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ORIGINAL SCIENTIFIC REPORT

Timing of Perioperative Chemotherapy Does Not Influence Long-Term Outcome of Patients Undergoing Combined Laparoscopic Colorectal and Liver Resection in Selected Upfront Resectable Synchronous Liver Metastases

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Abstract

Background The aim of this study was to compare patients undergoing combined colorectal and hepatic surgery with and without neoadjuvant chemotherapy to clarify the prognostic advantage of preoperative oncological treatment in a case-matched analysis using propensity scores and to identify factors predictive of good prognosis in a selected population of Synchronous ColoRectal Liver Metastases (SCRLM).

Methods A total of 73 patients who underwent upfront elective combined surgery without preoperative CT for SCRLM in two European tertiary referral centers were selected and constituted the study group (NoNACT group). The NoNACT group was matched (ratio 1:1) with patients who were operated after chemotherapy with neoadjuvant intent (NACT group, the control group). The matching was achieved based on six covariates representative of patients and disease characteristics.

Results While the characteristics of both colorectal and hepatic procedures were similar, the NoNACT group, as compared to the NACT group, had lower blood loss (200 mL vs. 550 mL). Postoperative stay (9 vs. 12 days) and morbidity rate (24.7% vs. 32.9%) were reduced in the NoNACT compared with the NACT group. Mid- and long-term outcomes were comparable. At multivariable analysis, predictors of long-term outcome were: right colonic neoplasms, RAS mutational status, CRS score $\geq$3 and the absence of perioperative chemotherapy.

Conclusion Preoperative neoadjuvant chemotherapy in patients with colorectal cancer and synchronous resectable liver metastases does not influence the risk of recurrence in patients with favorable tumor biology, while it was associated with increased intraoperative blood loss and morbidity. There is no strong evidence to recommend upfront chemotherapy in the absence of negative prognostic factors.

Introduction

The presence of synchronous liver metastases from colorectal cancer (SCRLM) represents a documented negative prognostic factor [1–4], being included in the Clinical Risk Score (CRS) score to stratify the risk of neoplastic relapse given the association with the risk of recurrence and consequent reduced expectancy of long-term survival [5].

In order to control the spread of the disease and to improve the oncological outcome, the use of systemic chemotherapy has been recommended for patients with SCRLM [3, 6, 7] in the setting of a multidisciplinary management involving surgeons and oncologists as main actors [8]. Despite this, while the need for preoperative conversion chemotherapy in unresectable disease is self-evident, the indication and timing of systemic treatments in resectable SCRLM are still a poorly investigated topic.

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The EORTC trial documented [9], in a randomized-controlled study including only patients with resectable liver disease (both synchronous and metachronous), an improved disease-free survival of patients receiving chemotherapy versus patients who did not, but left the dilemma regarding the optimal sequence for the administration of treatments still open. A comparative analysis from the Livermetsurvey [10] demonstrated no advantage of neoadjuvant treatments in synchronous disease, with the limits related to the registry nature (in particular heterogeneity of indications and treatments among centers).

Recently, the attention of the scientific community has been focused on safety and efficacy of combined versus staged resections of colorectal tumors and liver metastases, and a good level of evidence is now available to support the combined strategy (given its benefits in terms of reduced postoperative morbidity and shorter length of stay) in a wide proportion of candidates to surgery [11–15]. Furthermore, implementation into clinical practice of targeted molecules with a high profile of efficacy and safety [16, 17], together with a reduced biological impact of surgical therapies, thanks in particular to widespread adoption of minimally invasive approach [18–24], have changed the landscape of SCRLM, leading to an urgent need for reappraisal of the algorithm of treatment.

The primary endpoint of the present study is to compare the short- and long-term outcomes of patients undergoing combined hepatic and colorectal surgery for resectable SCRLM with and without the use of neoadjuvant chemotherapy after selection of groups according to propensity scores. The secondary endpoints were to analyze predictors of poor overall and disease-free survival in order to define a management algorithm and to investigate the potential role of minimally invasive techniques in this setting.

Methods

Study design

Data from prospectively collected bi-institutional databases (Hepatobiliary Surgery Division, San Raffaele Hospital, Milano—Italy and Department of Digestive Disease, Institut Mutualiste Montsouris, Paris—France), including 265 patients with SCRLM undergoing simultaneous colonic and hepatic resections between 2004 and 2017, were retrospectively analyzed for the purpose of this study. Patients with any of the following characteristics were excluded: candidates to staged resections (both colon-first and liver-first); unresectable liver disease at presentation; the presence of extrahepatic disease; patients with complicated colorectal cancer (bleeding, perforation or obstruction not amenable to endoscopic stenting); follow-up <12 months.

