Neoadjuvant Chemotherapy Followed by Hyperthermic Intraperitoneal Chemotherapy for Patients with Colorectal Peritoneal Metastasis: A Retrospective Study of its Safety and Efficacy

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Research

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Abstract

Background Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are effective routine treatments for colorectal peritoneal metastases (PMs). However, the safety and efficacy of neoadjuvant chemotherapy (NAC) before CRS+HIPEC are poorly understood. Therefore, this study aimed to assess the perioperative safety and long-term efficacy for patients with synchronous colorectal PM who received NAC prior to CRS+HIPEC.

Method Patients with synchronous colorectal PM who received NAC prior to CRS+HIPEC were systematically reviewed at the China National Cancer Center and Huanxing Cancer Hospital from June 2017 to June 2019. Clinicopathologic characteristics, perioperative parameters, and survival were compared between patients who underwent CRS+HIPEC with NAC (NAC group) and those who underwent CRS+HIPEC without NAC (non-NAC group).

Results The study enrolled 52 patients, with 20 patients in the NAC group and 32 in the non-NAC group. In the NAC group, the proportion of patients with a peritoneal carcinomatosis index (PCI) score < 12 was significantly higher than that in the non-NAC group (80.0% vs 50.0%, *P*=0.031), and more patients received complete cyoreduction (80.0% vs 46.9%, *P*=0.018). The two groups had comparable grade III/IV complications and similar reoperation and mortality rates (*P*>0.05). However, patients who received NAC prior to CRS+HIPEC experienced lower platelet counts (151.9 vs 197.7 $\times 10^9$/L, *P*=0.036) and neutrophil counts (4.7 vs 7.2$\times 10^9$/L, P=0.030) on postoperative day 1. Compared with the non-NAC group, more patients in the NAC group survived for two years (67.4% vs. 32.2%, respectively, *P* = 0.044). However, the CC score (HR, 2.99; 95% CI, 1.14-7.84; *P*=0.026), rather than NAC, was independently associated with OS in the multivariable analysis after controlling for confounding factors.

Conclusion NAC administration before CRS+HIPEC can be regarded as a safe and feasible treatment for patients with colorectal PM with comparably low mortality and acceptable morbidity. Nevertheless, the administration of NAC before CRS+HIPEC conferred a greater survival benefit to patients, even though NAC was not identified as an independent factor for OS after controlling for confounding factors.

Introduction

The peritoneum is the second most common site of colorectal cancer (CRC) metastasis after the liver[1], with evidence of synchronous peritoneal metastasis (PM) reported in 5–15 CRC patients[2–3]. It has long been known that peritoneal metastasis is a poor prognostic factor, and the median survival time of its natural course is usually only 5–7 months[4]. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has gradually become the standard treatment for PM arising from CRC after extensive exploration and experience[5–7]. For selected patients, the median survival can reach approximately 40 months after CRS and HIPEC treatment for PM arising from CRC[8].

CRS + HIPEC is a complicated and potentially life-threatening procedure, with postoperative complications as high as 37.9–60.5%[9–14], which can worsen general conditions and hamper subsequent systemic adjuvant chemotherapy. Nevertheless, neoadjuvant chemotherapy (NAC) has been shown to benefit survival in patients with stage IV colorectal cancer[15, 16]. On this basis, we speculate whether the administration of NAC before the CRS + HIPEC procedure could also bring survival benefits to colorectal cancer patients with synchronous PM. In addition, it remains to be confirmed whether CRS + HIPEC after NAC administration increases the incidence of postoperative complications. Therefore, we designed a single-centre retrospective analysis to investigate the survival benefits conferred to colorectal cancer patients with PM who received NAC before CRS + HIPEC as well as its perioperative safety.

Patients And Methods

The present study included 52 eligible patients with synchronous PM arising from CRC who underwent CRS+HIPEC at the National Cancer Center and Huanxing Cancer Hospital between June 2017 and June 2019. The inclusion criteria included the following: (1) pathologically confirmed colorectal cancer; (2) age between 18-75 years; and (3) Eastern Cooperative Group (ECOG) score ≤ 1. The exclusion criteria were as follows: (1) the presence of other malignant tumours; (2) palliative surgery such as bypass surgery or simple ostomy; and (3) NAC administration for at least 3 cycles. The study protocol was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences (NCC 2017-YZ-026, Oct 17, 2017).

Patients were divided into two groups: those who received NAC followed by CRS+HIPEC (NAC group) and those who underwent CRS+HIPEC first without NAC (non-NAC group). Preoperative demographic and clinical information of the two groups was prospectively collected in an institutional database and retrospectively analysed. The peritoneal carcinomatosis index (PCI) was used to assess the degree of PM and is scored from 0 to 3 for each of the 13 defined areas of the abdominal cavity[17]. The completeness of the cytoreduction score (CC score) was recorded as follows: CC 0/1, complete cytoreduction (CC 0 indicates no visible disease, and CC 1 indicates nodules smaller than 0.25 cm), or CC 2/3, incomplete cytoreduction[18]. Toxicity indexes of chemotherapy (blood, liver, and kidney toxicity), including the neutrophil count, platelet count, ALT level, and creatinine level, were measured in the morning on postoperative days (PODs) 1, 3, and 5. Patients with severe liver and kidney impairment or myelosuppression were deemed ineligible for an additional HIPEC procedure. Postoperative complications were recorded and staged according to the Common Terminology Criteria for Adverse Events (CTCAE) classification within 30 days[19].

CRS +HIPEC Procedure

The CRS +HIPEC procedures has been described previously[20]. All patients underwent a closed technique for HIPEC after cytoreduction and fashioning of the intestinal anastomoses. Oxaliplatin (350 mg/m2) and raltitrexed (4 mg/m2) with or without lobaplatin (50 mg/m2) were used for intraperitoneal chemotherapy. All patients were treated with a mixed solution of chemotherapy agents and 3 L of saline

solution in the abdominal and pelvic cavities for 60 min at 42-43°C. Thereafter, four catheters remained in the original position, and two more HIPEC procedures with the same chemotherapeutic regimens as well as perfusion times were performed again on the second and fourth days after surgery in the ward. CRS + HIPEC treatment was performed by two surgical specialists with more than 20 years of experience in gastrointestinal surgery at the two centres; the exact same HIPEC technique and postoperative treatment was performed at both centres.

