Blood transfusions and steatohepatitis are independent risk factors for complications following liver resection for colorectal cancer liver metastases

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Abstract. The aim of the present study was to evaluate the risk factors for postoperative complications following liver resection for colorectal cancer liver metastases. Patients who underwent hepatic resection for colorectal cancer liver metastases were stratified according to chemotherapy administration and body mass index (BMI) to eliminate potential confounding factors. A univariate analysis was conducted to identify potential risk factors for postoperative complications following liver resection. Variables that exhibited a potential association were evaluated by multivariable logistic regression analysis to identify those independently associated with postoperative morbidity. Between January 2012 and March 2012, 100 patients underwent hepatic resection for liver metastases from colorectal carcinoma at the Treviso Regional Hospital (Treviso, Italy) and at the Regina Elena National Cancer Institute (Rome, Italy). Of the 100 patients, 61 received preoperative oxaliplatin- or irinotecan-based chemotherapy. A total of 25 the patients had a BMI of ≥28 kg/m^2. On univariate analysis, BMI ≥28 kg/m^2 was found to be positively correlated with the presence of steatosis ($P<0.01$) and steatohepatitis ($P<0.01$). The administration of preoperative chemotherapy was correlated with the development of steatosis ($P<0.01$), steatohepatitis ($P=0.02$) and postoperative complications ($P=0.03$). Even following stratification for the use of preoperative chemotherapy, BMI ≥28 kg/m^2 maintained its positive association with steatohepatitis. On multivariate analysis, steatohepatitis (P=0.005, HR=0.118, 95% CI: 0.027-0.518) and blood transfusions (P=0.001, HR=0.131, 95% CI: 0.038-0.452) were independently associated with postoperative complications. BMI ≥28 kg/m^2 (P=0.004, HR=8.30, 95% CI: 2.39-28.7) and irinotecan treatment (P=0.016, HR=0.16, 95% CI: 0.037-0.711) were independent risk factors for steatohepatitis. In conclusion, steatohepatitis and perioperative blood transfusions were found to be the main determinant of postoperative complications following liver resection for colorectal liver metastases. Overweight patients may be more prone to the cytotoxic effects of irinotecan, harboring a higher risk of developing steatohepatitis.

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Introduction

The combined use of chemotherapy (CHT) and surgical resection for colorectal cancer liver metastases (CRLM) has been associated with a 5-year survival rate >50% following complete resection (1-3). Multidrug CHT regimens based on the use of irinotecan or oxaliplatin are increasingly being used in the preoperative setting, with the objective of achieving resectability in patients with unresectable disease, or as a neoadjuvant treatment for patients with resectable lesions (4,5). However, concerns have been raised due to the association of preoperative CHT with potentially harmful pathological changes in the remaining non-cancerous liver parenchyma. Namely, oxaliplatin-based regimens have been associated with an increased risk of sinusoidal injury, whereas irinotecan-containing regimens have been associated with an increased risk of steatosis or steatohepatitis (6-9). While reports on the clinical significance of sinusoidal injury are conflicting, steatosis and steatohepatitis have been associated with an increased morbidity and 90-day mortality following hepatic resection (9-11). In this context, it is important to take into account the presence of other, non CHT-related factors, that may contribute to the postoperative morbidity and mortality of this particular subset of patients. Among these, body mass index (BMI) is one of the most controversial. An increased BMI was associated with improved overall survival compared with normoweight and underweight patients in a large retrospective analysis including first- and subsequent-line clinical trials for metastatic colorectal cancer (12). However, overweight and obese patients were found to be more prone to postoperative complications following liver resection (13,14). In addition, a high BMI is a well-established risk factor for the development of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (15,16). Therefore, a high BMI rather than preoperative CHT may be the major contributor to the development of pathological liver changes, morbidity and mortality following liver resection.

The aim of the present study was to assess the role of preoperative CHT, BMI and other patient- and resection-related factors in the development of postoperative complications following major hepatic surgery for CRLM.

Patients and methods

Patients. Prospectively collected data on liver resections conducted for CRLM at the Treviso Regional Hospital (Treviso, Italy) and the Regina Elena National Cancer Institute (Rome, Italy) between January 2012 and March 2015 were retrospectively analyzed. The study protocol was approved by the Institutional Review Boards of the two hospitals. Patients who underwent preoperative hepatic arterial-based therapies, portal vein embolization or treatment with systemic CHT for malignancies other than colorectal cancer, were excluded from the study.