After the application of exclusion criteria, a group of 73 patients who were not treated with preoperative chemotherapy with neoadjuvant intent (NACT) was identified and constituted the study group (No NACT group). The NoNACT group was matched in a ratio of 1:1 with patients who underwent NACT for SCRLM (NACT group, constituting the control group). The matching was achieved based on propensity scores including the following six covariates: age, American Society of Anesthesiology (ASA) score, primary tumor location, CRS score [5], primary tumor staging and extent of hepatectomy.

Preoperative workup

The indication for timing and type of surgery and oncological treatment was systematically defined during disease tumor boards including liver and colorectal surgeons, radiologists and medical oncologists. Standard thoracoabdominal imaging (computed tomography and contrast enhanced magnetic resonance) was routinely performed in all candidates prior to surgery, as well as blood tests including serum concentrations of tumor markers (carcinoembryonic antigen, Ca 19.9). Selected patients also underwent positron emission tomography (PET), to rule out the presence of extrahepatic disease. Resectability of SCRLM was defined by expert hepatobiliary surgeons as the possibility to remove all liver disease by preserving an adequate volume of functional liver parenchyma, with adequate vascular inflow and outflow and maintaining the biliary drainage.

Patients with TRS score ≥ 2 were generally submitted to NACT. The repartition between NACT and No NACT was similar throughout the study period. Exceptions were the following:

- patients with contraindications to systemic treatment, patients who refused administration of chemotherapy before surgery, patients over 75 years of age were not treated with NACT
- patients referred to our centers after NACT (consequently, with NACT performed irrespectively of the TRS score).

Procedures

Surgical technique

A very similar surgical approach was adopted in both centers; under general anesthesia, the French position was adopted, with the first surgeon standing between the

patient's legs and having the first and the second assistant, respectively, on the left side and on the right side of the patient.

Intraoperative ultrasound was routinely performed to assess the liver anatomy and to confirm the resectability and relationship between the lesion and main hepatic structures. Liver transection was performed by an alternating use of the ultrasound dissector CUSA and bipolar forceps, exposing vascular structures which were selectively coagulated or sealed through clips or staplers, according to dimension.

The surgical specimen was placed in an impermeable retrieval bag and taken out, without fragmentation, through a Pfannenstiel incision. Pringle's maneuver was used as required to control intraoperative bleeding.

Variables

Data on preoperative patient and disease characteristics were collected, as well as on intraoperative and histopathological findings and on perioperative chemotherapy (meaning chemotherapy before [neoadjuvant] and/or after [adjuvant] surgery) were collected and analyzed. Clinical Risk Score (CRS) as defined by the Memorial Sloan Kettering Cancer Group was calculated for every patient, with one point assigned in the case of positivity of each factor of the following: synchronous presentation, CEA level >200 ng/mL, nodal positivity of primary tumor, >1 liver lesion, liver lesion with diameter >5 cm [5]. Patients were then dichotomized according to CRS into low-risk group (0–2) and high-risk group (3–5).

Ninety days morbidity was reviewed and assessed, and complications were classified according to the Dindo–Clavien classification [25]. Mortality was defined as any death during postoperative hospitalization or within 90 days after resection. Length of stay and interval time between surgery and adjuvant treatments were evaluated. Resections were considered R0 when the surgical margin was 1 mm or more. Data regarding follow-up, survival status and occurrence and type of recurrence were recorded. Three- and five-year overall survival (OS) and disease-free survival (DFS) were evaluated using the Kaplan–Meier method.

Statistical methods

After matching, all variables were compared using the χ^2 or Fisher's exact test for categorical data, the Mann–Whitney *U* test for non-normally distributed continuous data, and Student's *t* test for normally distributed continuous variables. All data are expressed as mean plus or minus the standard deviation or median and range. Survival curves were generated and compared using the Kaplan–Meier method. Univariable and multi-variable analyses were performed by the log rank test and the Cox proportional hazards. Cox regression was used to determine independent predictors of outcome, using recurrence-free and overall survival as the dependent variable and factors significant ($p < 0.05$) on univariate analysis as covariates. Multivariable analysis was optimized excluding factors significant at univariate analysis but already included in the CRS score. Significance was defined as $p < 0.05$. All analyses were performed using the statistical package SPSS 18.0 (SPSS, Chicago, IL, USA).

