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ORIGINAL ARTICLE

Does Chemotherapy-Induced Liver Injury Impair Postoperative Outcomes After Laparoscopic Liver Resection for Colorectal Metastases?

Maud Neuberg[1] · Ioannis Triantafyllidis[1,2] · Marine Lefevre[3] · Mostefa Bennamoun[4] · Anthony Sarran[5] · Marc Beaussier[1] · Christophe Louvet[4] · Brice Gayet[1] · David Fuks[1]

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Abstract

Background Chemotherapy-associated liver injuries (CALI) have been associated with poor postoperative outcome after open liver resection. To date, no data concerning any correlation of CALI and laparoscopic liver resection (LLR) are available. In the present study, we evaluated the impact of CALI on short-term outcomes in patients undergoing LLR.

Materials and Methods All patients who underwent in our department LLR for colorectal liver metastases (CRLM) from 2000 to 2016 were retrospectively reviewed. Patients were divided in 4 groups according to their pathological histology. In group 1 patients had normal liver parenchyma. Group 2 included patients with steatosis and steatohepatitis. Patients with sinusoidal obstruction syndrome (SOS) and nodular regenerative hyperplasia (NRH) were allocated to group 3, whereas the remaining with fibrosis and cirrhosis, were assigned to group 4.

Results A total of 490 LLR for CRLM were included in the study. Perioperative details and morbidity did not differ significantly between the four groups. Subgroup analysis showed that NRH was associated with higher amount of blood loss ($p = 0.043$), overall ($p = 0.021$) and liver-specific morbidity ($p = 0.039$).

Conclusion NRH is a severe form of CALI that may worsen the short-term outcomes of patients undergoing LLR for CRLM. However, the remaining forms of CALI do not have a significant impact on perioperative outcomes after LLR.

Keywords Colorectal liver metastases · Laparoscopic liver resection · CALI · Chemotherapy · Postoperative outcomes

There has been no previous communication with any society or meeting with regard to this paper.

✉ David Fuks
david.fuks@imm.fr

[1] Department of Digestive Oncologic and Metabolic Surgery, Institut Mutualiste Montsouris, Université Paris Descartes, 42 boulevard Jourdan, 75014 Paris, France

[2] Department of General Surgery, General Hospital of Veria, Veria, Greece

[3] Department of Pathology, Institut Mutualiste Montsouris, 42 boulevard Jourdan, 75014 Paris, France

[4] Department of Oncology, Institut Mutualiste Montsouris, 42 boulevard Jourdan, 75014 Paris, France

[5] Department of Radiology, Institut Mutualiste Montsouris, 42 boulevard Jourdan, 75014 Paris, France

Abbreviations

CRLM	Colorectal liver metastases
LLR	Laparoscopic liver resection
RFA	Radiofrequency ablation
NRH	Nodular regenerative hyperplasia
SOS	Sinusoidal obstruction syndrome
OLR	Open liver resection

Introduction

Colorectal cancer liver metastases (CRLMs) occur in approximately 50% of patients with colorectal cancer and liver resection remains the only potentially curative treatment.[1–3] Advances in medical management, as well as in surgical techniques and implemented multimodal strategies resulted in a higher proportion of patients with CRLM amenable to liver resection. In this context, administration of neoadjuvant

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chemotherapy has proved to be efficient and effective, as a strategy not only to downsize and downstage liver metastases, but to treat occult disease foci, as well.[4, 5]

However, neoadjuvant treatment is known to cause chemotherapy-associated liver injuries (CALIs), ranging from steatosis to more severe liver damage, such as sinusoidal obstruction syndrome (SOS) or nodular regenerative hyperplasia (NRH).[6–9] CALI has been associated with impaired postoperative outcomes, including higher morbidity and mortality.[10, 11] The exact mechanism underlying the negative influences of CALI on postoperative outcomes are still unknown.

A growing body of evidence has highlighted the advantages and improved outcomes of laparoscopic liver resections (LLRs) in comparison to open liver resections (OLR), in terms of postoperative complications, analgesic requirement, recovery of physical activity, and length of hospital stay.[12–14] Although the impact of CALI has vastly been described after OLR, data regarding results after LLR are still lacking. In this context, we hypothesized that LLR could possibly counteract the possible detrimental effects of CALI. The present study sought to analyze the impact of CALI on various operative parameters and on postoperative outcomes of patients with CRLM treated by LLR.