Follow-up

All patients were scheduled to receive follow-up through outpatient visits every 3 months for the first three years and then every 6-12 months for the 3 years thereafter. CT scans of the abdomen and pelvis and laboratory examinations, including tumour biomarkers (CEA and CA-199), were performed at every follow-up. The long-term endpoint of this study was 3-year overall survival (OS). OS was defined as the time from the date of surgery until death or last follow-up (July 31, 2020).

Statistical Analysis

All variables were compared between the groups using IBM SPSS Statistics software version 24.0 (IBM Corp, Armonk, NY, USA). Continuous variables are presented as the mean ± SD and were analysed with Student's t-tests and Mann-Whitney U-tests depending on the distribution. Differences between fractions were analysed by χ^2 tests or Fisher's exact tests as appropriate. Actuarial OS was estimated by the Kaplan-Meier method. Univariate analysis of variables potentially impacting OS was performed with the log rank test, and significant univariate variables were applied in the multivariate Cox regression model. A *P* value lower than 0.05 was regarded as statistically significant.

Results

In the present study, 52 patients with synchronous PM arising from CRC underwent CRS+HIPEC; 20 (38.5%) received NAC, and 32 (61.5%) underwent surgery without receiving NAC. Patients in the NAC group were treated with a chemotherapy regimen commonly used for colorectal cancer, and 6 patients received the antiangiogenic agent bevacizumab, as shown in Table 1. Patient demographics and clinical details are provided in Table 2. In the NAC group, 80.0% of patients received complete cytoreduction (CC 0/1) versus 46.9% in the non-NAC group (*P*=0.018). In addition, the proportion of patients with a PCI score < 12 in the NAC group was significantly higher than that in the non-NAC group (80.0% vs 50.0%, *P*=0.031). There were no significant differences between the two groups in terms of age, sex, body mass index, preoperative CEA level, comorbidity, tumour location, histology, T stage, N stage, liver metastases, ascites, HIPEC regimen, or adjuvant chemotherapy.

Table 3 lists the surgical outcomes and postoperative course. The mean operative time in the NAC group was shorter than that in the non-NAC group, but the difference was not statistically significant (245.5 vs 289.4 min, *P*=0.082). With regard to toxicity indexes after HIPEC, patients in the NAC group were more likely to experience thrombocytopenia after HIPEC than those in the non-NAC group (30.0% vs 6.3%,

P=0.043). There were no significant differences in the rates of grade III/IV complications (40.0% vs 31.3%, *P*= 0.519), hospital days (15.4 vs 13.9 days, *P*=0.333), or 30-day reoperation rate (1.9% vs. 0%, P=1.000) among patients in the NAC and non-NAC groups.

In addition, the mean platelet count (151.9 vs 197.7 $\times 10^9$/L, *P*=0.036) and leukocyte count (4.7 vs 7.2$\times 10^9$/L, *P*=0.030) in the NAC group were also significantly lower than those in the non-NAC group on postoperative day (POD) 1 (Figure 1 and Figure 2). There were no statistically significant differences between the two groups in terms of the ALT level or creatinine level on PODs 1, 3, and 5 (Figure 3, Figure 4).

Survival Analysis

The median follow-up time was 18.5 (range, 3-28) months. The median survival for all patients was 24 months, and the estimated 1- and 2-year OS rates for the entire cohort were 65.0% and 42.1%, respectively (Figure 5). Patients who received NAC prior to CRS + HIPEC experienced a longer 2-year OS (32.2% vs. 67.4%, p = 0.044) than those who underwent CRS+HIPEC without NAC (Figure 6).

The results of exploratory univariate and multivariable Cox regression analyses for OS are detailed in Table 4. The univariate analysis identified the following prognostic indicators for OS: neoadjuvant chemotherapy (HR, 0.36; 95% CI, 0.13-0.92; *P*=0.033), PCI score (HR, 2.98; 95% CI, 1.41-6.32; *P*=0.004), and CC score (HR, 4.20; 95% CI, 1.89-9.36; *P*<0.001). After correction of these variables with multivariate analysis, OS was significantly associated with the CC score (HR, 2.99; 95% CI, 1.14-7.84; *P*=0.026). Neoadjuvant chemotherapy (HR, 0.55; 95% CI, 0.22-1.39; *P*=0.204) and PCI score (HR, 1.49; 95% CI, 0.61-3.66; *P*=0.381) were not independently associated with OS.

Discussion

In contrast to mucinous appendiceal neoplasms, PM from CRC is usually a manifestation of extensive tumour progression and poor prognosis. However, CRS+HIPEC can improve the long-term survival rates of well-selected patients with PM[5-8]. In addition to CRS+HIPEC treatment, perioperative systemic chemotherapy has been shown to prolong the survival of patients with PM[15,16,21]. However, the optimal timing of chemotherapy, especially the safety and long-term efficacy of preoperative chemotherapy, remains unknown. Therefore, this study was conducted to investigate the perioperative safety and survival benefits of colorectal cancer patients with synchronous PM who received NAC before the CRS+HIPEC procedure. Our data revealed that patients who underwent CRS+HIPEC following NAC had a comparably low mortality and acceptable morbidity. Although NAC prior to CRS+HIPEC has a certain effect on platelets and neutrophils, these responses do not appear to translate to postoperative complications under close supervision and active surveillance. Nevertheless, while patients who underwent CRS+HIPEC following NAC experienced improvements in OS compared to those who underwent surgery only, NAC was not an independent improved prognostic factor for OS after controlling for confounding factors.