Results

Clinicopathological variables

Patients and disease characteristics are detailed in Table 1: As a result of propensity score matching, patients included in the NoNACT ($n = 73$) and in the NACT ($n = 73$) groups showed comparable age, sex, ASA score, comorbidities, characteristics of primary tumor (location within colon–rectum, staging, grading and nodal status) and liver metastases (number, dimension and distribution). Among patients with rectal cancer (35 and 34 in the No NACT and NACT groups, respectively), T2 stage patients were 21 and 18, T3 stage were 14 and 14, T4 stage were 0 and 2 in the No NACT and NACT groups, respectively. Low rectal lesions were detected in three patients in the No NACT and four in the NACT group. No patient in the No NACT group underwent preoperative radiation therapy, while three patients in the NACT group underwent short-course radiation therapy before surgery. In the NACT group, 38 patients (52%) had partial response to therapy, 33 (45.2%) had stable disease and 2 (2.7%) had progression during NACT (dimensional increase in the target lesion). Features of liver parenchyma were different between groups, as a result of a significantly higher incidence of chemotherapy-associated liver injury (CALI) in the NACT group. In particular, among 34 patients with CALI, 20 patients had signs of sinusoidal obstruction syndrome (with nine of them showing injury graded 2–3) and 14 patients had signs of steatohepatitis (with five of them showing injury graded 2–3). Median Clinical Risk score was the same between the groups, having 16.4% of patients in the NoNACT group and 19.2% in the NACT group with a CRS score ≥ 3.

Procedures

Operative characteristics are shown in Table 2. Major hepatectomies were performed in 16 (21.9%) and 15 patients (20.5%) in the NoNACT and NACT groups, respectively. Conversion to open surgery was required in

Table 1 Patients and disease characteristics

Variable	No NACT group (73)	NACT group (73)	*p*
Age, median (range)[a] (years)	60 (35–86)	62 (37–84)	0.934
Gender, *n* (%)			0.833
Male	41 (56.2)	39 (53.4)	
Female	32 (43.8)	34 (46.6)	
ASA Score, *n* (%)[a]			0.654
I	11 (15.1)	13 (17.8)	
II	47 (64.4)	51 (69.9)	
III	15 (20.5)	9 (12.3)	
CT regimen, *n* (%)			0.000
Oxaliplatin based	n.a	49 (67.1)	
Irinotecan based	n.a	24 (32.9)	
Associated biological therapy	n.a	31 (42.5)	
Associated comorbidities, *n* (%)	35 (47.9)	38 (52.1)	0.712
Features of non-tumorous parenchyma, *n* (%)			0.036
Normal	42 (57.5)	21 (28.8)	
steatosis	31 (42.5)	18 (24.7)	
CALI	0	34 (46.6)	
Primary tumor location, *n* (%)[a]			0.156
Right colon	17 (23.3)	19 (26)	
Left colon	21 (28.8)	20 (27.4)	
Rectum	35 (47.9)	34 (46.6)	
Staging, *n* (%)[a]			0.201
T1	3 (4.1)	4 (5.5)	
T2	32 (43.8)	25 (34.2)	
T3	32 (43.8)	34 (46.6)	
T4	6 (8.2)	10 (13.7)	
Grading, *n* (%)			0.378
G1	6 (8.2)	7 (9.6)	
G2	55 (75.3)	54 (74)	
G3	12 (16.4)	12 (16.4)	
Nodal status, *n* (%)			
N0	38 (52.1)	34 (46.6)	
N1	31 (42.5)	31 (42.5)	
N2	4 (5.5)	8 (11)	
Number of liver lesions, median (range)	2 (1–6)	2 (1–7)	0.189
Nodularity, *n* (%)			0.201
Monofocal	41 (56.2)	38 (52.1)	
Multifocal	32 (43.8)	35 (47.9)	
Lobe distribution of metastases, *n* (%)			0.098
Unilobar	45 (61.6)	39 (53.4)	
Bilobar	28 (38.4)	34 (46.6)	
Liver met diameter, median (range)	2.9 (0.9–11)	3.4 (1.2–12)	0.178
RAS mutation, *n* (%)	17 (23.3)	20 (27.4)	0.215
CRS score, median (range)[a]	3 (1–5)	3 (1–5)	0.389
CRS score >3, *n* (%)	12 (16.4)	14 (19.2)	0.318
CEA level, median (range)	78 (2–1190)	21.6 (3.1–498)	0.043

NACT neoadjuvant chemotherapy, *ASA* American Society of Anesthesiology, *CT* chemotherapy, *CRS* Clinical Risk Score, *CALI* chemotherapy-associated liver injury, *CEA* carcinoembryonic antigen