Staging. Preoperative staging included measurement of serum carcinoembryonic antigen levels, pan-colonoscopy, thoracoabdominal computed tomography (CT) and hepatic magnetic resonance imaging. All the cases were discussed during multidisciplinary meetings attended by surgeons, oncologists and radiologists. Patients with initially unresectable metastases were treated with neoadjuvant CHT. Unresectability was defined as follows: Bilateral lesions not eligible for two-stage hepatectomy or associating liver partition and portal vein ligation for staged hepatectomy, >4 metastases, major vessel invasion, and single metastases that would require a major hepatectomy but may be treated with a minor resection after downsizing with neoadjuvant CHT.

CHT regimens. The different CHT regimens followed either the FOLFOX or the FOLFIRI protocol, if indicated patients received additional targeted therapy with monoclonal antibodies such as cetuximab or bevacizumab (17,18). Patients with evidence of KRAS or BRAF mutations were considered not eligible for treatment with cetuximab. When administered, cetuximab was associated with irinotecan-based treatment. Bleeding diathesis or a clinically relevant hypertension were the main contraindications for treatment with bevacizumab. The number of CHT cycles was non-standardized and left to the discretion of the treating oncologist. Preoperative CHT was defined as treatment with any CHT regimen within 6 months prior to liver resection.

Surgical treatment. The operative management was performed using a laparotomic approach in all patients, and included a thorough exploration of the abdominal cavity to rule out extrahepatic spread of the lesions and the use of intraoperative liver ultrasound and palpation to accurately determine the location of CRLM and their association with hepatic blood flow. Parenchymal transection was performed with the crushing clamp method or with an ultrasound dissector. A tape was placed around the hepatic pedicle and an intermittent Pringle maneuver was performed whenever significant bleeding occurred. Bile duct division was commonly performed during the parenchymal transection. A sealant (TachoSil®, Baxter, Deerfield, IL, USA) was usually placed at the cut surface. Hepatectomy was classified according to the Brisbane 2000 terminology (19): Resection of <1 liver segments was considered as wedge resection; major and minor resection were defined as resection of ≥3 and <3 anatomic segments, respectively.

Evaluation of CHT-related liver alterations. Experienced hepatic pathologists were blinded to the patients' preoperative CHT regimens, and evaluated the hepatic lesions as well as the non-cancerous liver parenchyma for CHT-associated pathological alterations. Sinusoidal dilation was graded according to the Rubbia-Brandt semi-quantitative histological score (6). Steatohepatitis was graded as defined by Kleiner *et al* (20). Steatosis was graded according to the percentage of involved hepatocytes as follows: Absent (grade 0); ≤30% of hepatocytes (grade 1); 30-50% of hepatocytes (grade 2); and >50% of hepatocytes (grade 3). In the present study, only grade 2-3 steatosis, grade 2-3 sinusoidal dilation, and Kleiner score ≥4 steatohepatitis were taken into account.

Classification of patients by BMI. BMI was calculated as weight in kilograms divided by the square of the height in meters, according to the World Health Organization (WHO) criteria (21). Dividing patients with a BMI ≥25 kg/m^2 into overweight (BMI 25-29 kg/m^2) and obese (BMI ≥30 kg/m^2) patients, as classified by the WHO, would have led to a loss in statistical power, as only 6 patients in our population had a BMI ≥30 kg/m^2. Conversely, the use of a BMI threshold of 25 to define overweight status would have been overly stringent, leading to the inclusion of patients without a clinically relevant metabolic alteration in the overweight group. Thus, for the purpose of evaluating the role of BMI in the postoperative outcome, the patients were divided into two groups, namely normoweight (BMI <28 kg/m^2) and overweight (BMI ≥28 kg/m^2).

Postoperative complications. The postoperative complications were graded on a scale of 0-5 according to the Dindo-Clavien classification (22). Grade 0 corresponds to absence of complications, whereas grade 5 corresponds to death. Clinically relevant complications were defined as those graded ≥2. In light of the minimal effect of grade 1 complications on the postoperative course, the affected patients were grouped with those with no complications. Bile leakage was defined as an output of ≥50 ml of bile from a surgical drain or following drainage of an abdominal collection, lasting ≥3 days (23). Liver failure was defined as the presence of a prothrombin time (PT) <50% (international normalized ratio ≥1.7) together with a serum bilirubin level ≥5 mg/dl on or after postoperative day 5 (24). Ascites was defined as an output of ≥500 ml/day after the third postoperative day. Acute kidney injury was defined as a ≥2-fold increase in serum creatinine from the preoperative baseline, or a decrease in estimated glomerular filtration rate of ≥50%, as defined by the RIFLE criteria (25). Pleural effusion requiring drainage, symptomatic lung infections, pulmonary embolism end respiratory insufficiency requiring artificial ventilation for >48 h were considered as respiratory complications.