CRS+HIPEC is a complex and potentially life-threatening procedure with a morbidity rate ranging from 12 to 52% and a mortality rate ranging from 0.9-5.8% in 10 specified international treatment centres[22]. Therefore, it is worth exploring whether the side effects caused by NAC, such as myelosuppression, neurotoxicity, and gastrointestinal reactions, will further increase morbidity and mortality after CRS+HIPEC. The retrospective study of Devilee et al. assessed the safety and efficacy of NAC for 91 patients undergoing CRS and HIPEC, and the results showed that NAC prior to CRS+HIPEC did not significantly increase the incidence of severe complications (24% vs 17%, *P*=0.55) or mortality (0 vs 1.5%, *P*=1.000)[23]. Similarly, Leimkühler et al. observed that the severity and timing of complications were comparable between patients who received NAC prior to CRS+HIPEC and those who did not[24]. Our study also found that patients who underwent NAC prior to CRS+HIPEC were more likely to experience thrombocytopenia after surgery (30.0% vs 6.3%, *P*=0.043). Moreover, the mean platelet count (151.9 vs 197.7 $\times 10^9$/L, *P*=0.036) and neutrophil count (4.7 vs 7.2$\times 10^9$/L, P=0.030) in the NAC group were significantly lower than those in the non-NAC group on POD 1. However, we found that these adverse effects on platelets and neutrophils did not appear to translate into severe postoperative complications (40.0% vs 31.3%, *P*= 0.519).

In theory, NAC can effectively downstage the primary tumour and peritoneal tumour burden and thus improve long-term survival. In the present study, patients who underwent NAC had significantly lower PCI scores at the time of CRS+HIPEC, and a higher proportion of these patients achieved complete cytoreduction (CC 0/1). Moreover, although the CC score, rather than NAC, was independently associated with OS in the multivariable analysis, more patients who received NAC prior to CRS + HIPEC survived for 2 years than those who did not (67.4% vs. 32.2%, respectively, *P*=0.044). Lessons learned from large-scale multi-institutional registry studies were that both the PCI score and completeness of cytoreduction were associated with long-term survival after CRS+HIPEC[25,26], and the use of NAC to reduce tumour burden and increase the odds of achieving complete cytoreduction is an effective and valuable strategy. Consistent with these findings, a retrospective analysis of 298 patients conducted by Beal et al. demonstrated that NAC could bring survival benefit to patients undergoing CRS+HIPEC, although NAC was not identified as an independent factor for OS after controlling for confounding factors[13]. Similarly, Devilee et al reported that treatment with NAC was associated with improved OS before CRS+HIPEC[23].

Several limitations should be taken into account in the current study. The most significant limitation was the small size, especially the NAC group, which included only 20 patients; this might have caused some of the differences observed between the two groups. Second, this study was also a retrospective design and had inherent selection bias. Furthermore, we only included and analysed patients who successfully underwent CRS+HIPEC after NAC; those who did not undergo surgery after NAC were excluded for various reasons, which may lead to controversial results in this study. Multicentre, large-scale randomized controlled studies are needed to further verify our results.

In conclusion, the results of our study demonstrate that NAC prior to CRS+HIPEC achieved comparably low mortality and acceptable morbidity. Although NAC exerts certain effects on platelets and neutrophils,

these effects do not appear to translate to severe postoperative complications. Nevertheless, the administration of NAC before CRS+HIPEC conferred a survival benefit to patients, even though NAC was not identified as an independent factor for OS after controlling for confounding factors.

Abbreviations

Colorectal cancer (CRC); Peritoneal metastasis (PM); Cytoreductive surgery (CRS); Hyperthermic intraperitoneal chemotherapy (HIPEC); Neoadjuvant chemotherapy (NAC); Eastern Cooperative Group (ECOG); Peritoneal carcinomatosis index (PCI); Completeness of the cytoreduction score (CC score); Postoperative days (PODs); Common Terminology Criteria for Adverse Events (CTCAE); Overall survival (OS);

Declarations

Ethics approval and consent to participate

The ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College approved this study. Prior written informed consent was obtained from all study participants.

Consent to publish

Not Applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the data is confidential patient data but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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044-KF). The funders had no role in the design of the study, data collection, analysis, and manuscript writing.

Authors' contributions

Contributions: (I) conception and design: JWL, SCZ, and WP; (II) administrative support: JWL and ZXZ; (III) provision of study materials or patients: YJJ and WP ; (IV) collection and assembly of data: SCZ; (V) data analysis and interpretation: SCZ and JWL. All authors read and approved the final manuscript.

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Tables

Table 1. Neoadjuvant chemotherapy regimen of 20 patients

Preoperative chemotherapy regimen	N(%)
XELOX	5 (25.0)
XELOX+Bevacizumab	2 (10.0)
FOLFOX	5 (25.0)
FOLFIRI	3 (15.0)
FOLFOX+Bevacizumab	2 (10.0)
FOLFIRI+Bevacizumab	2 (10.0)
5-FU+Leucovorin	1 (5.0)

XELOX ,Capecitabine+ Oxaliplatin; *FOLFOX*, Leucovorin Calcium+ 5-Fluorouracil+ Oxaliplatin; *FOLFIRI* ,Leucovorin Calcium+5-Fluorouracil+Irinotecan

Table 2. Clinical characteristics of 52 enrolled patients

Variables	All patients (n=52)	NAC (n=20)	Non-NAC (n=32)	*P*
Age (years)				0.350
< 65	35 (67.3)	15 (75.0)	20 (62.5)	
≥ 65	17 (22.7)	5 (25.0)	12 (37.5)	
Gender				0.508
Male	29 (55.8)	10 (50.0)	19 (59.4)	
Female	23 (44.2)	10 (50.0)	13 (40.6)	
Body mass index (kg/m^2)	22.5±3.5	22.8±3.3	22.4±3.6	0.542
Preoperative CEA level (ng/ml)				0.744
< 5	17 (32.7)	6 (30.0)	11 (34.4)	
≥ 5	35 (67.3)	14 (70.0)	21 (65.6)	
Comorbidity	14 (26.9)	4 (20.0)	10 (31.3)	0.374
Tumor location				0.636
Colon	42 (80.8)	15 (75.0)	27 (84.4)	
Rectum	10 (19.2)	5 (25.0)	5 (15.6)	
Histology				0.289
Adenocarcinoma	29 (55.8)	13 (65.0)	16 (50.0)	
Mucinous/signet-ring	23 (44.2)	7 (35.0)	16 (50.0)	
T stage				0.287
T3	6 (11.5)	4 (20.0)	2 (6.3)	
T4	46 (88.5)	16 (80.0)	30 (93.7)	
N stage				0.506
N0	8 (15.4)	3 (15.0)	5 (15.6)	
N1	16 (30.8)	8 (40.0)	8 (25.0)	
N2	28 (53.8)	9 (45.0)	19 (59.4)	
PCI score				0.031
< 12	32 (61.5)	16 (80.0)	16 (50.0)	
≥ 12	20 (38.5)	4 (20.0)	16 (50.0)	