[a]Covariate used for propensity score matching

Table 2 Surgery characteristics according to treatment group

Variable	No NACT group (73)	NACT group (73)	*p*
Colorectal resection, *n* (%)			0.715
Right colectomy	17 (23.3)	19 (26.0)	
Left colectomy	23 (31.5)	21 (28.8)	
Anterior rectal resection	23 (31.5)	22 (30.1)	
Rectum–sigma resection	10 (13.7)	11 (15.1)	
Stoma, *n* (%)	13 (17.8)	15 (20.5)	0.155
Extent of liver resection, *n* (%)[a]			0.301
Major	16 (21.9)	15 (20.5)	
Minor	57 (78.1)	58 (79.5)	
Liver resection, *n* (%)			0.598
Right hepatectomy	4 (5.5)	6 (8.2)	
Left hepatectomy	12 (16.4)	9 (12.3)	
Left lateral sectionectomy	12 (16.4)	7 (9.6)	
Bisegmentectomy	3 (4.1)	7 (9.6)	
Segmentectomy	12 (16.4)	13 (17.8)	
Single nodulectomy	9 (12.3)	6 (8.2)	
Multiple nodulectomies	12 (16.4)	16 (21.9)	
Right posterior sectionectomy	6 (8.2)	5 (6.8)	
Right anterior sectionectomy	3 (4.1)	4 (5.5)	
Approach, *n* (%)			0.407
Open	4 (5.5)	3 (4.1)	
Laparoscopic	58 (79.5)	58 (79.5)	
Open + laparoscopic	11 (15.1)	12 (16.4)	
Conversion, *n* (%)[b]	4 (5.8)	7 (9.6)	0.048

n.a. not assessable

[a]Covariate used for propensity score matching

[b]Percentage is referred to the total number of cases operated by laparoscopic approach

four patients (5.8%) in the NoNACT and seven patients (9.6%) in the NACT group, being hemorrhage (two and five patients in the NoNACT and NACT group) and oncological concerns (two patients in each group) the most frequent reason for impossibility to proceed with the laparoscopic approach.

Short-term results

The median operative time was 290 min (range 170–540) in the TLA group and 330 min (range 150–540) in the control group ($p = 0.033$). In spite of comparable use and length of Pringle maneuver in NoNACT and NACT groups, a significantly higher intraoperative blood loss was recorded in the study (200 mL in median, range 100–1000) compared with the control group (550 mL in median, range 200–1300); and consequently a higher rate of intraoperative transfusions was required in the NACT versus NoNACT group (8.2% and 19.2%, respectively).

Table 3 Intra- and postoperative outcomes according to treatment group

Variable	No NACT group (73)	NACT group (73)	*p*
Operating time, median (range) (min)	290 (170–540)	330 (150–730)	0.033
Number of removed nodes, median (range)	22 (8–35)	26 (7–36)	0.076
Blood loss, median (range) (mL)	200 (100–1000)	550 (200–1300)	0.029
Pringle maneuver, *n* (%)	36 (49.3)	41 (56.2)	0.659
Length of Pringle maneuver, median (range) (min)	35 (10–60)	40 (15–85)	0.096
Intraoperative blood transfusion, *n* (%)	6 (8.2)	14 (19.2)	0.024
R1 colorectal resection, *n* (%)	3 (4.1)	2 (2.7)	0.076
R1 liver resection, *n* (%)	0	2 (2.7)	0.068
Depth of liver margin, median (range) (mm)	4 (0–12)	5 (0–11)	0.279
Time to first flatus, median (range) (days)	3 (2–6)	4 (2–7)	0.155
Morbidity, *n* (%)	18 (24.7)	24 (32.9)	0.043
Complications, *n* (%)			
Hemorrhage[a]	0	2 (8.3)	0.034
Liver failure[a]	1 (5.6)	3 (12.5)	0.045
Biliary fistula[a]	3 (16.7)	4 (16.7)	1
Abdominal abscess[a]	1 (5.6)	3 (12.5)	0.039
Fever[a]	4 (22.2)	6 (25)	0.099
Pneumonia[a]	0	2 (8.3)	0.033
Pleural effusion[a]	4 (22.2)	5 (20.8)	0.084
Arrhythmia[a]	0	4 (16.7)	0.032
Low urinary tract infection[a]	3 (16.7)	5 (20.8)	0.066
Colonic anastomosis leakage[a]	6 (33.3)	9 (37.5)	0.042
Morbidity according to grade, *n* (%)			
Minor (Dindo–Clavien I–II)	12 (16.4)	14 (19.2)	0.048
Major (Dindo–Clavien III–V)	6 (8.2)	10 (13.7)	0.027
Mortality, *n* (%)	0	0	1
Total transfusions, *n* (%)	12 (16.4)	18 (24.7)	0.035
Length of postoperative stay, median (range) (days)	9 (4–17)	12 (7–35)	0.026
Adjuvant chemotherapy, n (%)	63 (86.3)	32 (43.8)	0.018
Perioperative chemotherapy, n (%)	63 (86.3)	73 (100)	0.013
Interval surgery-adjuvant treatments, median (range) (days)	42 (35–53)	51 (41–69)	0.032

R1, positive resection margin

[a]Percentage is calculated dividing the number of patients with a specific complication by total number of patients with complications

Oncological adequacy of procedures was evaluated in terms of free margins (colon/rectum and liver), depth of margins on liver parenchyma and number of nodes retrieved for primary lesion. Details are reported in Table 3.