Statistical analysis. The statistical review of the present study was performed by a biomedical statistician. Preoperative characteristics, intraoperative and pathological data and postoperative outcomes were evaluated based on the BMI class and on the use of preoperative CHT using univariate analysis. The same parameters were compared between the normoweight and the overweight groups by univariate analysis, following stratification according to the administration or non-administration of preoperative CHT. All the variables identified as potential risk factors for postoperative morbidity on univariate analysis were subsequently entered into a multivariate analysis using the Cox model.

The univariate analysis was performed using the Chi-squared test or the Fisher's exact test for categorical variables, as appropriate. For continuous variables, the two-sample Student's t-test or the Mann-Whitney U-test were used as appropriate. Variables with an overall P-value <0.1 on univariate analysis were evaluated by multivariable logistic regression. Only variables with an overall P<0.05 were considered statistically significant. Quantitative variables were expressed as mean (± standard deviation) when normally distributed; otherwise, they were expressed as median (interquartile range). The hazard ratio (HR) and 95% confidence interval (95% CI) are also reported for multivariate analysis. Statistical analysis was performed using SPSS 13.0 software for Windows (SPSS Inc, Chicago, IL, USA).

Table I. Demographic, preoperative, operative and postoperative characteristics of the study population (n=100).

Variables	Values
Age (years)	63.9 (±10.3)
Sex	
Male	64
Female	36
BMI (kg/m^2)	25.8 (±3.3)
≥28	25
<28	75
Chemotherapy regimen	
FOLFOX	36
FOLFOX + bevacizumab	10
FOLFIRI	3
FOLFIRI + bevacizumab	10
FOLFIRI + cetuximab	2
Number of metastases	
1-3	64
4-10	20
>10	16
Synchronous metastases	51
Metachronous metastases	49
Size of largest metastasis (cm)	2.9 (±1.7)
Surgical procedure	
Right hepatectomy	8
Extended right hepatectomy	4
Left hepatectomy	7
Extended left hepatectomy	9
Segmental resection	27
Wedge reresection	45
Blood transfusion	23

Data are presented as absolute numbers or as mean (± standard deviation). BMI, body mass index.

Results

Patient characteristics. A total of 100 patients presented with CRLM from colorectal carcinoma in the reported time interval, of whom 64 were male and 36 were female. The mean patient age was 63.9 (±10.3) years. The mean BMI for the entire population was 25.8 (±3.3) kg/m^2. A total of 25 patients were overweight (BMI ≥28 kg/m^2) and 75 patients had a BMI <28 kg/m^2.

The demographic data, preoperative, operative and postoperative characteristics of the study population are summarized in Table I. A total of 39 patients had solitary metastases and 36 patients had >4 metastases. The median diameter of the nodules was 2.9 (±1.7) cm. A total of 51 patients presented with synchronous disease. Systemic CHT was administered to 61 patients, 46 of whom (75.4%) received an oxaliplatin-based regimen, whereas the remaining 15 (24.6%) received an irinotecan-based regimen. In the CHT group, 20 patients (32.8%) received bevacizumab and 2 patients received cetuximab (3%). The median duration of therapy was 7.8 (±4.1) cycles.

Treatment and complications. A major liver resection was performed in 28 patients; 26 patients underwent bilateral resection. A Pringle maneuver was required in 36 patients, and the mean time of pedicle clamping was 8.4 (±14) min. The mean perioperative blood loss was 524.5 (±560.4) ml and 23 patients required a transfusion of blood or plasma in the perioperative period; overall, a mean of 194.21 (±451.14) ml of blood and 121.5 (±343.1) ml of plasma were transfused.

The median Intensive Care Unit stay was 1 (0-1) days, and the mean hospital stay was 14.2 (±19.5) days. Dindo-Clavien grade ≥2 postoperative complications occurred in 22 patients and included liver failure (n=5); intra-abdominal collection requiring drainage (n=4); pleural effusion requiring drainage (n=4); acute kidney injury (n=2); symptomatic lung infections requiring high-dose intravenous antibiotics (n=2); biliary leakage (n=1); ascites (n=1); pulmonary embolism (n=1); hemoperitoneum requiring re-laparotomy (n=1); and respiratory insufficiency (n=1).

Table II. Preoperative, operative and postoperative characteristics stratified for the use of CHT.