Liver metastases	9 (17.3)	4 (20.0)	5 (15.6)	0.977
Ascites	22 (42.3)	8 (40.0)	14 (43.8)	0.790
HIPEC regimen				0.930
Lobaplatin+Oxaliplatin+Raltitrexed	23 (44.2)	9 (45.0)	14 (43.8)	
Oxaliplatin+Raltitrexed	29 (55.8)	11 (55.0)	18 (56.2)	
CC score				0.018
0-1	31 (59.6)	16 (80.0)	15 (46.9)	
2-3	21 (40.4)	4 (20.0)	17 (53.1)	
Adjuvant chemotherapy				0.738
Yes	44 (84.6)	16 (80.0)	28 (87.5)	
No	8 (15.4)	4 (20.0)	4 (12.5)	

PCI, peritoneal carcinomatosis index; *CC*, cytoreduction score

Table 3. Surgical outcomes and postoperative course of 52 enrolled patients

Variables	All patients (n=52)	NAC (n=20)	Non-NAC (n=32)	*P*
Operative time (min, mean ± SD)	276.3 ± 60.1	245.5 ± 59.1	289.4 ± 63.4	0.082
Intraoperative blood loss (mL, mean ± SD)	104.3± 111.1	115.0 ± 111.3	100.8 ± 111.0	0.661
Postoperative complication (Grade 3-4)	18 (34.6)	8 (40.0)	10 (31.3)	0.519
Arrhythmia	1 (1.9)	1 (5.0)	0 (0)	
Pneumonia	3 (5.8)	2 (10.0)	1 (3.1)	
Anastomotic leakage	3 (5.8)	1 (5.0)	2 (6.3)	
Ileus	7 (13.5)	3 (15.0)	4 (12.5)	
Abdominal abscess	3 (5.8)	1 (5.0)	2 (6.3)	
Intra-abdominal hemorrhage	1 (1.9)	0 (0)	1 (3.1)	
Wound infection	5 (9.6)	2 (10.0)	3 (9.4)	
Toxicity Indexes after HIPEC	22 (42.3)	10 (50.0)	12 (37.5)	0.375
Abnormal change of neutrophil	6 (11.5)	3 (15.0)	3 (9.4)	0.864
Abnormal change of platelet	8 (15.4)	6 (30.0)	2 (6.3)	0.043
Abnormal change of ALT	8 (15.4)	2 (10.0)	6 (18.8)	0.463
Abnormal change of creatinine	3 (5.8)	1 (5.0)	2 (6.3)	1.000
Time to first flatus (day, mean ± SD)	3.8 ± 1.8	4.1 ± 1.9	3.6 ± 1.8	0.811
Total hospital stay (day, mean ± SD)	14.4 ± 5.0	15.4 ± 6.0	13.9 ± 3.9	0.333
Re-operation	1 (1.9)	1 (5.0)	0 (0)	1.000
Mortality (%)	0 (0)	0 (0)	0 (0)	1.000

Table 4. Univariate and Multivariable Cox Regression Analysis for Overall Survival

Variables	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR(95%CI)	P	HR(95%CI)	P
Gender: male/female	1.13 (0.53-2.43)	0.753		
Age at operation (< 65 years/≥ 65 years)	2.12 (0.98-4.60)	0.056		
Preoperative chemotherapy (no/yes)	0.36 (0.13-0.92)	0.033	0.55 (0.22-1.39)	0.204
T stage (T3/T4)	1.61 (0.73-3.54)	0.235		
N stage				
N0	Reference	Reference		
N1	1.29 (0.57-2.94)	0.545		
N2	2.26 (0.71-7.16)	0.167		
Site of original (Colon/Rectum)	1.48 (0.63-3.51)	0.373		
Histology (adenocarcinoma/mucinous)	2.05 (0.96-4.40)	0.065		
Preoperative CEA level (< 5 ng/ml/≥ 5 ng/ml)	1.68 (0.78-3.58)	0.183		
Liver metastases (no/yes)	1.24 (0.50-3.08)	0.648		
HIPEC regimen (lobaplatin/non-lobaplatin)	1.38 (0.62-3.05)	0.427		
Presence of ascites (no/yes)	1.20 (0.55-2.60)	0.650		
PCI score (< 12 /≥ 12)	2.98 (1.41-6.32)	0.004	1.49 (0.61-3.66)	0.381
CC score (0-1/2-3)	4.20 (1.89-9.36)	<0.001	2.99 (1.14-7.84)	0.026
Grade 3-4 Postoperative complication (no/yes)	1.62 (0.74-3.57)	0.229		

