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CHEMOTHERAPY HEPATOTOXICITY - HISTOLOGIC INJURY AND IMPACT ON MORBIDITY AFTER HEPATECTOMY FOR COLORECTAL CANCER LIVER METASTASES

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Abstract

Introduction: Advances on neoadjuvant chemotherapy (NCT) have allowed surgical treatment in otherwise unresectable patients with colorectal liver metastases (CRLM). It is well known that NCT induces liver lesions such as sinusoidal obstruction syndrome (SOS) and steatohepatitis (SH). However, whether it affects postoperative morbidity remains controversial. The aim of this study was both to evaluate the impact of NCT on liver parenchyma and postoperative morbidity and to identify preoperative predictive markers for liver injury.

Patients and Methods: Among 140 patients undergoing liver resection for CRLM between 2010 and 2013, 70 underwent systemic NCT. Liver function tests, pathology, postoperative morbidity and mortality were compared between the two groups.

Results: Univariate analysis revealed NCT as a cause of sinusoidal dilation ($p=0.09$), peliosis ($p=0.028$), NRH ($p=0.049$) and moderate to severe SOS ($p=0.004$) and bevacizumab as a protective agent against moderate to severe SOS ($p=0.045$). Diabetic patients were identified as having a lower incidence of sinusoidal dilation ($p=0.034$). Multivariate analysis confirmed sinusoidal dilation as an independent cause for morbidity ($p=0.02$) and liver-specific complications ($p=0.016$). Preoperative level of GGT was identified as predictive factor for moderate to severe SOS and peliosis ($p<0.001$ and $p=0.004$, respectively).

Conclusion: The administration of NCT induces SOS lesions, but can be partially prevented by bevacizumab. Sinusoidal dilation is an individual cause of postoperative morbidity. Preoperative GGT level can be used to predict the presence of SOS.

Keywords: liver metastases, colorectal cancer, hepatectomy, chemotherapy, liver injury, sinusoidal dilation, sinusoidal obstruction syndrome

Introduction

Approximately 50% of patients with Colorectal Cancer (CRC) develop Colorectal Liver Metastases (CRLM). For them, surgical resection is the only potential curative treatment. (1,2) However, without treatment, about 85% of the patients are considered unresectable and therefore unable to undergo surgery. (3) Preoperative chemotherapy can be offered to these patients in order to convert them to resectability. (2,4,5) Moreover, chemotherapy administered to resectable patients in a neoadjuvant fashion has been shown to improve overall survival (6) and reduce the risk of tumor relapse (7) in patients undergoing hepatic resection. Modern neoadjuvant chemotherapy (NCT) consists of 5-FU in association with irinotecan and oxaliplatin. More recently, the addition of molecular-targeted agents, such as cetuximab and bevacizumab, has improved response rates and resectability. (8,9) However, these chemotherapeutical agents are known to inflict liver toxicity. Oxaliplatin-based chemotherapy has been widely associated with sinusoidal obstruction syndrome (SOS) (10–14), while irinotecan has been reported to cause steatohepatitis (SH), also known as chemotherapy-associated steatohepatitis (CASH). (11) Furthermore, NCT has been proved to increase morbidity and mortality after liver resection. (15)

The primary objective of this study was to evaluate the impact of neoadjuvant chemotherapy for CRLM on liver parenchyma and the associated postoperative morbidity and mortality. The secondary objective was to determine whether preoperative data such as biochemical markers could predict the occurrence of liver lesions.

Patients and Methods

Clinical and pathological review of patients who underwent liver resection for CRLM at Serviço de Cirurgia A from Centro Hospitalar e Universitário de Coimbra (Head of Department: Prof. Dr. Francisco Castro e Sousa, Coimbra, Portugal) between January 2010 and July 2013. Exclusion criteria were poor histological material and/or insufficient clinical information (Figure 1). Given the retrospective nature of the study, ethics committee was not consulted.