Materials and Methods

Patients' Selection

From January 2000 to January 2016, all consecutive patients who underwent LLR for CRLM with curative intention (R0 or R1), at Institute Mutualiste Montsouris, Paris, France, were identified. Patients with incomplete data were excluded from this analysis. Data were retrospectively retrieved from a prospectively maintained database. Follow-up was updated in June 2019. The data included demographic variables, primary tumor characteristics and management, operative data, tumor pathology, and short-term outcomes. To further assess the influence of CALI on the intraoperative parameters and on the postoperative outcomes, the patients were divided into groups and compared according to the pathological evaluation of the resected specimens. This study was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki.

Preoperative Evaluation

Primary tumor data included pathology results, synchronous or metachronous onset of metastases and extrahepatic metastatic site. Levels of carcinoembryonic antigen (CEA) were assessed, as well, at initial diagnosis. The decision for administration of neoadjuvant chemotherapy, with or without targeted therapy, was taken by a multidisciplinary board that included surgeons, medical oncologists and radiologists. The overall surgical strategy aimed to complete tumor resection and disease control, by chemotherapy. In case of neoadjuvant treatment, patients were treated with 4 cycles of chemotherapy and the lesions were subsequently evaluated. If the lesion became surgically resectable or if no progression was noted, LLR was performed. If the lesion were not clearly resectable, 4 or 6 cycles of chemotherapy were added and the liver lesions were re-evaluated. Liver resection was performed at least 4 weeks after the last course of chemotherapy and at least 6 weeks after the last administration of bevacizumab. Preoperative percutaneous biopsy of the nontumorous parenchyma was performed on a case-by-case basis, unless it was contraindicated. When the background liver demonstrated severe fibrosis or cirrhosis, patients under consideration for extended resection underwent PVE when the volume of the FLR was ≤ 40%. Furthermore, steatosis or steatohepatitis and fibrosis induced by chemotherapy were determined either by liver biopsy or, alternatively, by MRI imaging.

Surgical Procedures

Operative procedures, including positioning of trocars, were as previously described.[15–17] Resectability of metastases was always assessed by intraoperative ultrasonography. The overall surgical policy was to attempt parenchymal-sparing hepatectomy whenever possible, while maintaining a margin of 1 mm from the tumor. Major hepatectomy was defined as resection of three or more liver segments. For all procedures, tissue dissection and hemostasis were performed using an ultrasonic dissector, such as the Thunderbeat (Olympus Co, Tokyo, Japan); bipolar forceps (MicroFrance CEV134, Medtronic, Minneapolis, MN) provided retraction and rescued hemostasis. When required, hepatectomy was associated with radiofrequency ablation. Operative time, total intraoperative blood loss, transfusion rate and conversion were evaluated.

Postoperative Outcomes and Definitions

Posthepatectomy morbidity and mortality were assessed within 90 days after surgery using Clavien-Dindo classification.[18] Major postoperative complications were defined as Clavien-Dindo ≥ III. Liver failure was defined according to the "50–50" criteria (prothrombin time < 50% and serum bilirubin > 50 μml/l) on postoperative day 5.[19] Ascites was defined as abdominal drainage output of > 10 ml/kg/day after postoperative day 3 and biliary leakage was defined as a bilirubin concentration in the drainage fluid of more than threefold that in serum. Postoperative bleeding was defined as a drop of hemoglobin level > 3 g/dl after the end of surgery compared to postoperative baseline level and/or any postoperative transfusion of packed red blood cell units for a falling hemoglobin and/or the need for invasive reintervention.

Patients were followed up regularly and subjected to surveillance protocols including thoracic and abdominal CT scan and liver MRI during the most recent years. Follow-up evaluation was performed every 3 to 4 months during the first 3 years, and every 6 months thereafter.