Variables	Preoperative CHT, n (%) (n=61)	Surgery alone, n (%) (n=39)	P-value
BMI ≥28 (kg/m^2)	18 (29.5)	7 (17.9)	0.24
Comorbidities			
Diabetes	10 (16.4)	9 (23)	0.44
Ischemic heart disease	1 (1.6)	6 (15.4)	0.07
Hypertension	33 (54)	9 (23)	<0.01
Dyslipidemia	3 (4.9)	7 (17.9)	0.04
Pulmonary disease	4 (6.5)	6 (15.4)	0.18
Kidney disease	4 (6.5)	4 (10.3)	0.7
Liver disease	6 (9.8)	2 (5)	0.47
Metastases			<0.01
1-3	34 (55.7)	30 (76.9)	
4-10	13 (21.3)	7 (17.9)	
>10	16 (26.2)	0	
Synchronous metastases	35 (57.4)	16 (41)	0.15
Operative characteristics			
Major resection	21 (34.4)	7 (17.9)	0.07
Blood transfusion	19 (31.1)	4 (10.3)	0.02
Time of pedicle clamping (min)	23 (15-30)	17 (12-25)	0.27
Patients requiring pedicle clamping	24 (39.3)	12 (30.8)	0.38
Liver injury			
Sinusoidal dilation (grade 2 or 3)	3 (4.9)	1 (2.6)	>0.9
Steatosis (grade 2 or 3)	27 (44.3)	8 (20.5)	0.03
Steatohepatitis (Kleiner ≥4)	21 (34.4)	5 (12.8)	0.02
Complications (Dindo-Clavien ≥2)	18 (29.5)	4 (10.3)	0.03

Data are presented as number (percentage) or median (range). BMI, body mass index; CHT, chemotherapy.

The histological examination of the non-cancerous liver parenchyma revealed the presence of steatosis in 35, sinusoidal dilation in 4 and steatohepatitis in 26 patients. Concomitant presence of steatosis and steatohepatitis was detected in 16 patients.

Stratification by CHT. The univariate analysis of preoperative, operative and postoperative characteristics stratified for the use of CHT is presented in Table II. There was no difference in the proportion of overweight patients between the two groups (P=0.24). A significantly higher proportion of patients who received CHT prior to surgery had preoperative comorbidities, including hypertension (P<0.01) and dyslipidemia (P=0.04). Patients in the CHT group had more liver metastases at presentation (P<0.01) and were more frequently treated with major liver resection compared with the non-CHT group (34.4 vs. 17.9%, respectively); however, these differences did not reach statistical significance (P=0.07). Both steatosis and steatohepatitis exhibited a positive association with preoperative CHT. Steatosis was detected in 44.3% of the CHT-treated and in 20.5% of the untreated patients (P=0.03). Steatohepatitis was present in 34.4% of CHT-treated and in 12.8% of the untreated patients (P=0.02). An higher rate of complications following surgery was detected in the CHT group (P=0.03): A total of 5 patients had respiratory complications, including pleural effusion (n=4) and respiratory insufficiency (n=1); 4 patients had CT detected intra-abdominal collections that required percutaneous (n=3) or surgical drainage (n=1); 3 patients had liver failure; 2 patients had acute kidney injury and were treated with continuous diuretics infusion; 1 patient underwent re-laparotomy for development of hemoperitoneum; 1 patient had ascites; 1 patient had pulmonary embolism treated with high-dose low-molecular-weight heparin; and 1 patient had lung infection. A significantly higher number of patients in the CHT group required perioperative blood transfusions (P=0.02).

Stratification by BMI. Table III represents the preoperative, operative and postoperative characteristics of the study population stratified according to the BMI group. Overall, there were no statistically significant differences in the proportion of patients with preoperative comorbidities, including renal, hepatic, respiratory and cardiovascular disease.

The proportion of patients receiving CHT was similar between the normoweight and overweight groups (P=0.24); overweight patients were more frequently treated with irinotecan (P=0.02) and bevacizumab (P=0.01). A total of 26 normoweight patients (34.7%) and 10 overweight patients (40%) had ≥4 liver metastases at presentation (P=0.6). A higher

Table III. Preoperative, operative and postoperative characteristics stratified for BMI.