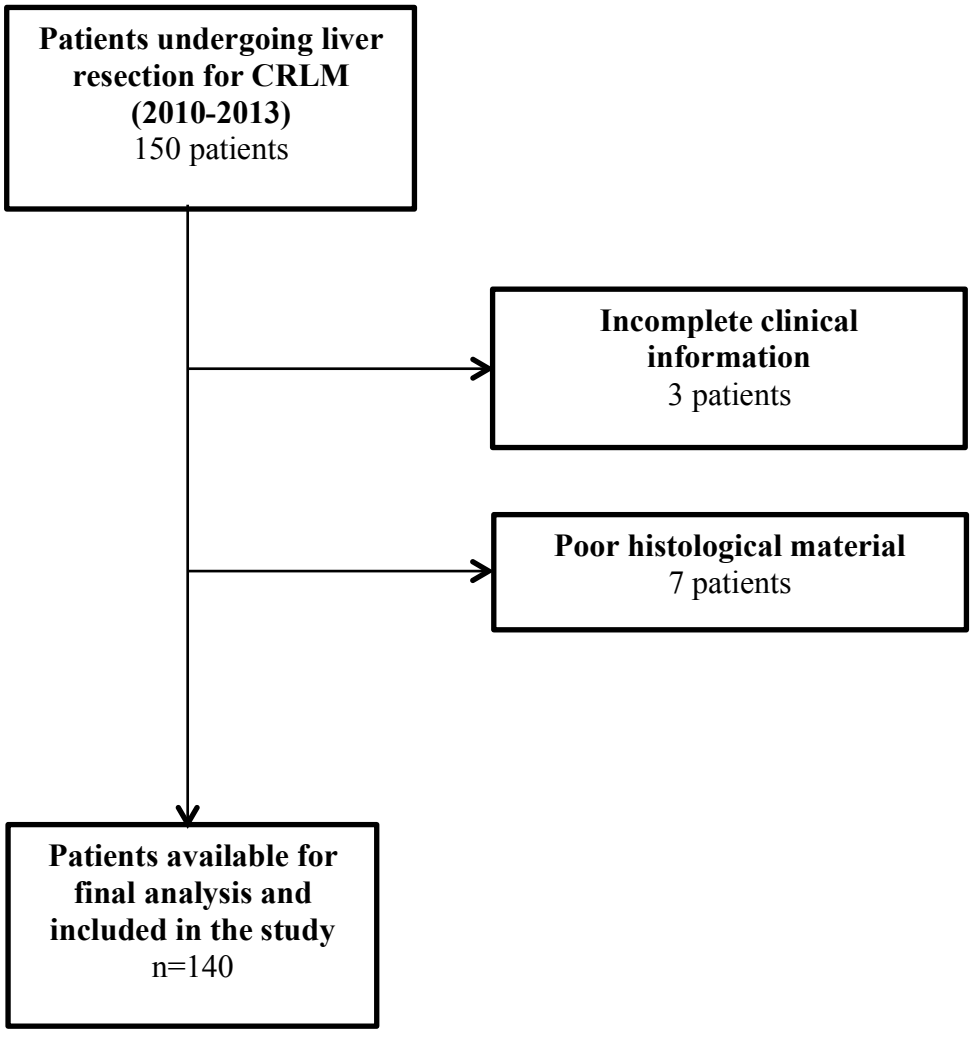

Figure 1. Study population and exclusion criteria

1. Study Population

The study comprised a total of 140 patients, 100 men and 40 women. The mean age was 64±10 years (range 33-82 years), two thirds being older than 70 years. Twenty-seven (19%) patients suffered from diabetes mellitus.

Primary tumor was located in the colon in 90 (64%) patients, in the rectum in 45 (32%) patients and in both sites in five (4%) patients. According to TNM classification, 91 (67%) patients were classified as node-positive (presence of metastatic regional lymph nodes).

The study population had a mean of 2.9±2.9 liver metastases (range 1-16) and a mean diameter of 4.1±3.2cm (range 0.5-22cm) for the biggest lesion. Sixty (43%) patients had a single nodule, while the remaining 80 (57%) presented multiple metastases. The location of the lesions was restricted to the right liver in 50 (36%) patients, to the left liver in 37 (26%) and was bilobar in 53 (38%) patients.

Clinical presentation of liver metastases was synchronous with the primary tumor in 74 (53%) patients and metachronous in 66 (47%). Of the patients with synchronous disease, 12 (18.2%) underwent synchronous resection and 54 (71.8%) metachronous resection: 44 were first operated on the primary tumor while 10 were first operated on their hepatic lesions ("Liver First" strategy); five of these were never operated on their primary lesion due to systemic tumor progression or major morbidity after hepatectomy. Furthermore, 26 (18.6%) cases were re-hepatectomies and 14 of those (10%) were planned two-stage hepatectomies, separated by a median of 6 weeks (range 3-27 weeks).