Study Design

After resection, the specimen was assessed by a rigorous pathologic examination. In addition to the pathological assessment of metastatic tumors, evaluation of surgical margins and nontumorous liver parenchyma were assessed. The histological features of the nontumorous parenchyma that were analyzed, included: steatosis, steatohepatitis, SOS, NRH, centrilobular vein and perisinusoidal fibrosis, and cirrhosis (Fig. 1). Steatosis and steatohepatitis were graded according to the system of Kleiner et al..[20] Severe steatosis was defined as more than 33% of parenchyma affected by steatosis.[20] Steatohepatitis was defined as the presence of steatosis associated with lobular inflammation and hepatocyte ballooning.[20] The SOS group included sinusoidal dilatation, congestion, nodular regenerative hyperplasia changes, and/or venous obstruction.[9, 21] Liver fibrosis was assessed according to the METAVIR classification (F1 to F4).[22]

To further assess the influence of CALI on the postoperative outcomes, the patients were divided into 4 groups according to the pathological findings as follows: normal liver parenchyma (with or without neoadjuvant chemotherapy) (group 1), severe steatosis and/or steatohepatitis (Group 2), SOS (including NRH) (group 3), and fibrosis (including F1 to F4 cirrhosis) (group 4).

Statistical Analysis

Baseline characteristics of the studied population, intraoperative details and pathological characteristics, as well as postoperative outcomes were analyzed. Categorical variables were compared using the χ^2 test or Fischer's exact test when appropriate, and any differences identified, were compared using ANOVA. All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL), and statistical significance was set at 0.05.

Results

Studied Population

During the study period, 780 patients underwent LLR. Among them, 520 (66.7%) patients underwent LLR for CRLM with curative intention, with or without neoadjuvant chemotherapy. Thirty (3.8%) patients without any pathological histology report of the nontumorous parenchyma liver were excluded. Four hundred ninety patients with detailed data regarding histological features were finally included in the analysis. There were 317 (64.7%) men and 173 women with a median age of 64 (range 24–89) years. Demographic and tumor's characteristics are detailed in Table 1. CRLM were synchronous in 350 (71.4%) patients. Three hundred eight (62.9%) patients received neoadjuvant chemotherapy, based on oxaliplatin in 78.9% ($n = 243$) of cases and on irinotecan in the remaining 21.1% ($n = 65$) cases. Chemotherapy was associated with targeted therapy in 129 (42%) of patients—bevazicumab in 71% ($n = 92$) and cetuximab in 29% ($n = 37$). Prevalence of neoadjuvant chemotherapy according to group is detailed in Table 1. The percentage of patients treated with neoadjuvant chemotherapy was significantly higher in group 3 ($p = 0.002$). Furthermore, the prevalence of oxaliplatin-based regimens was significant higher in Groups 3 and 4 in comparison to Group 2 ($p = 0.047$), whereas the respective value for irinotecan-based regimens was significant higher in group 2.

Pathological examinations revealed that 275 (56.1%) patients had normal liver parenchyma (group 1), 126 (25.7%)