Postoperative morbidity was lower in the NoNACT versus NACT group (respectively, 24.7% and 32.9%, $p = 0.043$). The detailed analysis of complications documented a significantly higher proportion of patients with

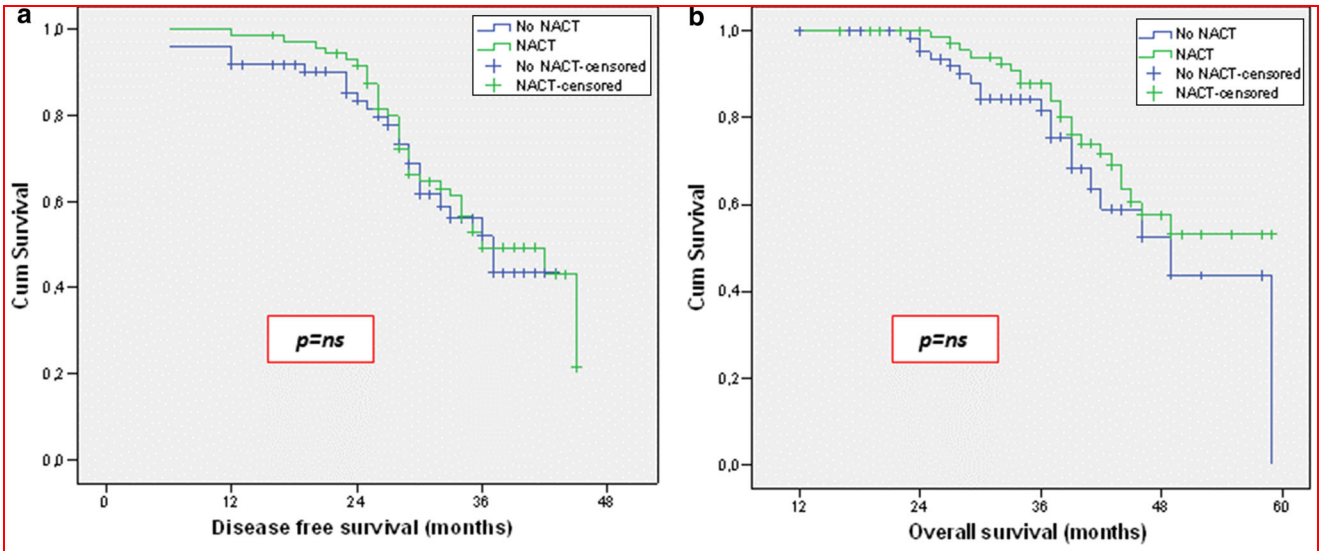

Fig. 1 **a** Disease-free survival stratified according to treatment group. **b** Overall survival stratified according to treatment group

hemorrhage, liver failure, infectious problems and colonic anastomosis leakage in the NACT compared with the NoNACT group.

Finally, both discharge and return to adjuvant treatments were faster in the NoNACT (9 and 42 days, respectively) compared with the NACT group (respectively, 12 and 51 days).

Long-term outcome and prognostic factor for survival

The whole series 1-year and 3-year survival was 98.6% and 56.8%, respectively, with no significant differences between the two groups (Fig. 1a); the recurrence-free survival at 1 year and 3 years was 93.9% and 35.7%, respectively, for the entire cohort (Fig. 1b). The overall recurrence rate in the NoNACT and NACT groups was 47.9% and 45.2%, respectively (p = ns), with a comparable pattern of recurrence. Details are reported in Table 4.

Factors potentially affecting disease-free and overall survival resection were evaluated in the whole series of patients (146 patients). On univariate analysis, 22 clinicopathological factors were analyzed and, among them, 14 resulted significantly associated with prognosis (as reported in Table 5). Multivariate analysis for factor resulting significant at univariate evaluation (nodal status of primary