2. *Neoadjuvant Chemotherapy*

NCT was administered to 70 patients (50%), mostly with the purpose of conversion to resectability but in some cases, as true neoadjuvant therapy. The remaining 70 patients (50%) formed the non-neoadjuvant chemotherapy (Non-NCT) group. Sixty-three patients received only one line of chemotherapy, while seven patients were treated with a second line. Chemotherapeutic regimens included 5-FU in only two (3%) patients, FOLFIRI in 48 (72%) patients and FOLFOX in 21 (31%) patients. Twenty-nine (43%) patients had additionally bevacizumab and 19 (28%) cetuximab in their chemotherapy protocol. A mean of 10.7±5.5 cycles (range 2-24) were administered. Thirty-eight (56%) patients received long-duration chemotherapy (more than nine cycles) while 30 (44%) received short-duration treatment (one to eight cycles). As is policy in our department, patients treated with or without bevacizumab underwent hepatectomy respectively six and four weeks after the end of NCT.

3. *Preoperative Liver Function*

Preoperative markers of hepatic function, such as transaminase levels [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], bilirubin, gamma-glutamyl transpeptidase (GGT), International Normalized Ratio (INR) and platelet count were collected (Table 1). The AST/ALT ratio, AST to Platelets Ratio Index (APRI) and Fibrosis 4 (Fib4) Score were also calculated, according to Ratti et al. (16)

Table 1. Preoperative laboratory data (mean value and standard deviation)

	NCT Group (n=70)	*Non-NCT Group (n=70)*	*p*
AST (IU/L)	32.2±15.4	30.56±20.5	0.608
ALT (IU/L)	31.36±25	31.24±29.177	0.979
GGT (IU/L)	118.1±160	87.2±140.1	0.226
Total Bilirubin (mg/dL)	0.92±1.45	0.75±0.58	0.367
Platelets ($x10^9$/L)	206.2±61.3	213.3±71.1	0.53
INR	1.077±0.115	1.077±0.118	0.971
AST/ALT	1.164±0.391	1.169±0.512	0.956
APRI	0.577±0.451	0.513±0.351	0.356
Fib4	2.016±1.01	1.887±0.829	0.416

4. Intraoperative Data

In all patients, the operative technique consisted of abdominal exploration for exclusion of extrahepatic disease and intraoperative ultrasonography for confirmation of preoperative imaging. Parenchymal transection was performed with ultrasonic dissection with CUSA™ Ultrasonic Surgical Aspirator or Kelly-clamp crush technique, with hepatic inflow occlusion in intermittent strategy (15 minutes clamping with 5 minutes reperfusion for patients with normal liver; in patients with chronic liver disease, clamping time was 10 minutes).

Surgical procedures are summarized in Table 2. Minor resection was performed in 87 (62%) patients, while the remaining 53 (38%) underwent major hepatectomy (resection of three or more Coinaud segments). During the study period only three patients (2%) underwent laparoscopic CRLM surgery. Nineteen patients underwent additional portal vein embolization or ligation as a remnant liver volume manipulation technique.

Table 2. List of hepatectomies (per type of surgery performed)

	n (%)
Right Hepatectomy	
Classic	21 (15%)
Extended	6 (4.3%)
Classic + Left Atypical Resections	5 (3.6%)
Extended + Left Atypical Resections	1 (0.7%)
Left Hepatectomy	
Classic	4 (2.9%)
Extended	3 (2.1%)
Classic + Right Atypical Resections	1 (0.7%)
Extended + Right Atypical Resections	2 (1.4%)
Other anatomical resections	
Segmentectomy	19 (13.6%)
Bisegmentectomy	14 (10%)
Trisegmentectomy	3 (2.1%)
Atypical resections	
< 4	24 (17.1%)
≥ 4	9 (6.4%)
Other anatomical resections + Atypical resections	28 (20%)

Sixty-four (46%) patients underwent simultaneous cholecystectomy, three (2%) biloma or abscess drainage during rehepatectomy, two (1%) simultaneous splenectomy and four (3%) patients splenic artery ligation. Two (1%) patients were submitted to radiofrequency ablation. A mean of 346.5±855 and 217.5±350 mL of red blood cells and fresh-frozen plasma, respectively, were administered (range of 0-5850 and 0-1500 mL, respectively). Hepatic pedicle clamping was performed in 98 patients, for a mean time of 28.2±23.2 minutes (range 0-104 minutes).