Figures

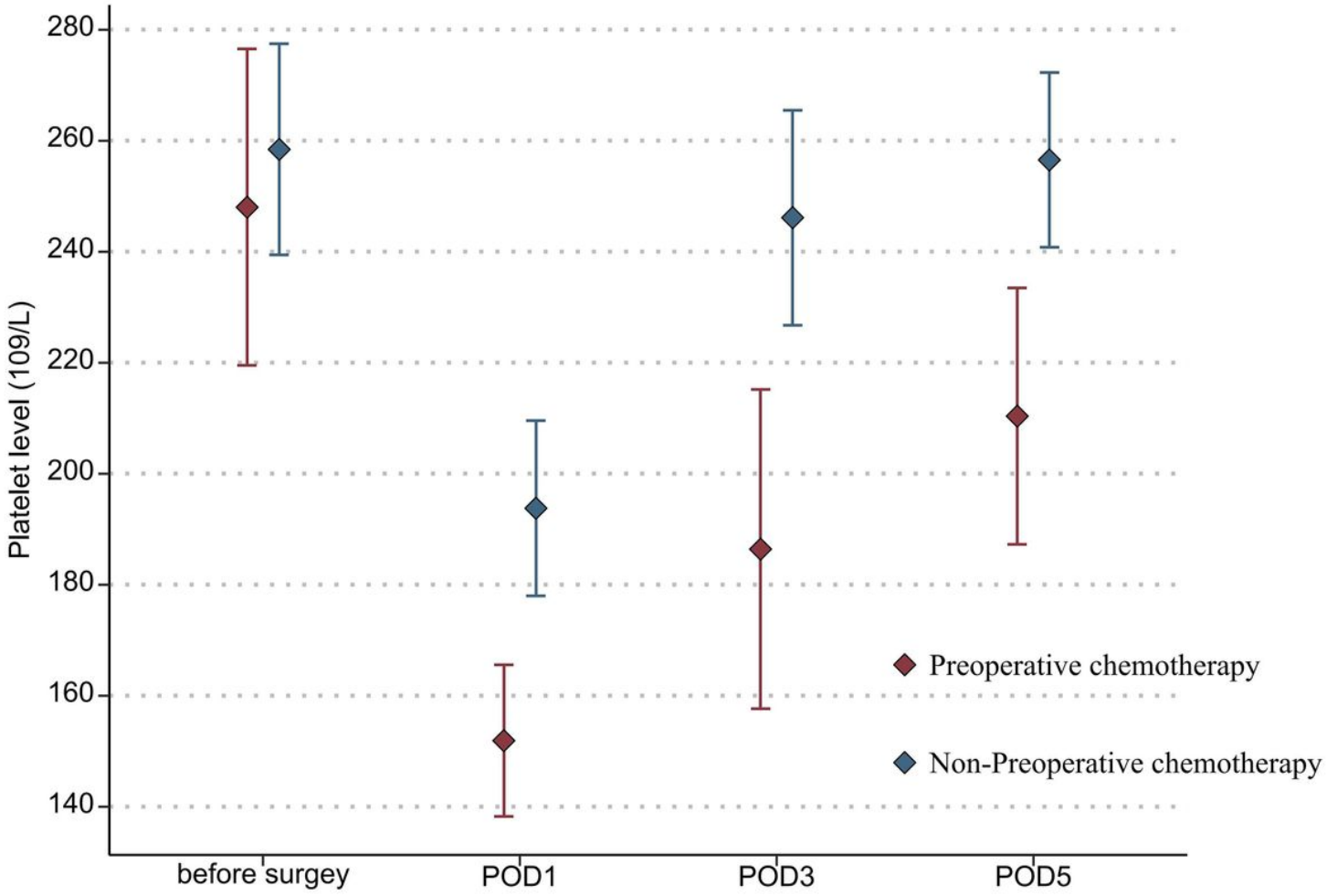

Figure 1

Changes in the platelet level in NAC and Non-NAC groups on days 1, 3, and 5 after surgery. POD1,3,5： postoperative day1,3,5 The mean platelet count (151.9 vs 197.7 ×109/L, P=0.036) in the NAC group was significantly lower than those in the non-NAC group on postoperative day (POD) 1