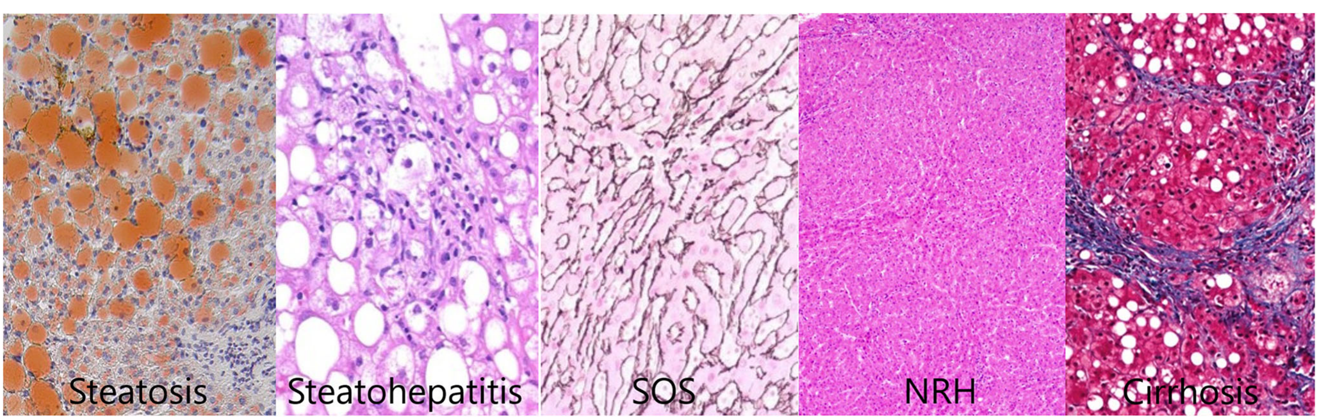

Fig. 1 Histological features of the nontumorous parenchyma. Hematoxylin and eosin counterstain of the nontumorous parenchyma revealing: steatosis, steatohepatitis, SOS, NRH, and cirrhosis

Table 1 Baseline characteristics of the patients and the tumors

	Group 1 $N = 275$	Group 2 $N = 126$	Group 3 $N = 67$	Group 4 $N = 22$	*p* value
Male gender	166 (60.4%)	91 (72.2%)	44 (65.7%)	16 (77.7%)	0.110
Median age (years) (range)	64 (25–85)	64 (26–89)	63 (31–85)	65 (3–88)	0.988
Median BMI (kg/m^2) (range)	24.7 (16.9–41.2)	26.8 (16.4–41.8)	24.5 (15.9–33.6)	24.8 (18.4–31.2)	0.955
ASA score > II	31 (11.3%)	15 (11.9%)	9 (13.4%)	1 (4.5%)	0.650
Diabetes mellitus	14 (5.1%)	16 (12.7%)	6 (9%)	3 (13.6%)	0.046
CAD	13 (4.7%)	8 (6.3%)	4 (6%)	2 (9.1%)	0.786
COPD	19 (6.9%)	8 (6.4%)	4 (6%)	0	0.646
Alcohol consumption	57 (20.7%)	15 (11.9%)	21 (31.3%)	3 (13.6%)	0.010
Hypertension	68 (24.7%)	43 (34.1%)	22 (32.8%)	3 (13.6%)	0.08
Dyslipidemia	54 (19.6%)	30 (23.8%)	12 (17.9%)	5 (22.7%)	0.728
Tobacco use	50 (18.2%)	19 (15.1%)	10 (14.9%)	4 (18.2%)	0.843
Hepatitis status (B or C)	12 (4.4%)	7 (5.6%)	4 (9.1%)	3 (13.6%)	0.089
Synchronous liver metastasis	207 (75.3%)	81 (64.3%)	46 (68.7%)	16 (72.7%)	0.126
Neoadjuvant chemotherapy	156 (56.7%)	81 (64.3%%)	57 (85%)	14 (63.6%)	0.002
Oxaliplatin-based	144 (92.3%)	32 (39.5%)	54 (94.7%)	13 (92.9%)	0.047
Irrinotecan-based	12 (7.7%)	49 (60.5%)	3 (5.3%)	1(7.1%)	0.019
Bevazicumab	38 (24.4%)	27 (33.3%)	21 (36.8%)	6 (42.9%)	0.067
Cetuximab	10 (6.4%)	12 (14.8%)	12 (21.1%)	3 (21.4%)	0.132
Number of chemo cycles, median, (range)	4 (4–10)	8 (4–10)	8 (4–10)	8 (4–10)	0.541
Number of the lesions (range)	2.4 (1–15)	1.9 (1–9)	2.6 (1–11)	2.9 (1–12)	0.624
Diameter of the largest lesion (mm)	29.8 (3–75)	20.5 (4–42)	38.3 (2–61)	27.5 (4–81)	0.742
CEA (range)	53.6 (0.5–1626)	51.7 (0.8–2095)	36.6 (1–1274)	15.6 (0.3–87.3	0.829

CAD: coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CEA* carcinoembryonic antigen

patients had steatosis or steatohepatitis (group 2), 67 (13.7%) patients had moderate to severe sinusoidal injury (group 3), and 22 (4.5%) patients had liver fibrosis (group 4). In group 1, 119 (43.3%) patients did not receive any chemotherapy. Group 2 included 99 (78.6%) patients with severe steatosis and 27 patients (21.4%) with non-alcoholic steatohepatitis. Group 3 included cases of SOS ($n = 56$) and NRH ($n = 11$). Group 4 included 12 patients with fibrosis (F1 to F3) and 4 patients with cirrhosis (F4).