5. *Postoperative Course*

Transaminase levels (AST and ALT), bilirubin and INR were collected on postoperative days one, three, five and seven (Table 3). The median hospital length of stay (LOS) was 7 days (range 3-71).

Table 3. Postoperative laboratory data (mean value and standard deviation)

	NCT Group (n=70)	*Non-NCT Group (n=70)*	*p*
1st Day			
AST (IU/L)	838.6±1202.2	652.6±649.0	0.264
ALT (IU/L)	735.4±633.6	738.2±629.4	0.979
Total Bilirubin (mg/dL)	1.64±1.74	1.57±1.23	0.787
INR	1.556±0.281	1.486±0.237	0.117
3rd Day			
AST (IU/L)	252.4±248.1	185.4±187.3	0.084
ALT (IU/L)	481.3±396.9	421.1±335.7	0.342
Total Bilirubin (mg/dL)	1.70±2.40	1.49±1.78	0.579
INR	**1.397±0.257**	**1.292±0.192**	**0.01**
5th Day			
AST (IU/L)	114.5±165.6	124.0±368.0	0.864
ALT (IU/L)	252.1±208.4	274.6±342.0	0.674
Total Bilirubin (mg/dL)	1.82±2.90	1.78±2.18	0.941
INR	1.331±0.371	1.222±0.227	0.081
7th Day			
AST (IU/L)	61.5±45.8	108.0±234.1	0.253
ALT (IU/L)	144.64±117.8	175.45±217.5	0.473
Total Bilirubin (mg/dL)	2.19±3.45	2.34±3.84	0.872
INR	1.309±0.204	1.240±0.288	0.268

Postoperative morbidity was definedand graded up to the 90th postoperative day, according to Dindo-Clavien.(17)Patients grading IIIa or higher were further classified with major morbidity.Postoperative liver failure (POLF) was defined by the "Fifty-Fifty criteria", according to Balzan et al, (18)as the presence, on fifth postoperative day, of bilirubin levels above 2.9 mg/dL (50µmol/L) and INR above 1.7 (prothrombin time <50%).Severity of liver failure was defined according to Rabhari et al.(19) Bile leakage and biloma were defined and graded according to Koch et al.(20)Liver-specific morbidity was defined as any complication directly related to liver resection, namely POLF, bile leakage, biliary stenosis, bleeding or intra-abdominal abscess.

6. *Patient characteristics: Neoadjuvant CT vs. Non-Neoadjuvant CT*

Comparing the *NCT Group* with *Non-NCTGroup*, we can verify that both number (4.04 vs. 1.79, p<0.001) and diameter (4.63cm vs. 3.53cm, p=0.045) of hepatic lesions were bigger in patients that underwent NCT. Also the proportion of cases with synchronous CRLM diagnosis (77.1% vs. 17.1%, p<0.001), major hepatectomies (48.6% vs. 27.1%, p=0.014) and two-stage hepatectomies (20% vs. 0%, p<0.001) was significantly larger in *NCT Group* when compared to *Non-NCT Group*. The remaining variables had a similar distribution between both groups (Table 4).

Table 4. Neoadjuvant Chemotherapy (NCT) Group vs. Non-NCT Group

	NCT Group (n=70)	*Non-NCT Group (n=70)*	*OR*	*CI 95%*	*p*
Patients					
Age (years)	62.61±9.28	64.94±10.75			0.172
Lesions					
Number	**4.0±3.55**	1.79±1.54			**<0.001**
Diameter (millimeters)	**4.63±4.11**	3.53±1.86			**0.045**
Diagnosis					
Synchronous	**54 (77.1%)**	**12 (17.1%)**	**16.313**	**7.076-37.605**	**<0.001**
Metachronous	16 (22.9%)	58 (82.9%)			
Resection					
Synchronous	9 (12.9%)	3 (4.3%)	3.295	0.853-12.735	0.128
Metachronous	61 (87.1%)	67 (95.7%)			
Type of Hepatectomy					
Major	**34 (48.6%)**	**19 (27.1%)**	**2.535**	**1.252-5.131**	**0.014**
Minor	36 (51.4%)	51 (72.9%)			
Two-stage Hepatectomy					
Yes	**14 (20%)**	**0 (0%)**	**0.444**	**0.366-0.540**	**<0.001**
No	56 (80%)	70 (100%)			
Intraoperative					
RBC Transfusion (mL)	450±1093.5	247.5±549			0.186
Plasma Transfusion (mL)	255±390	180±312.5			1.240
Pringle Maneuver (minutes)	30.34±24.87	25.95±21.32			0.285