Table 4 Long-term outcome according to treatment group

	No NACT group (73)	NACT group (73)	p
Overall survival (months) [Median (range)]	33 (12–60)	39 (12–60)	0.068
Death (n, %)	20 (27.4)	22 (30.1)	0.156
Cause of death (n, %)			0.659
Tumor progression	20 (27.4)	20 (27.4)	
Other	0	1 (1.4)	
Disease-free survival (months) [Median (range)]	29 (12–60)	32 (12–60)	0.198
Disease recurrence n (%)	35 (47.9)	33 (45.2)	0.078
Modality of recurrence, n (%)[a]			0.065
Intrahepatic	16 (45.7)	14 (40.0)	
Extrahepatic	6 (17.1)	7 (20)	
Extrahepatic + intrahepatic	14 (40)	12 (34.3)	
Therapy of recurrence, n (%)[a]			0.102
Re-resection	8 (22.9)	5 (14.3)	
Radiofrequency ablation	3 (8.6)	2 (5.7)	
Medical therapy	24 (68.6)	26 (74.3)	

[a]Percentages are calculated based on the number of patients who developed recurrence

Table 5 Uni- and multivariate analyses for factors affecting recurrence-free and overall survival in the whole series

Variable	Recurrence-free survival			Overall survival		
	Univariate, *p*	Multivariate, *p*	Risk ratio (95% confidence interval)	Univariate, *p*	Multivariate, *p*	Risk ratio (95% confidence interval)
Age >65 years	–	–		–	–	
Male sex	–	–		–	–	
BMI >25	–	–		–	–	
ASA Score 3–4	–	–		–	–	
Concurrent ablation	–	–		–	–	
Right colon primary cancer	0.029	0.042	2.38 (1.46–2.75)	0.035	0.046	2.41 (1.39–2.81)
Rectal primary cancer	0.035	–		–	–	
T3–T4 primary cancer	0.031	0.044	1.96 (1.55–3.01)	0.029	0.048	1.86 (1.43–2.78)
CEA level >200	0.028	–		0.031	–	
Positive nodal status of primary	0.045	–		0.039	–	
RAS mutation	0.033	0.039	2.12 (1.33–2.96)	0.026	0.037	2.22 (1.42–3.07)
n of SCRLM >4	0.036	–		0.041	–	
SCRLM >5 cm	0.021	–		0.037	–	
CRS score >3	0.017	0.029	2.57 (1.68–3.65)	0.022	0.032	2.75 (1.83–3.62)
Major liver resection	–	–		–	–	
Laparoscopic approach	–	–		–	–	
Intraoperative blood loss >700 mL	0.046	–		–	–	
Length of surgery >300 min	0.038	–		–	–	
Postoperative complications	0.05	–		–	–	
No neoadjuvant chemotherapy	–	–		–	–	
No adjuvant chemotherapy	0.040	–		0.046	–	
No perioperative chemotherapy	0.029	0.039	2.31 (1.39–3.21)	0.033	0.042	2.16 (1.40–3.06)

ASA American Society of Anesthesiology, *CRS* Clinical Risk Score, *CEA* carcinoembryonic antigen

tumor, number and size of liver lesions and CEA level were excluded since they contribute to CRS score) revealed that right colonic location of primary tumor, T stage of primary, RAS status, CRS ≥ 3 and the use of perioperative chemotherapy have a significant impact on prognosis.

Long-term outcome analysis of patients, stratified according to their CRS score (dichotomization between patients with CRS < 3 and patients with CRS ≥ 3), showed comparable disease-free survival between the NoNACT and NACT groups in patients with CRS < 3 (Fig. 2a), while it revealed a poorer prognosis ($p = 0.037$) in patients with CRS ≥ 3 who did not undergo a neoadjuvant program (Fig. 2b).

Discussion

Although the need for systemic treatment in the disease course of patients with SCRLM is strongly suggested to improve the long-term outcome by controlling the risk of recurrence [3, 6–10], the preoperative allocation of chemotherapy is not free from potential harms and increased complexity in the whole management.

Advocated benefits of systematic use of preoperative chemotherapy in the setting of resectable SCRLM are: (1) prevention of tumor progression within the liver and spread of extrahepatic micrometastases; (2) evaluation of tumor biology and potentially avoidance of "oncologically unnecessary" resections in patients with disease progression. If the administration of irinotecan- and oxaliplatin-based chemotherapy courses has dramatically changed the scenario of modern oncology, providing an effective instrument to enhance the benefits of 5-fluorouracil and positively affecting the outcome of patients, even side effects related to a severe hepatotoxicity of these agents are well known [26, 27]. Sinusoidal obstruction syndrome—related to oxaliplatin—and steatohepatitis—related to irinotecan—are the best known forms of chemotherapy-associated liver injury (CALI): In a recent systematic review by Zhao et al. [28], an increased rate of major complications and of liver-related complications, in particular, was reported in patients with CALI after liver surgery; and authors concluded that doubts about the real