All groups were comparable regarding baseline patients' characteristics except the incidence of diabetes mellitus that was more frequent in group 4 ($p = 0.046$) and alcohol consumption that was more frequent in group 3 ($p = 0.01$). CRLM were synchronous in 372 (75.9%) patients. One hundred seventy-nine (36.5%) underwent repeat hepatectomy.

Intraoperative Parameters

Intraoperative data are depicted in Table 2. Mean operative time of all procedures was 236 (range 20–720) minutes whereas median estimated blood loss was 292 mL (range 0–3600). Operative time, estimated blood loss and blood transfusion rate were similar, irrespectively if patients neoadjuvant chemotherapy (Table 3).

There were 275 (56.1%) major hepatectomies without any difference among the four groups ($p = 0.847$). Thirty-three (6.7%) patients received intraoperative blood transfusion and this rate was distributed among groups as follows: 6.2%, 6.4%, 7.5%, 13.6% for groups 1, 2, 3, and 4, respectively ($p = 0.497$). Blood loss did not differ among studied groups ($p = 0.210$), although it increased up to 363 ml in group 3.

In group 3, NRH patients had longer operative time (352 vs. 215 min, $p = 0.069$), higher amount of blood loss (495 vs. 270 mL $P = 0.043$), and higher transfusion rate (1.8% vs 36.4%, $p = 0.048$) compared to patients with SOS.

Short-Term Outcomes

Overall, the 90-day postoperative mortality rate was 0.4% ($n = 2$). The postoperative short-term outcomes did not vary significantly between groups, irrespectively of the administration or not of neoadjuvant chemotherapy (Table 3). The overall morbidity rate was 40.4% ($n = 198$) and did not differ among studied groups ($p = 0.405$) although it increased up to 63.6% in group 4 (Table 4).

Table 2 Intraoperative details

	Group 1 N = 275 n (%)	Group 2 N = 126 n (%)	Group 3 N = 67 n (%)	Group 4 N = 22 n (%)	p value
Major hepatectomy	169 (61.5%)	67 (53.2%)	28 (41.8%)	11 (50%)	0.847
Conversion rate	12 (4.4%)	5 (4%)	1 (1.5%)	2 (9.1%)	0.756
Pringle maneuver	45 (16.4%)	14 (11.1%)	17(25.4%)	5 (22.7%)	0.069
Abdominal drainage	55 (20%)	29(23%)	16 (23.9%)	7 (31.8%)	0.553
Operative time (min)	218 (20–720)	226 (25–515)	238 (60–540)	279 (80–540)	0.074
Estimated blood loss (ml)	258 (0–2900)	314 (0–3600)	363 (0–3000)	358 (0–2000)	0.210
Intraoperative transfusion	17 (6.2%)	8 (6.4%)	4 (6.0%)	3 (13.6%)	0.497

Liver-related complications, as well as general morbidity were comparable among the four groups although bile leakage rates almost tripled (3.3% vs. 9.1%, $p = 0.489$) when comparing patients with normal liver parenchyma to those in group 4. Median length of stay did not differ significantly among studied groups ($p = 0.627$) but increased up to 7 and 9 days in Groups 3 and 4, respectively.

In group 3, subgroup of patients with NRH experienced increased overall postoperative morbidity (90.9% vs. 26.8%, $p = 0.021$) and liver-specific morbidity (81.8% vs. 3.6%, $p = 0.001$) compared to subgroup of patients with SOS (Table 5).