7. *Pathological Analysis*

We reviewed archival material from each patient. A sample of non-tumoral liver parenchyma distant from the neoplasm was collected and a routine staining with hematoxylin and eosin (H&E), Masson's trichrome and reticulin was conducted. The histopathologic review was blinded, without previous knowledge of patient's data (such as preoperative chemotherapy) or outcome.

SOS-related lesions were classified as follows: sinusoidal dilation, according to Rubbia-Brandt et al (13): absent, mild (centrilobular involvement limited to less than one-third of lobular area), moderate (centrilobular involvement up to two-thirds of lobular area) and severe (complete lobular involvement); nodular regeneration, classified according to Wanless et al (21): absent, mild (focal occasional nodular hyperplasia, detected only on reticulin staining), moderate [focal distinct nodular regenerative hyperplasia (NRH), detected on H&E and confirmed on reticulin staining] and severe (diffuse NRH, distinct on H&E and highlighted in reticulin staining); perisinusoidal hemorrhage, peliosis, necrosis and fibrosis: absent or present (Figure 2).

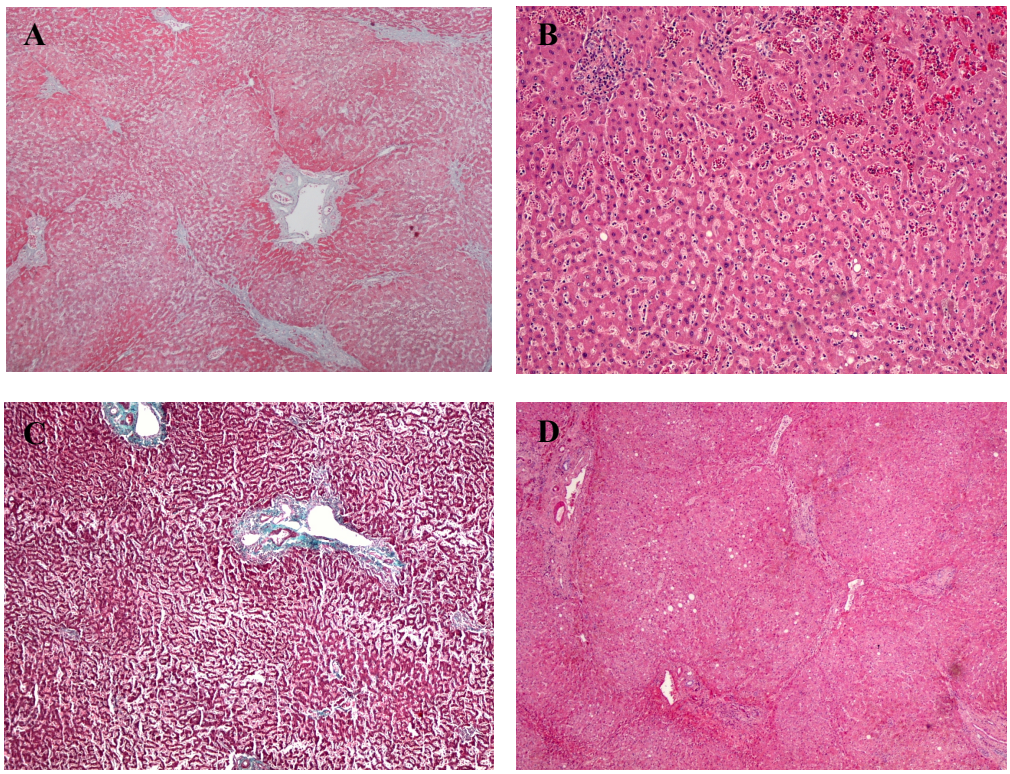

Figure 2. **(A)** Moderate fibrosis, H&E, 40x; **(B)** Severe sinusoidal dilation with perisinusoidal hemorrhage, H&E, 100x; **(C)** Sinusoidal dilation, Masson's trichrome, 40x; **(D)** Severe HNR, H&E, 40x.