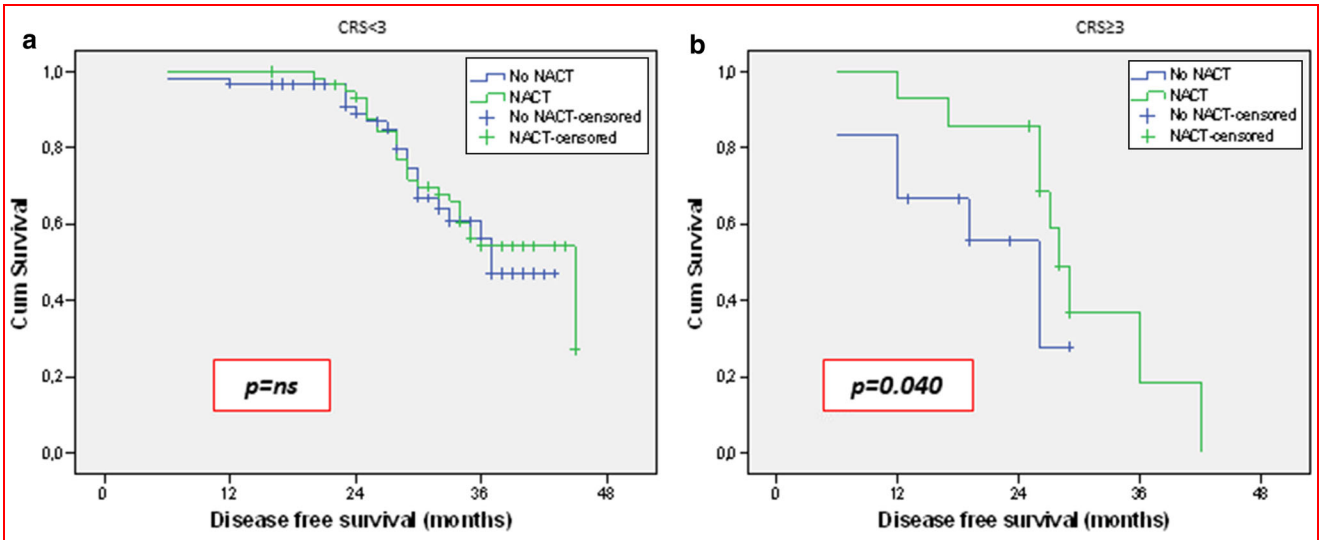

Fig. 2 **a** Disease-free survival stratified according to treatment group in patients with MSKCC score <3. **b** Disease-free survival stratified according to treatment group in patients with MSKCC score = or >3

usefulness of neoadjuvant chemotherapy in certain groups of patients might indicate the need for upfront resection. In the present study, only 28.8% of patients in the NACT group had normal liver parenchyma, while 46.6% of them had signs of CALI at final pathology: despite beyond study aims it is reasonable the hypothesis that this last proportion of patients in the control group constitutes the background for an increased risk of intraoperative bleeding (mean blood loss in the NACT was 550 mL vs. 200 mL in the NoNACT group, $p = 0.029$, in spite of a comparable complexity of both colonic and hepatic surgery) and for a higher incidence of postoperative complication (32.9% in the NACT vs. 24.7% in the NoNACT group). Interestingly, within a series with a high penetration of laparoscopic approach due to a strong commitment of the two institutions toward minimally invasive techniques, a higher rate of conversion was recorded in the group of patients preoperatively submitted to chemotherapy (9.6% vs. 5.8% in the NoNACT group). All these factors together might have contributed to determine a longer need for hospital stay in the control group and a consequent delay in the resumption of adjuvant treatments. On the contrary, the favorable biological context—influenced by a procedure completed by laparoscopy, a perioperative management leaded according to a fast-track program and the absence of complications—created in the NoNACT group has allowed an early return to oncological treatments. This assumption should be regarded as a mainstay in the modern treatment of patients with colorectal cancer and liver metastases since this situation is a newborn result of recent improvements in surgical, nursing and anaesthesiological care [29], while it is generally underestimated in the definition of management algorithms.

The hypothesis that these encouraging results are the consequence of the selection of patients included in the NoNACT group is overcome by the design of the study: In the absence of randomization indeed, control for self-selection can be addressed via propensity scores which proved to adjust for confounders in small datasets, where they clearly appear less biased, more robust and more precise than standard multivariable methods. Furthermore, despite the retrospective nature of the present study, the collection of data was prospectively and systematically made in institutional databases including all potentially significant variables, so that no data needed to be retrieved specifically for the purpose of this study.