Discussion

Surgical treatment remains the only curative option for CRLM, but advances in oncological management with contemporary chemotherapeutic agents in a multimodal context have increased the proportion of patients amenable to CRLM resection.[1, 23]

Despite, traditionally being administered postoperatively, currently, systemic chemotherapy is increasingly used in a neoadjuvant setting[4, 24] with the intention to convert initially unresectable disease to resectable and increase the R0 rates. Furthermore, preoperative administration of chemotherapy is used to identify patients that may not benefit from a liver resection such as those with disease progression, as well as the responders so that postoperative chemotherapy may be tailored according to preoperative response.[5, 25]

However, multiple studies indicate a clear association between chemotherapy and incidence of steatosis, steatohepatitis, and sinusoidal injury.[9, 25] CALI is often observed in patients with CRLM and depends on the administered regimen. It is well known that oxaliplatin-based regimens are related to SOS and in its advanced form which is NRH.[26, 27] Furthermore, irinotecan treatment is associated to the development of steatohepatitis.[10, 28] However, co-administration of bevacizumab with oxaliplatin decreases the incidence and ameliorates the severity of SOS.[26, 27] The effect of these histopathologic changes of the liver on perioperative outcome after hepatectomy remains controversial. Several studies concluded to a negative impact of CALI on morbidity and mortality,[10, 11] whereas others reported no effect on outcomes[29–33] after liver resection. It is noteworthy that no study, till nowadays, deals with the impact of CALI on LLR.

To the best of our knowledge, the present study represents the first series analyzing the impact of CALI on perioperative outcomes of patients undergoing LLR for CRLM. This single

Table 3 Effect of neoadjuvant chemotherapy on intraoperative and postoperative outcome

	Neoadjuvant chemotherapy group (n = 308)	No neoadjuvant chemotherapy (n = 182)	p value
Surgical procedure			
Operative time (min)	211 (20–678)	276 (34–720)	0.675
Estimated blood loss (ml)	295 (0–2500)	212 (0–3600)	0.853
Transfusion rate	24 (7.8%)	9 (4.9%)	0.098
Morbidity	120 (38.9%)	78 (42.8%)	0.876
Liver-related complications	101 (32.7%)	44 (24.2%)	0.649
Major complications	5 (1.6%)	1 (0.5%)	0.452
Mortality	2 (0.6%)	0	0.923
Reoperation	17 (5.5%)	2 (1.1%)	0.097

Table 4 Short-term outcomes

	Group 1 $N = 275$	Group 2 $N = 126$	Group 3 $N = 67$	Group 4 $N = 22$	p value
Mortality	1 (0.4%)	1 (0.8%)	0	0	0.844
Overall morbidity	106 (38.6%)	52 (41.3%)	26 (38.8%)	14 (63.6%)	0.405
Major morbidity	4 (1.5%)	1 (0.8%)	3 (4.5%)	1 (4.5%)	0.424
Hemorrhage	1 (0.4%)	0	0	1 (4.5%)	0.492
Biliary leakage	9 (3.3%)	7 (5.6%)	3 (4.5%)	2 (9.1%)	0.489
Liver Failure	9 (3.3%)	9 (7.2%)	3 (4.5%)	0	0.202
Ascites	18 (6.6%)	7 (5.6%)	5 (7.5%)	4 (18.2%)	0.189
Intraabdominal collection	34 (12.4%)	20 (15.9%)	10 (14.9%)	4 (18.2%)	0.706
Respiratory complications	12 (4.4%)	6 (4.8%)	4 (7.1%)	3 (13.6%)	0.289
Neurological complications	1 (0.4%)	1 (0.8%)	1 (1.5%)	0	0.721
Renal Failure	1 (0.4%)	3 (2.4%)	1 (1.5%)	0	0.277
Reoperation for complications	12 (4.4%)	5 (4%)	2 (3%)	0	0.751
Length of hospital stay	4 (1–12)	5(1–10)	7 (3–19)	9 (5–17)	0.627

institution-study represents a large and comprehensive series over a long period of time, and it shows that CALI, according to the histopathological changes of the liver parenchyma, do not impact intraoperative and postoperative outcomes with the exception of NRH cases, when compared to the respective SOS cases in group 3.

Fernandez et al. proposed a correlation between neoadjuvant administration of irrinotecan and steatohepatitis.[34] Traditionally, steatosis and steatohepatitis have been associated with obesity and diabetes mellitus.[35, 36] However, in the present study, the risk of steatosis and steatohepatitis was not related to BMI ($p = 0.0955$), but it was significantly pronounced in diabetic patients ($p = 0.046$).