Variables	BMI ≥28 kg/m², n (%) (n=25)	BMI <28 kg/m², n (%) (n=75)	P-value
CHT	18 (72)	43 (57.3)	0.24
Comorbidities			
Diabetes	7 (28)	12 (16)	0.24
Ischemic heart disease	2 (8)	5 (6.7)	0.32
Hypertension	14 (56)	28 (37.3)	0.32
Dyslipidemia	4 (16)	6 (8)	0.26
Pulmonary disease	3 (12)	7 (9.3)	0.7
Kidney disease	2 (8)	6 (8)	>0.9
Liver disease	2 (8)	6 (8)	>0.9
Metastases			0.79
1-3	15 (60)	49 (65.3)	
4-10	5 (20)	15 (20)	
>10	5 (20)	11 (14.7)	
Synchronous metastases	13 (52)	38 (50.7)	>0.9
Operative characteristics			
Major resection	11 (44)	17 (22.7)	0.07
Blood transfusion	6 (24)	17 (22.7)	0.8
Time of pedicle clamping (min)	16 (13-21)	25 (15-30)	0.03
Patients requiring pedicle clamping	10 (40)	26 (34.7)	0.63
Liver injury			
Sinusoidal dilation (grade 2 or 3)	2 (8)	2 (2.6)	0.24
Steatosis (grade 2 or 3)	17 (68)	18 (24)	<0.01
Steatohepatitis (Kleiner ≥4)	14 (56)	12 (16)	<0.01
Complications (Dindo-Clavien ≥2)	4 (16)	18 (24)	0.58

Data are presented as number (percentage) or median (range). BMI, body mass index; CHT, chemotherapy.

proportion of patients in the overweight group (44 vs. 22.7%) underwent a major hepatic resection; however, the difference was not statistically significant (P=0.07).

Steatosis was observed in 17 patients (68%) in the overweight group and in 18 patients (24%) in the normoweight group (P<0.01). Steatohepatitis also exhibited a positive association with the BMI status, as it was present in 14 patients (56%) in the overweight group and 12 patients (16%) in the normoweight group (P<0.01). Despite the positive association between BMI ≥28 kg/m², steatosis and steatohepatitis, overweight patients did not exhibit an increased rate of complications following hepatic resection (P=0.58). Even after stratification for major liver resection (data not shown), there was no significant difference in the complication rate between overweight and normoweight patients (P=0.9).

Comparison of BMI groups following stratification by CHT. The preoperative, operative and postoperative characteristics of the study population were compared between the normoweight and overweight groups by univariate analysis following stratification for the use of preoperative CHT (Table IV). In the CHT-treated group, a positive association was maintained between BMI ≥28 kg/m² and steatosis (P<0.01) and steatohepatitis (P<0.01), while the complication rate remained non-significantly different between the two subgroups (P=0.22).

There was no significant difference in the preoperative, operative and postoperative characteristics between overweight and normoweight patients in the untreated group.

Analysis of risk factors for complications. The results of the univariate and multivariate analyses of risk factors for complications following liver resection for CRLM are presented in Table V. On univariate analysis, the administration of any preoperative CHT (P=0.02); perioperative blood transfusions (P<0.01) and the presence of steatohepatitis in the non-cancerous liver parenchyma (P=0.02) were associated with an increased risk of postoperative complications. Steatohepatitis (P=0.005) and blood transfusions (P=0.001) were the only independent predictors of postoperative complications on multivariate analysis.

On univariate analysis, BMI ≥28 kg/m² (P<0.01), preoperative administration of CHT (P=0.02) and treatment with irinotecan (P<0.01) were associated with a postoperative finding of steatohepatitis. On multivariate analysis, BMI ≥28 kg/m² (P=0.004, HR=8.30, 95% CI: 2.39-28.7); and irinotecan treatment (P=0.016, HR=0.16, 95% CI: 0.037-0.711) were independent risk factors for steatohepatitis.

Table IV. Preoperative, operative and postoperative characteristics compared between the BMI ≥28 and <28 groups following stratification for any preoperative CHT (univariate analysis).

	Preoperative CHT (n=61)			Surgery alone (n=39)		
Variables	BMI ≥28 (n=18)	BMI <28 (n=43)	P-value	BMI ≥28 (n=7)	BMI <28 (n=32)	P-value
Comorbidities						
Diabetes	5	5	0.1	2	7	0.7
Ischemic heart disease	1	0	0.3	1	5	>0.9
Hypertension	11	22	0.7	3	6	0.3
Dyslipidemia	2	1	0.19	2	5	0.59
Pulmonary disease	1	3	>0.9	2	4	0.29
Kidney disease	1	3	>0.9	1	3	0.56
Liver disease	2	4	>0.9	0	2	>0.9
Metastases			0.6			0.58
1-3	11	23		4	26	
4-10	3	10		2	5	
>10	5	11		0	0	
Synchronous metastases	9	26	0.6	4	12	0.6
Operative characteristics						
Major resection	8	13	0.4	3	4	0.09
Blood transfusion	6	13	>0.9	0	4	>0.9
Time of pedicle clamping (min)	NA	NA	NA	NA	NA	NA
Patients requiring pedicle clamping	NA	NA	NA	NA	NA	NA
Liver injury						
Sinusoidal dilation (grade 2 or 3)	NA	NA	NA	NA	NA	NA
Steatosis (grade 2 or 3)	15	12	<0.01	2	6	0.6
Steatohepatitis Kleiner ≥4)	12	9	<0.01	2	3	0.21
Complications (Dindo-Clavien ≥2)	3	15	0.23	1	3	0.56

BMI measured as kg/m^2. BMI, body mass index; CHT, chemotherapy; NA, not applicable.