Accordingly, we classified SOS as absent, mild (in the presence of mild sinusoidal dilation without necrosis or peliosis), and moderate to severe (in the presence of mild sinusoidal dilation combined with necrosis, in the presence of moderate or severe sinusoidal dilation, or in the presence of peliosis) (Table 5).

CASH-related lesions were classified according to Kleiner et al (22) as follows: steatosis (0-3): 0 for absent (less than 5% of hepatocytes involved), 1 for mild (5 to 33%), 2 for moderate (33% to 66%) and 3 for severe (more than 66%); lobular inflammation (0-3): 0 for absent, 1 for mild (less than two foci per 200x field), 2 for moderate (two to four foci per 200x field) and 3 for severe (more than 4 foci per 200x field); ballooning degeneration (0-2): 0 for absent, 1 for mild (few cells) and 2 for moderate to severe (many cells) (Figure 3).

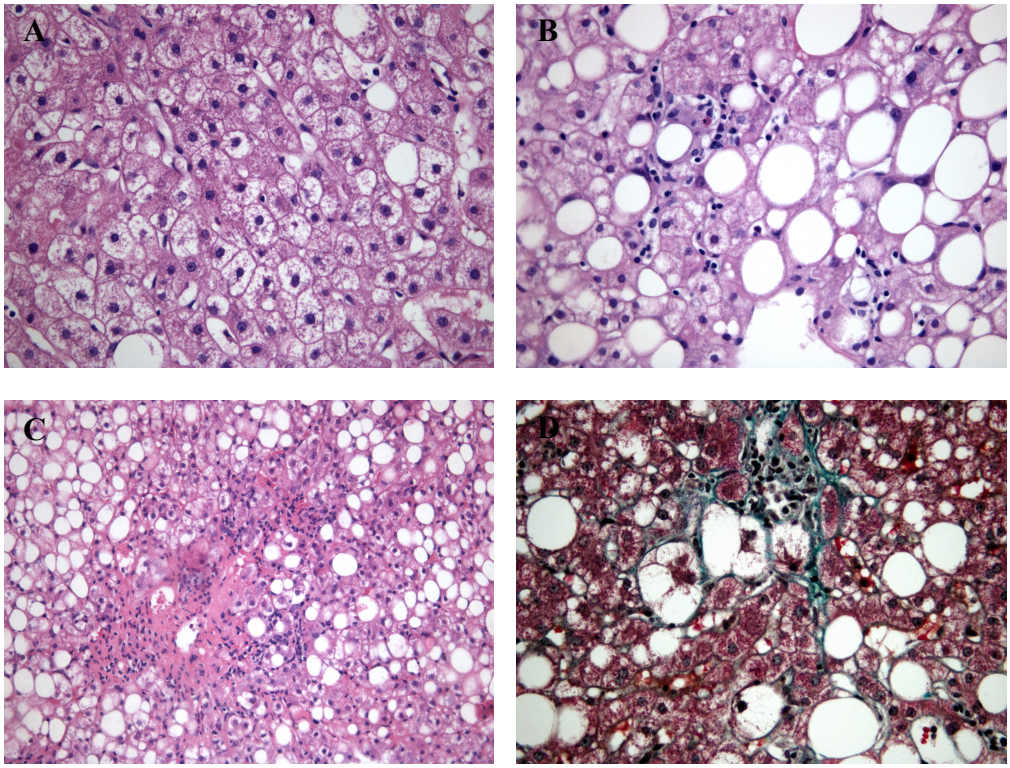

Figure 3. **(A)** Ballooning degeneration, H&E, 400x; **(B)** Steatosis, H&E, 400x; **(C)** CASH, H&E, 200x; **(D)** CASH and pericellular fibrosis, Masson's trichrome, 400x.

A score from 0 to 8 was calculated for every patient and used to classify CASH as it follows (Table 5): absent (less than 3 points), borderline CASH (3 or 4 points) and definite CASH (more than 4 points). (22)

Other evaluated lesions included apoptosis and atrophy, classified either as absent or present.