Table 5 Subgroup analysis of group 3

	SOS $N = 56$ n (%)	NRH $N = 11$ n (%)	p value
Operative data			
Operative time (min)	235	352	0.069
Estimated blood loss (ml)	270	495	0.043
Abdominal drainage	9 (16.1%)	9 (81.8%)	0.038
Pringle maneuver	10 (17.9%)	7 (63.6%)	0.026
Transfusion	0	4 (36.4%)	0.048
Liver-specific morbidity	2 (3.6%)	9 (81.8%)	0.001
Biliary leakage	0	3 (27.2%)	0.017
Ascites-liver failure	2 (3.6%)	8 (72.7%)	0.036
Overall morbidity	16 (28.6%)	10 (90.9%)	0.021
Major morbidity	0	3 (27.3%)	0.621
Reoperation for complications	0	1 (9.1%)	0.845
Median length of hospital stay	7	11	0.078

Whether steatosis and steatohepatitis result in adverse postoperative outcomes has not previously been adequately addressed. In various studies, mitochondrial structural defects in hepatocytes, diminished liver regeneration through alterations of the nuclear factor kappa B (NF-κB) pathway, and humoral and cellular immune responses to enhanced oxidative stress, resulting in an increased overall postoperative mortality and morbidity, especially liver-related, were found in patients with steatohepatitis, but not with steatosis.[37–39] However, severe steatosis significantly affected perioperative outcomes according to several previous studies.[40, 41]

In the present series, severe steatosis and steatohepatitis did not significantly influence morbidity (38.8%, $p = 0.405$) and mortality rates (0%, $p = 0.844$) after LLR. Noteworthy, we did not found a remarkable association between steatohepatitis and the risk of perioperative liver failure (7.2%, $p = 0.202$). In contrast, Vauthey et al.[10] reported that patients with irinotecan-associated steatohepatitis were at an increased risk of both liver failure and postoperative death. Furthermore, there is increasing evidence that LLR is associated with decreased oxidative stress and systemic inflammation and improved short-term outcomes in comparison to open liver resection for the management of CRLM.[14] This beneficial effect of LLR may counteract the diminished response of the hepatocytes to oxidative stress caused by severe steatosis and steatohepatitis and thus, resulting in fewer complications, especially liver-related ones, when performing LLR for CRLM.

Rubbia Brandt et al. showed an increased incidence of sinusoidal dilatation, perisinusoidal and occlusive fibrosis (48%) and NRH in 16% of patients receiving neoadjuvant chemotherapy based mainly on oxaliplatin.[9] The most severe form of CALI is NRH, and describes a proliferative process in which regenerative nodules replace the liver parenchyma which consequently becomes congested and exhibits sinusoidal dilatation. NRH is of interest to the HPB surgeon performing LLR as it is associated with the presence of portal hypertension, and consequently may adversely affect the outcome.[42] The pathophysiology of this condition was delineated by DeLeve et al. who identified its origin from the hepatic sinusoid and suggested that it represents a chronic ischemic injury secondary to disturbance to the blood flow within the liver.[9, 42] They described the characteristic histological features of SOS namely: sinusoidal congestion and dilatation; disruption of the sinusoidal membrane; and collagen deposition within the perisinusoidal space. All these lesions lead to a blue appearance of the liver, and the alternative name for the condition namely "blue liver syndrome".[9]

A correlation between sinusoidal injury and postoperative morbidity and mortality has been reported.[11, 31, 43] Mechanisms underlying the negative impact of liver veno-occlusive disease on major morbidity are unknown. However, impairment of liver regeneration, dysfunction of Kupffer cells, congestion and fragility of the hepatic parenchyma, increased bleeding and hepatocellular necrosis, can all be reasons for increased morbidity in cases of SOS .[42–44] Clinical importance of SOS is reflected in the development of hepatomegaly, ascites, splenomegaly, thrombocytopenia, portal hypertension, and elevation of liver enzymes.[45, 46] Severe SOS with regard to liver surgery has been associated with postoperative liver failure and longer hospital stay, as well as impairment of postoperative liver regeneration.[11, 43] However, several studies did not confirm this negative impact of SOS.[31, 32, 34, 47]