Similarly, steatosis was associated with BMI ≥28 kg/m^2 (P<0.01), preoperative administration of CHT (P<0.01) and treatment with irinotecan (P<0.01) on univariate analysis. On multivariate analysis, BMI ≥28 kg/m^2 (P=0.002, HR=10.68, 95% CI: 2.88-39.56), irinotecan treatment (P=0.02, HR=0.164, 95% CI: 0.036-0.750) and dyslipidemia (P=0.03, HR=31.19, 95% CI: 1.29-751.68) were independent risk factors for steatosis.

Discussion

The publication of the EORTC trial in 2008 demonstrated the beneficial role of perioperative oxaliplatin-based CHT (FOLFOX 4) in primarily resectable CRLM (3), reporting an absolute increase of 7.3% in progression-free survival at 3 years. However, the same study also demonstrated that this significant improvement in the oncological outcome was accompanied by an increased rate of postoperative complications in the CHT group compared with the surgery alone group. The reported rate of reversible perioperative complications was 25% in the CHT group and 16% in the surgery alone group. The most relevant findings were a doubling in the rate of biliary fistula development and severe hepatic failure, and a three-fold increase in the rate of intra-abdominal infections.

Since then, the increased use of preoperative CHT for CRLM has led to a growing awareness of the pathological changes of the liver tissue caused by some of these agents, and their potential role in postoperative morbidity and mortality.

The association between sinusoidal injury and oxalipatin-based CHT was first reported by Rubbia-Brandt *et al* (6), who detected the presence of such lesions in 78% of the oxaliplatin-treated patients vs. none in the control group. This finding was subsequently confirmed by Vauthey *et al* (9), who demonstrated that oxaliplatin was associated with grade 2-3 sinusoidal dilation compared with no CHT (18.9 vs. 1.9%, respectively); however, the authors reported no association between the use of oxaliplatin and an increase in morbidity or mortality rates. Nakano *et al* (7) found that treatment with 6 cycles of oxaliplatin was an independent predictor of risk for sinusoidal dilation, while Karoui *et al* (10) reported a significantly higher postoperative morbidity in patients who received ≥6 cycles of oxaliplatin (38% complications in the CHT group vs. 14% in the control group). In a more recent series by Reissfelder *et al* (26), the authors confirmed these findings,

Table V. Univariate and multivariate analysis of risk factors for postoperative complications.

	Univariate analysis	Multivariate analysis	
Variables	P-value	P-value	Hazard ratio (95% CI)
Age	NS		
Sex			
Male	NS		
Female	NS		
BMI ≥28 kg/m^2	NS		
Chemotherapy regimen			
FOLFOX	NS		
FOLFIRI	NS		
Any CHT	0.02	NS	
Comorbidities			
Diabetes	NS		
Ischemic heart disease	NS		
Hypertension	NS		
Dyslipidemia	NS		
Pulmonary disease	NS		
Kidney disease	NS		
Liver disease	NS		
Metastases >4	NS		
Synchronous metastases	NS		
Operative characteristics			
Major resection	NS		
Blood transfusion	<0.01	0.001	0.131 (0.038-0.452)
Time of pedicle clamping	NS		
Liver injury			
Sinusoidal dilation (grade 2 or 3)	NS		
Steatosis (grade 2 or 3)	NS		
Steatohepatitis (Kleiner ≥4)	0.02	0.005	0.118 (0.027-0.518)

CHT, chemotherapy; NS, non-significant; CI, confidence interval; BMI, body mass index.

reporting a significantly increased complication rate in patients with sinusoidal dilation after oxaliplatin therapy, stating that patients with >6 cycles of therapy exhibited a significantly increased complication rate. In the present study, only 4 patients, all treated with oxaliplatin (9%), exhibited evidence of Rubbia-Brandt grade 2-3 sinusoidal dilation on liver histology. This proportion was lower compared with previously reported findings in other series, where 5-79% of patients exhibited evidence of this type of liver injury. In addition, no association between sinusoidal dilation and postoperative complications was observed. Wolf *et al* (8) reported similar findings in a large cohort of patients from a single institution, with a 10.8% rate of sinusoidal dilation among 166 patients treated with oxaliplatin. The authors also described no association between sinusoidal dilation and postoperative morbidity, concluding that, regardless of a potential association with oxaliplatin use, this histopathological finding does not independently increase the operative risk of liver resection for CRLM.