Table 5. SOS and CASH classification

Lesion	***Parameters***
Sinusoidal Obstruction Syndrome (SOS)	
Absent	None of the below
Mild SOS	Sinusoidal dilation < 1/3 lobular area
Moderate to Severe SOS	Sinusoidal dilation < 1/3 lobular area + Necrosis
	Sinusoidal dilation > 2/3 lobular area
	Peliosis
Chemotherapy-Associated Steatohepatitis (CASH)	
Absent	Score 0-2
Borderline CASH	Score 3-4
Definite CASH	Score ≥5

8. *Statistical Analysis*

Metric variables were described by mean ± SD, and mean values were compared using Student's *t* tests. Categorical variables were described by absolute and relative frequencies, and the distributions were compared using Chi squared tests. A two-sided *p* value of ≤0.05 was considered to indicate statistical significance. A binary logistic regression was conducted to examine the individual effect of each parameter on postoperative morbidity and mortality. SPSS (Version 22.0, Chicago, IL) was used for statistical calculations.

Results

1. *Postoperative Morbidity and Mortality*

Postoperative complications were present in 31 (22.1%) patients and are displayed in both figure 4 and table 6. Non-liver-specific morbidity was reported in 7 (5%) patients. Liver-specific complications, present in 25 (17.9%) patients, accounted for biloma or intra-abdominal abscess in seven patients, biliary fistula in five, biliary stenosis in two, liver hemorrhage in two, and liver failure in nine (6.4%) patients (Table 6). Twenty-one (15%) patients were classified with major morbidity. Six (4.3%) postoperative fatalities were reported, five of which due to liver failure.