In the present study, presence of SOS did not significantly influence short-term overall morbidity ($p = 0.405$), or major morbidity ($p = 0.424$) after LLR for CRLM and the mortality was zero. The operative time, the estimated blood loss as well as the transfusion rates increased along with the stepwise increase of the severity of the liver injury, although without statistical difference ($p = 0.074$, $p = 0.210$, $p = 0.497$, respectively). In fact, none of the patients with SOS had major hemorrhage and this was the reason for a decreased implementation of Pringle's maneuver in the present series, without difference among studied groups ($p = 0.069$). The association of reduced blood loss and reduced liver ischemia, both well-known causes of postoperative morbidity after liver resections,[48] may explain the low morbidity rate in our series. It is important to mention that and the rate of major LLR did not differ ($p = 0.847$) among studied groups, as this could have favored a specific group in terms of blood loss and thus bias the results.

Most studies focus on the impact of simple isolated SOS lesions on perioperative outcome but special attention should be paid on NRH, especially taking into account that the incidence of NRH following chemotherapy for CRLM and analysis of its effect on outcome are scarce. NRH is considered to be the end-stage of a chronic ischemic injury associated to oxaliplatin-based chemotherapy and is associated with the presence of portal hypertension that can significantly compromise liver function and increase postoperative morbidity. Taking into account this clinical impact of NRH on outcome, we performed a subgroup analysis of group 3 which confirmed that NRH increased the postoperative morbidity compared to SOS patients. Liver failure increased from 3.6% in patients without NRH to 72.7% in patients with NRH ($p = 0.036$). Estimated blood loss and implementation of Pringle's maneuver significantly increased in patients with NRH ($p = 0.043$ and $p = 0.026$, respectively). According to the present data, NRH, and not sinusoidal dilatation, is the true determinant of short-term outcomes in patients undergoing LLR after chemotherapy. The impact of NRH on postoperative outcomes underlines the importance of diagnosing it preoperatively. Theoretically, the presence of pneumoperitoneum is helpful to decrease blood loss during laparoscopic hepatectomy and venous oozing.[49, 50] During parenchymal transection, the rate of intravenous fluid administration is decreased and the central venous pressure is maintained ≤ 5 cm H_2O to facilitate the hemostatic effect of the pneumoperitoneum on the transection surface.[51] Apart from pneumoperitoneum which is likely to reduce bleeding from the hepatic veins, placement of the patient in the reverse Trendelenburg position should help decrease the venous pressure and improve exposure by gravitationally shifting visceral structures away from the liver hilum, in cases deemed to be difficult at the preoperative assessment.

The present study has several limitations. This is a single-center, retrospective study covering a long-time period during which the surgical techniques, cross-sectional imaging and instrumentation have evolved tremendously. Furthermore, it may implicate time lead bias, especially regarding management approaches. Obviously, the retrospective nature of the study constitutes an inherent selection bias and along with the small patient population size of group 4 ($n = 22$) and the inclusion of just 11 cases of NRH in group 3, weaken the statistical power of our results. The clinical impact of fibrosis on outcome is uncertain as numbers of patients reported in the literature are currently too small to try and subanalyze according to grade of NRH nor in relation to duration or dose of administered chemotherapy regimens. However, one should take into consideration that perisinusoidal fibrosis and NRH changes might be difficult to detect without the use of special stains such as trichrome and reticulin, which are not routinely performed on liver specimens harvesting CRLM.[52] A further point that is not clear is whether the SOS and especially NRH are rare, dose-dependent or ubiquitous complications of neoadjuvant chemotherapy. Notwithstanding, the data presented in the current study suggest that LLR in patients with CALI can be performed safely, coinciding with recently presented data from the EORTC.[53]

In conclusion, neoadjuvant chemotherapy for CRLM may induce specific histopathologic changes in the liver parenchyma. Nevertheless, in this series, CALI was not associated with an increased risk of perioperative morbidity or mortality after LLR for the management of CRLM in comparison to patients with normal liver parenchyma, with the exception of patients with NRH. However, despite these promising results, the benefit of laparoscopic approach—regarding amelioration of any detrimental effects of CALI—needs to be further assessed, in order to establish an optimal strategy for preventing or minimizing the adverse effects of a hepatectomy, among patients receiving neoadjuvant chemotherapy.

Compliance with ethical standards

Disclosures The authors declare that they have no conflicts of interest.

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