In the present study, no association between the presence of grade 2 or 3 steatosis and postoperative complication rate was observed. Behnrs *et al* (27) were the first to report an association between steatosis and an increased morbidity and mortality rate following major hepatic resection for CRLM. Consequently, Kooby *et al* (11) reported similar results in a large study including 325 patients with steatosis and 160 matched controls. The authors concluded that steatosis was an independent predictor of perioperative complications on multivariate analysis. However, in those studies, steatosis was not distinguished from steatohepatitis. In a subsequent study by Vauthey *et al* (9), the authors separated steatosis from steatohepatitis graded according to the NASH score. In that systematic analysis of 406 patients who underwent liver resection for CRLM, there was no reported association between any CHT regimen and severe (>30%) steatosis. Moreover, the authors reported no increase in complications, even in the presence of severe steatosis. In a retrospective analysis of 684 liver resections, Balzan *et al* (13) reported that steatosis was not a significant predictor of postoperative complications on multivariate analysis. Similarly, Reissfelder *et al* (26) found that steatosis exerted no effect on postoperative morbidity (P=0.69).

Liver steatosis is a relatively common liver injury, with a well-recognized association with overweight status (11,28,29). This was confirmed in the present study, as a BMI ≥28 kg/m^2 was an independent risk factor for the development of steatosis in our cohort. Interestingly, steatosis was also independently associated with the administration of irinotecan, and the same finding was reported in the series by Wolf *et al* (8). However, these data were possibly biased by the presence of 16 patients with overlapping steatosis and steatohepatitis on histological examination in the present study.

In our cohort, steatohepatitis was the only CHT-related liver injury that was independently associated with postoperative morbidity on multivariate analysis. The independent risk factors for the development of this injury were BMI ≥28 kg/m^2 and preoperative irinotecan administration.

The association between CHR and the development of steatohepatitis was first described in a small series published by Fernandez *et al* (30). In that study, the authors reported a higher rate of steatohepatitis in 12 patients treated with irinotecan. Similar results were reported by Pawlik *et al* in 55 patients (31). The association between irinotecan, steatohepatitis and postoperative morbidity was best demonstrated by Vauthey *et al* (9); in their study on a cohort of 406 patients, 248 of whom received preoperative CHT, the authors reported a 20.2% rate of steatohepatitis in irinotecan-treated patients. Of note, irinotecan was associated with steatohepatitis, irrespective of BMI. In the same study, the higher rate of steatohepatitis appeared to have clinically relevant consequences: Patients with steatohepatitis had a significantly increased 90-day mortality rate following major hepatectomy (14.7 vs. 1.4%; P=0.001) and a higher risk of death from postoperative liver failure (6 vs. 1%; P=0.01). These results were confirmed by Reissfelder *et al* (26); in their series of 119 patients, borderline steatohepatitis and steatohepatitis developed in 34 (29%) and 14 (12%) of the patients, and perioperative morbidity occurred in 14 (41%) and 8 (57%) of these patients, respectively (P=0.03). It should be noted that in the study published by Pawlik *et al* (31) and in the more recent series by Wolf *et al* (8), the authors did not observe differences in morbidity or mortality in patients treated preoperatively with irinotecan. In the latter series of 384 patients, 16 patients developed steatohepatitis, 9 of whom were treated with irinotecan preoperatively (P=0.01). However, on univariate analysis, treatment with any CHT or irinotecan was associated with a decreased risk of complications (P=0.019 and 0.026, respectively).

A limited number of studies have focused on the role of BMI in postoperative outcome following hepatic resection. In a retrospective analysis of 684 liver resections, Balzan *et al* (13) reported that overall postoperative morbidity and mortality were not affected by BMI. However, during major resections, Dindo-Clavien grade ≥3 complications were more frequent among obese (57%) and overweight (54%) compared with normoweight patients (35%; P<0.05). On multivariate analysis, obesity and overweight status were identified as independent predictors of morbidity. However, in that series, only 68% of the patients were treated for malignant lesions. In a case-control study involving 85 obese patients matched with 170 non-obese patients, Viganò *et al* (14) reported a significantly higher grade 2 morbidity in obese compared with non-obese patients (14.1 vs. 1.8%, respectively; P<0.01). However, this was mainly due to abdominal wall complications; moreover, that study also included liver resections conducted for benign conditions and patients with cirrhosis.