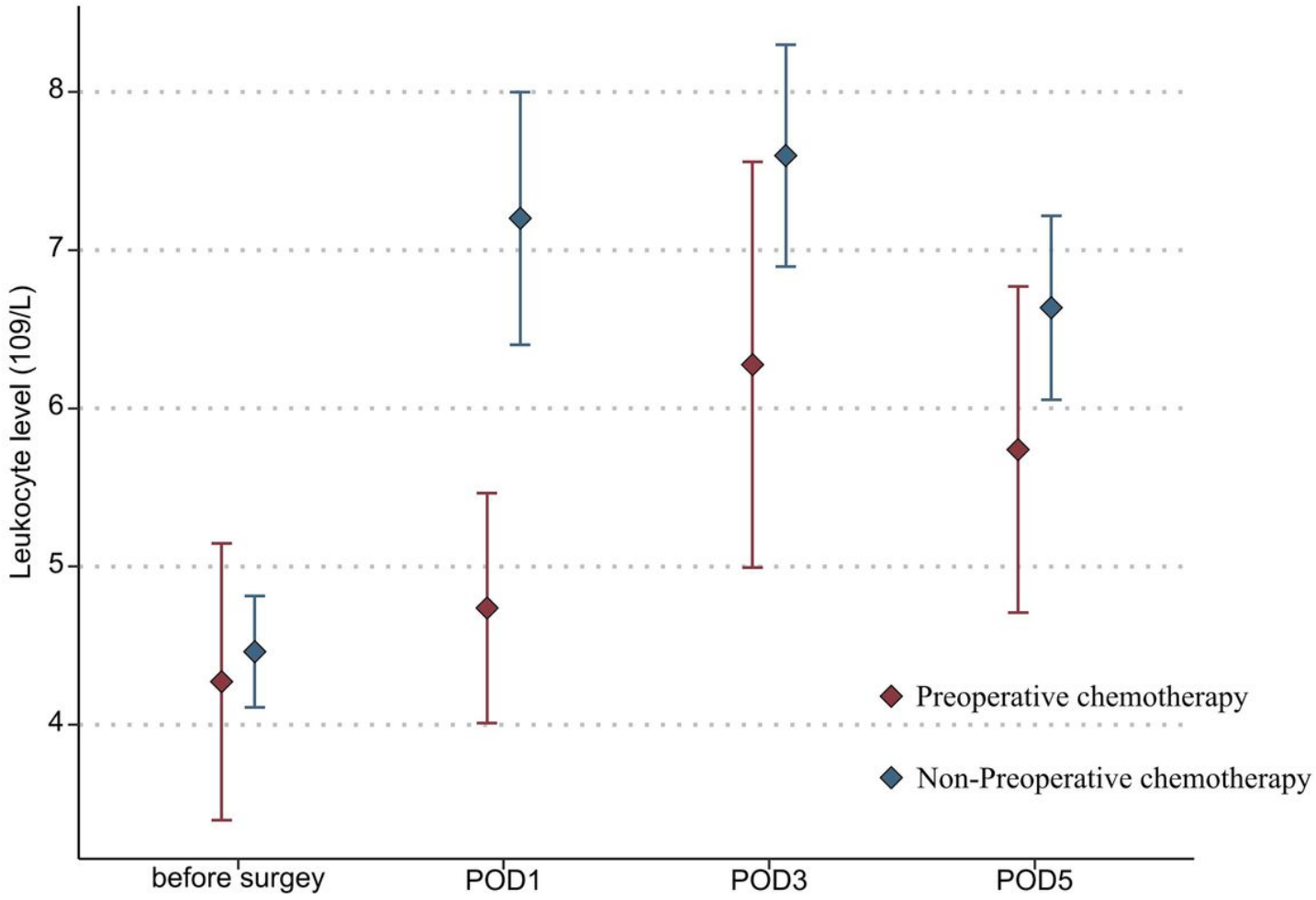

Figure 2

Changes in the leukocyte level in NAC and Non-NAC groups on days 1, 3, and 5 after surgery. POD1,3,5 postoperative day1,3,5 The mean leukocyte count (4.7 vs 7.2×109/L, P=0.030) in the NAC group was significantly lower than those in the non-NAC group on postoperative day (POD) 1

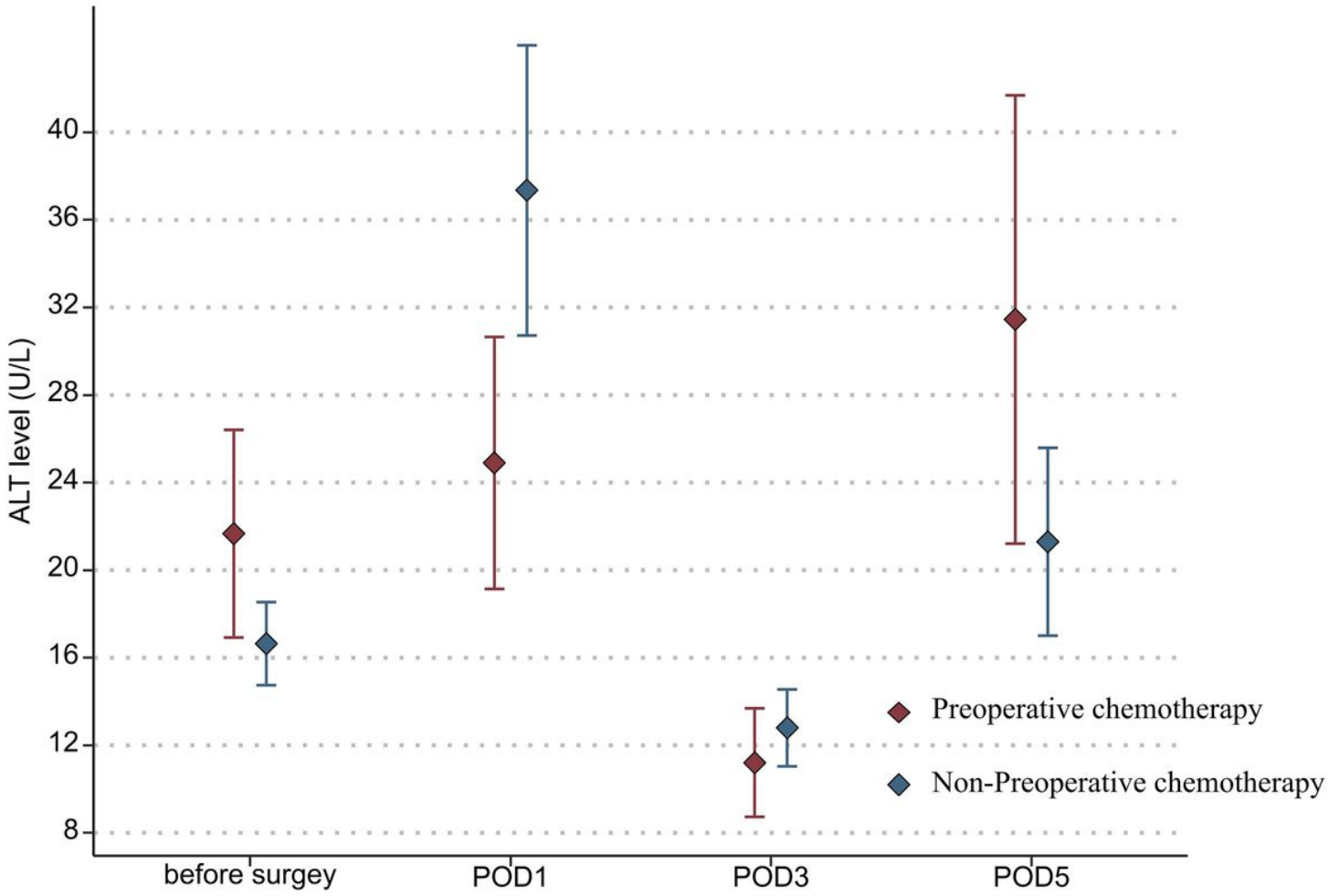

Figure 3

Changes in the ALT level in NAC and Non-NAC groups on days 1, 3, and 5 after surgery. POD1,3,5： postoperative day1,3,5 There were no statistically significant differences between the two groups in terms of the ALT level on PODs 1, 3, and 5

