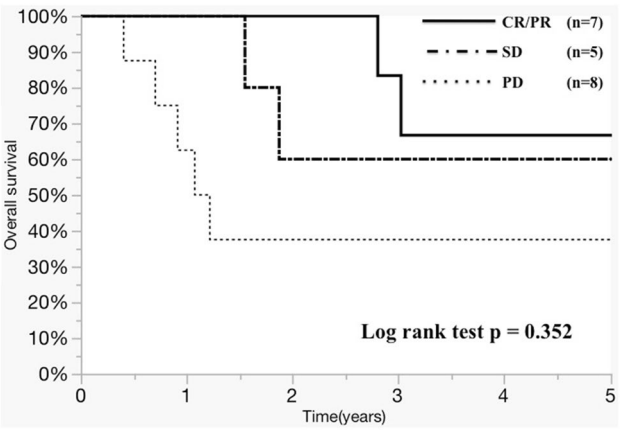

Fig. 3 Overall survival (OS) after initial hepatectomy for resectable colorectal liver metastasis by response to chemotherapy in the NAC$^+$ group. The OS rates did not differ significantly according to the NAC response ($P = 0.352$). The respective 1-, 3-, and 5-year OS rates were CR/PR ($n = 7$, thick line): 100%, 83%, and 67%; SD ($n = 5$, dashed–dotted line): 100%, 60%, and 60%; PD ($n = 8$, dotted line): 63%, 38%, and 38%

chemotherapy, preservation of as much liver parenchyma as possible for repeated hepatectomy in case of recurrence is a more recent policy [36, 37]. We think that tolerance does not differ between pre- and postoperative chemotherapy, even in patients who have already received chemotherapy.

In conclusion, we propose that patients with resectable CRLM undergo upfront hepatectomy, as the efficacy of NAC cannot be confirmed, except in exceptional cases.

Compliance with ethical standards

Conflict of interest We declare no commercial interest in the subject of this study.

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