Mathur *et al* (32) retrospectively reviewed 279 patients who underwent hepatectomy for malignancy and detected a nearly two-fold increase of liver-specific complications in obese patients (20.1%), with a nearly two-fold higher biliary leak rate, compared with the non-obese group (18.6 vs. 9.9%, respectively). However, only 47% of the obese patients in that study were treated for CRLM, and the authors stated that BMI was not a statistically significant predictor of outcome when testing the patients within each diagnostic group. A recent study by Langella *et al* (33) reported the first analysis focusing on the short-term outcome of obese patients who underwent hepatectomy for CRLM. The authors reported an overall higher morbidity in obese patients (41 vs. 31%, P=0.12), mainly due to pulmonary complications. On multivariate analysis, obesity, age ≥65 years, major hepatectomy and associated resections, were found to be independent predictors of overall morbidity (P<0.001). Interestingly, Langella *et al* found no difference in steatohepatitis between obese and non-obese patients (P=0.097), whereas steatosis was more frequent among obese patients (P<0.001).

In the present study, a BMI ≥28 kg/m^2 was not found to be associated with an increased rate of Dindo-Clavien grade ≥2 complications. The complication rate remained non-significantly different between the normoweight and the overweight groups, even following stratification for the administration of preoperative CHT. Conversely, overweight status was associated with the development of steatohepatitis, one of the two major determinants of postoperative complications in our series. Of note, the association between BMI ≥28 kg/m^2 and steatohepatitis was maintained even after stratification for the administration of any CHT, suggesting its independent role in the development of this type of liver injury, which was confirmed after multivariate analysis. These findings are in line with the published literature. Bruquet *et al* (29) reported a BMI ≥27 kg/m^2 to be the only independent risk factor for the development of hepatic steatohepatitis. Reissfelder *et al* (26) reported that BMI was associated with steatohepatitis (described by the NAS score), and was 27.8 kg/m^2 in the NAS borderline group and 30.9 kg/m^2 in the group with definitive steatohepatitis (P=0.0001). In a review of 208 patients who underwent resection for CRLM, Bower *et al* (34) reported that BMI was the strongest predictor of steatosis and steatohepatitis in patients with CRLM, and the risk was independent of the use of preoperative CHT. In the same study, despite increased rates of steatosis and steatohepatitis, obese patients did not exhibit an increased rate of perioperative complications.

Taken together, these findings appear to support the 'second hit' hypothesis proposed by Day *et al* (35). According to the authors, patients with a baseline level of steatosis may develop steatohepatitis once exposed to the cytotoxic effect of certain CHT drugs, such as irinotecan. In this context, as proposed by Reissfelder *et al* (26), the use of preoperative liver biopsy for selected patients at high risk of developing postoperative morbidity (namely overweight patients who underwent preoperative CHT with FOLFIRI) may be a helpful tool in guiding the selection of the optimal operative procedure.

The positive association between blood transfusions and postoperative complications in the present study is in line with the published literature. The mechanism through which transfusion negatively affects the perioperative course of surgical patients, mainly relies in the altered immune function following administration of blood products, an effect that has long been recognized (36). An association between transfusions and postoperative complications has been shown in pre-clinical models and in other cancer types (37,38). The largest series focusing on the postoperative outcome following hepatic resection for CRLM is the one published by Kooby *et al* (39), involving 1,351 patients, half of whom received perioperative transfusions. The authors reported a significantly lower rate of complications in non-transfused patients compared with those receiving blood products (33 vs. 46%, P=0.0001). This association was confirmed on multivariate analysis.

The findings of the present study may be limited by its retrospective nature and the relatively low number of patients, which may have precluded potential differences in the subgroup analysis and the developing of a rigorous model for multivariate analysis. Another limitation lies with the poor standardization of pathological reports describing the histological findings on the non-cancerous liver specimens. This may have caused the investigators to overlook a diagnosis of CHT-related liver injury, causing a loss in statistical power. Since CHT was frequently administered by oncologists outside the two referring centers, data on the number of cycles and the duration of preoperative CHT could not always be retrieved. Finally, there were no perioperative deaths in our series; therefore, this variable could not be analyzed.

In conclusion, overweight patients, despite not constituting a high-risk category *per se*, may be more prone to the cytotoxic effects of irinotecan treatment for CRLM, harboring a higher risk of developing steatohepatitis from a baseline of liver steatosis. In this particular subset of patients, a preoperative biopsy may be a useful tool in guiding the operative approach to minimize the risk of postoperative complications. In addition, the use of perioperative transfusion of blood products should be avoided unless absolutely necessary.

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