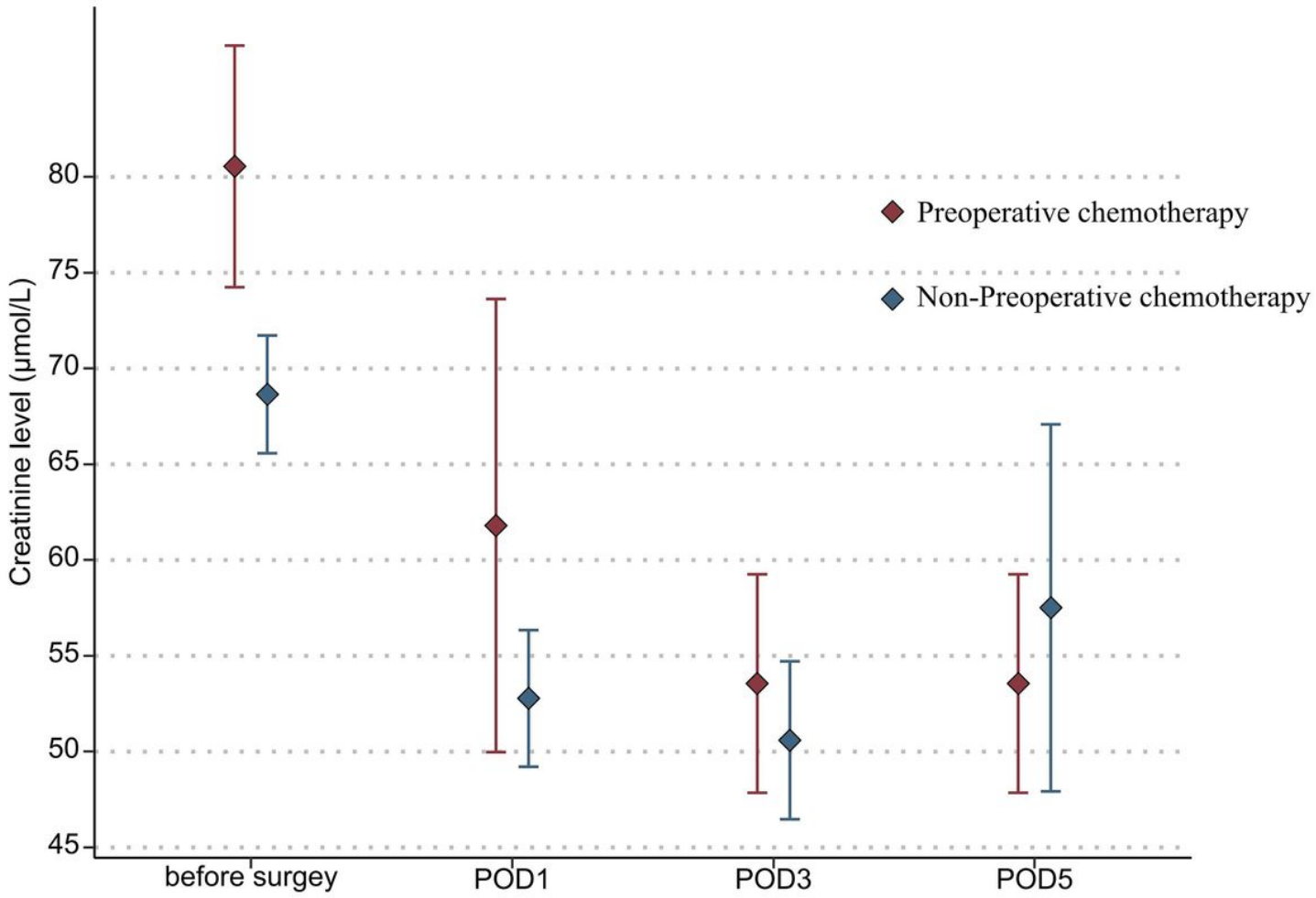

Figure 4

Changes in the creatinine level in NAC and Non-NAC groups on days 1, 3, and 5 after surgery. POD1,3,5 postoperative day1,3,5 There were no statistically significant differences between the two groups in terms of the creatinine level on PODs 1, 3, and 5