Since many concerns regarding a presumptive higher risk of morbidity and of colonic anastomosis leakage in particular were raised when the first series of combined resections were published, the attention of the scientific literature has been focused on the definition of the optimal timing to perform hepatic and colonic surgery and on the need to stratify the perioperative risk of patients [10–14]: In the review by Yin et al. published in 2013 [15], simultaneous resection proved to be as efficient as a delayed procedure for long-term survival, being therefore considered an acceptable and safe option with carefully selected conditions (age <70, minor resections, colonic surgery). The growing trend of totally laparoscopic approach for SCRLM has somehow enhanced the attitude toward combined treatment, thanks to its encouraging results (shorter time required for functional recovery and consequent reduced surgery–chemotherapy interval) [10–15]. Despite

favorable outcomes, combined hepatic and colonic surgery (in particular when performed by laparoscopic approach) still has to be considered a complex and demanding procedure, due to intrinsic fragility of patients and technical challenges: This characteristic, together with the need for multidisciplinary management both from the oncological and surgical point of view, constitutes the rationale for a monocentric management of patients, in tertiary referral centers. Viganò et al., in a series of 106 patients with resectable SCRLM, found an advantage in both the short- and long-term outcomes for patients managed within hepatobiliary groups, with shorter preoperative chemotherapy, better disease control and fewer surgical procedures [7]. The need for a dedicated training and a specific expertise to perform laparoscopic combined procedures [23], without increasing the risk of intraoperative adverse events and maintaining an acceptable rate of conversion, should be regarded as a confirmation of this concept.

Data from the literature regarding the utility of neoadjuvant chemotherapy in synchronous resectable liver metastases are scarce, and studies regarding specifically its need in candidates to combined treatment are still lacking, to the best of our knowledge.

The EORTC trial documented, in a randomized-controlled study including only patients with resectable liver disease (both synchronous and metachronous), an improved disease-free survival of patients receiving perioperative chemotherapy with FOLFOX4 and surgery versus patients who received surgery alone [9]. The documented survival was observed in both adjuvant and neoadjuvant settings, so the dilemma regarding the optimal timing for administration of treatments remained unsolved [9]. The use of oncological treatments in patients with negative prognostic factors was further analyzed in patients from the Livermetsurvey including a large number of patients with heterogeneous disease spread, within varied surgical programs (combined surgery, colon-first or liver-first), in centers with different expertise and outside of a strong study design [10]. In the present series, the use of perioperative chemotherapy (either pre- or postoperative) provided a survival benefit compared with chemotherapy-free patients: Despite this, a clear prognostic advantage to strongly suggest a neoadjuvant or adjuvant approach was not demonstrated for patients with CRS < 3. On the contrary, when multiple negative prognostic factors (CRS ≥ 3) are present, an advantage in terms of disease-free and overall survival is provided by the use of neoadjuvant chemotherapy even in resectable patients. In resectable SCRLM eligible to combined approach, NACT should be therefore reserved to those patients presenting with two or more of the following characteristics: positivity of primary tumor nodes, CEA > 200 ng/mL, >1 liver lesion, >5 cm of liver lesion diameter. Anyway, there is a critical element to obtain the CRS value preoperatively calculated: Indeed, CT and MRI have a diagnostic accuracy for nodal involvement of the primary tumor between 70 and 75% according to different series. As a consequence—in patients with radiologically negative nodes—the inclusion among "favorable" characteristics should be reserved only to patients showing a single, <5 cm liver metastases with a CEA level <200: Using this criteria, the CRS score would be 2 at maximum if nodes are found positive at the final pathology. Furthermore, a negative prognostic impact of KRAS mutation could be speculated [30]. Due to the relatively limited number of patients with advanced disease qualifying for radiation therapy before surgery, no specific conclusion can be drawn in this subset of patients specifically. Anyway, in patients requiring preoperative radiation therapy for locally advanced rectal cancer, neoadjuvant systemic treatment when synchronous liver metastases are present is strongly recommended, in order to control and prevent liver disease progression during radiation therapy. Among limitations of the study, although propensity scores matching is a valid tool for strengthening statistical analysis, a risk of cumulating non-significant differences accounting for a poorer prognosis in the NACT group still exists due to the retrospective nature of the study and due to the absence of randomization in the allocation of patients in treatment arms. A prospective randomized comparative study would be methodologically preferable because it would go beyond patient selection biases and differences in inclusion criteria to NACT, therefore overcoming the present study bias.

Conclusion

Despite the presence of synchronous metastases from colorectal cancer representing a negative prognostic factor, in a selected population of patients with upfront resectable synchronous liver metastases, preoperative neoadjuvant chemotherapy does not influence the risk of recurrence, while it was associated with increased intraoperative blood loss and morbidity. There is no strong evidence to recommend upfront chemotherapy in the absence of negative prognostic factors.

Compliance with ethical standards

Conflict of interest The authors of this manuscript have no conflicts of interest to disclose and further disclose any commercial interest that they may have in the subject of study and the source of any financial or material support.

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