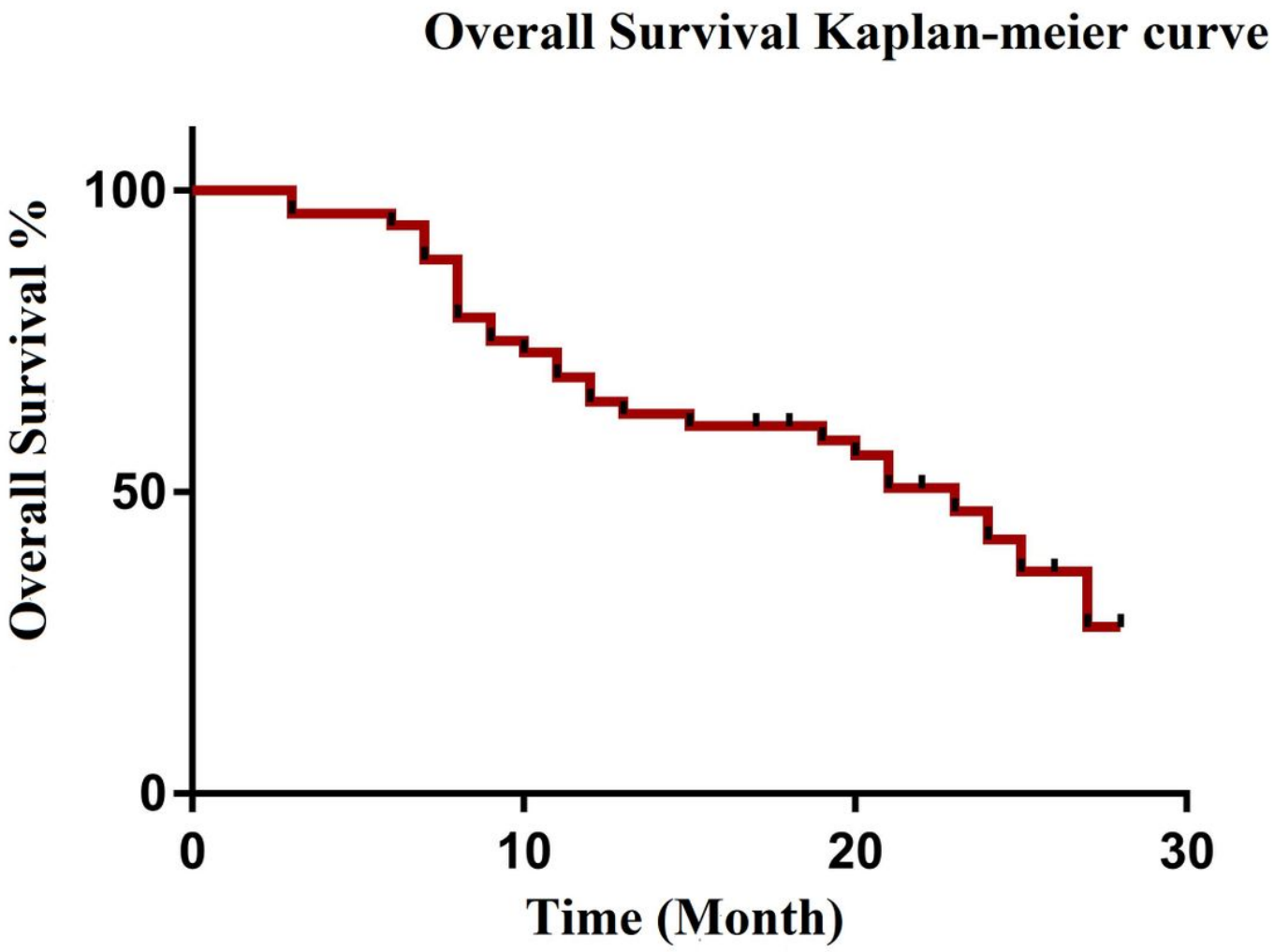

Figure 5

Overall survival rate of 52 patients underwent CRS+HIPEC after neoadjuvant Chemotherapy. The median survival for all patients was 24 months, and the estimated 1- and 2-year OS rates for the entire cohort were 65.0% and 42.1%, respectively.

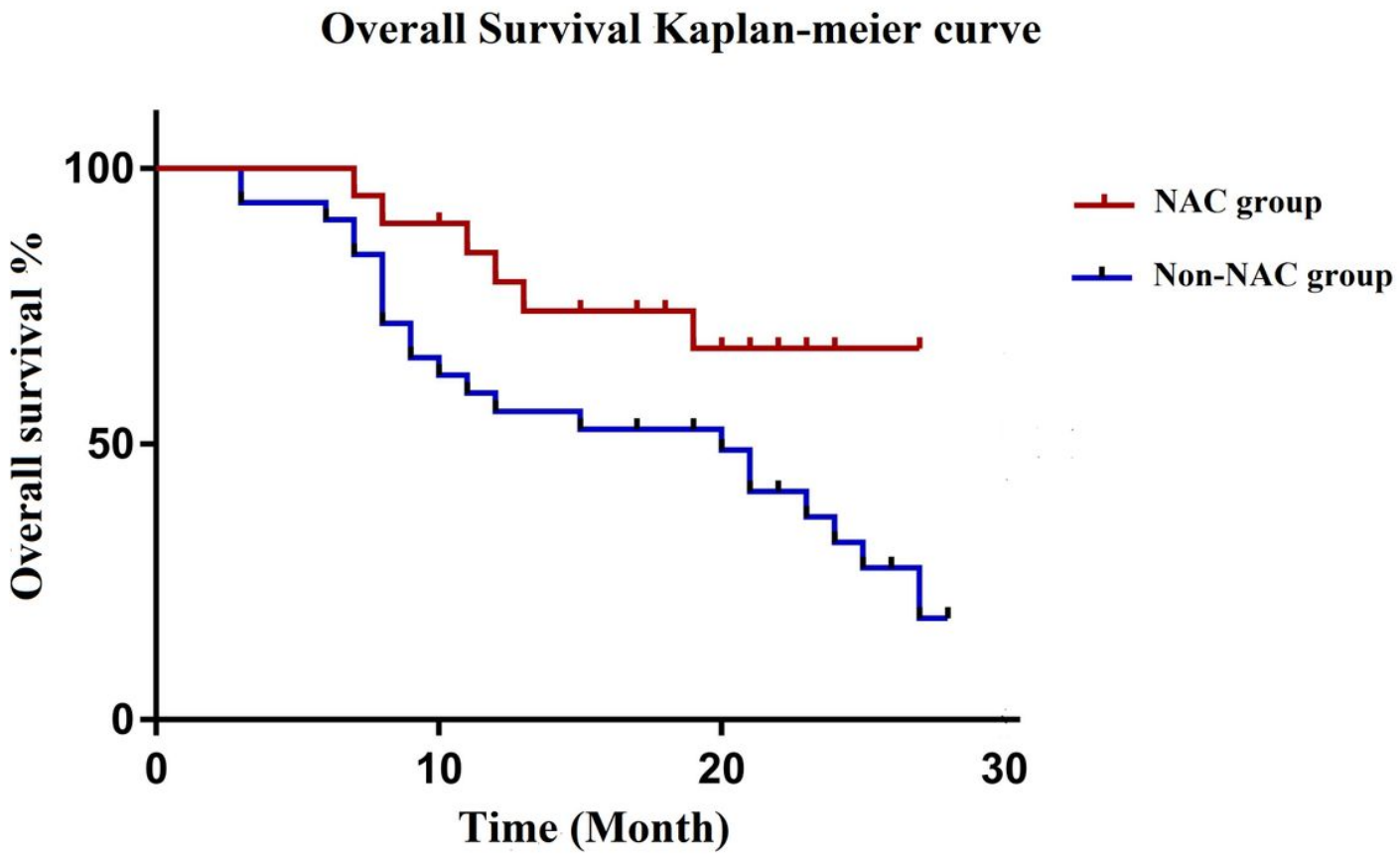

Figure 6

Overall survival curve in NAC and Non-NAC groups. Patients who received NAC prior to CRS + HIPEC experienced a longer 2-year OS (32.2% vs. 67.4%, p = 0.044) than those who underwent CRS+HIPEC without NAC.