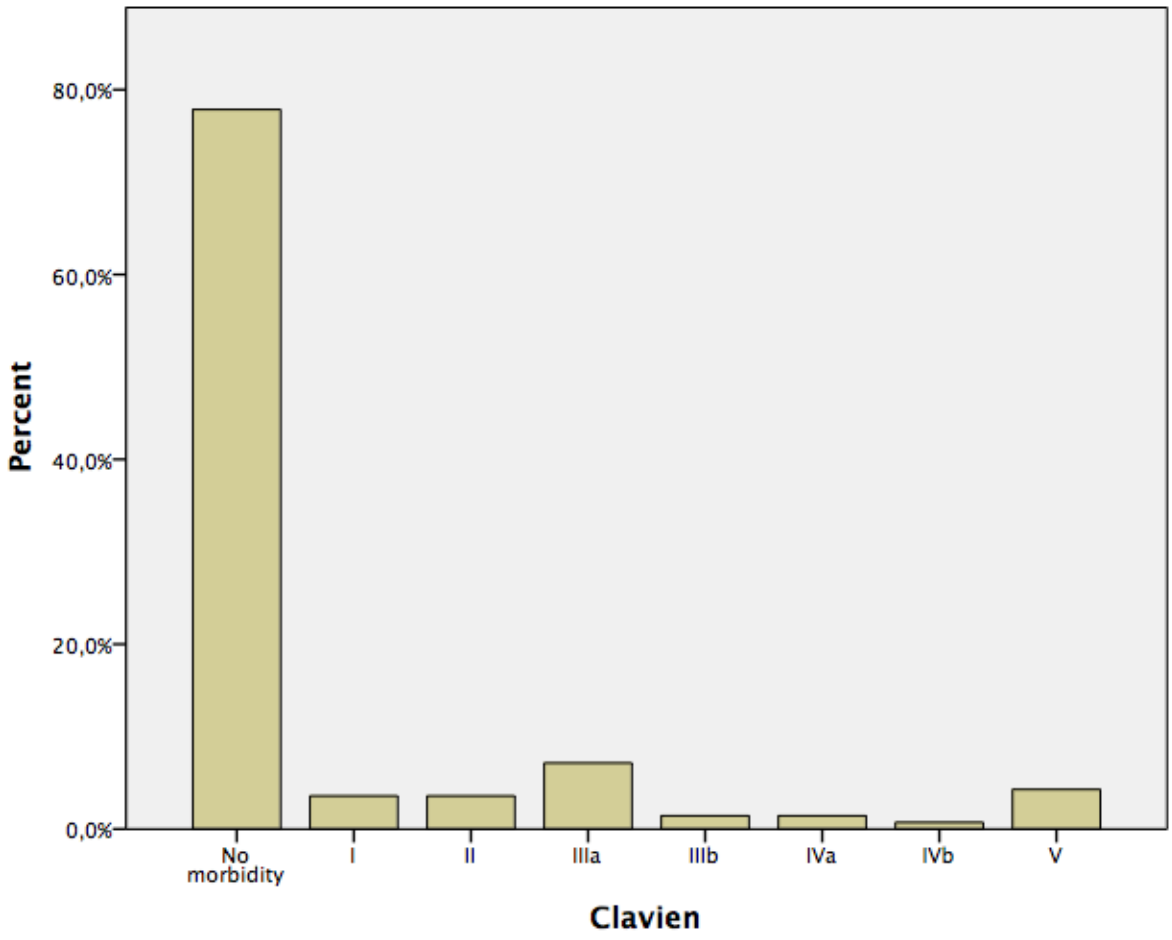

Figure 4. Postoperative complications, according to Dindo-Clavien

Table 6. Postoperative morbidity and mortality

	n (%)
Liver-specific morbidity	25 (17.9%)
Biloma/Abscess	7 (5%)
Biliary Fistula	5 (3.6%)
Biliary Stenosis	2 (1.4%)
Liver Hemorrhage	2 (1.4%)
Postoperative Liver Failure	9 (6.4%)
Grade B	4 (2.9%)
Grade C	5 (3.6%)
Non-liver-specific morbidity	7 (5%)
Surgical Site Infection	2 (1.4%)
Pleural Effusion	2 (1.4%)
Venous Thrombosis	1 (0.7%)
Other	2 (1.4%)
Mortality	6 (4.3%)

2. *Impact of Neoadjuvant Chemotherapy on Liver Injury*

Patients who underwent NCT showed a higher prevalence of peliosis (25.7% vs. 11.6%, p=0.049), NRH (25.7% vs. 11.6%, p=0.049) and moderate to severe SOS (21.4% vs. 4.3%, p=0,004), when compared with the non-NCT group (Table 7). The type of chemotherapeutical agent (oxaliplatin or irinotecan) did not significantly correlate with any particular lesion. However, bevacizumab offered significant protection against severe and moderate SOS. Only 3 (10.3%) patients treated with bevacizumab presented moderate to severe SOS, against 12 (31,6%) not treated with this agent (OR 0.25, CI 95% 0.063-0.991, p=0.045). Longer NCT (more than 9 cycles) did not associate with more liver injury.

Table 7. Impact of neoadjuvant chemotherapy on liver injury

	NCT Group (n=70)	*Non-NCT Group (n=70)*	*OR*	*CI 95%*	*p*
SOS lesions					
Sinusoidal Dilation	42 (60%)	31 (44.3%)	1.887	0.964-3.694	0.09
Peliosis	**6 (8.6%)**	**0 (0%)**	**1.094**	**1.018-1.175**	**0.028**
Fibrosis	16 (22.9%)	18 (25.7%)	1.168	0.539-2.532	0.844
NRH	**18 (25.7%)**	**8 (11.4%)**	**2.639**	**1.061-6.566**	**0.049**
Moderate to Severe SOS	**15 (21.4%)**	**3 (4.3%)**	**6.091**	**1.677-22.124**	**0.004**
CASH lesions					
Steatosis	24 (34.3%)	23 (32.9%)	1.066	0.529-2.151	1
Moderate to Severe Steatosis	9 (12.9%)	6 (8.6%)	1.574	0.529-4.685	0.586
CASH	14 (20%)	9 (12.9%)	1.694	0.680-4.220	0.362

3. *Impact of previous morbidity on liver injury*

Diabetes Mellitus

Diabetic patients had significantly higher prevalence of both steatosis (59.3% vs. 27.4%, p=0.003) and moderate to severe steatosis (25.9% vs. 7.1%, p=0.01). However, a reduced risk for sinusoidal dilation (33.3% vs. 56.6%, p=0.034) was also reported (Table 8).

Table 8. Impact of diabetes mellitus on chemotherapy-induced liver injury

	Diabetes Mellitus (n=27)	*No Diabetes Mellitus (n=113)*	*OR*	*CI 95%*	*p*
Steatosis	**16 (59.3%)**	31 (27.4%)	**3.848**	**1.609-9.200**	**0.003**
Moderate to Severe Steatosis	**7 (25.9%)**	8 (7.1%)	**4.594**	**1.497-14.099**	**0.01**
Sinusoidal Dilation	9 (33.3%)	**64 (56.6%)**	**0.383**	**0.158-0.925**	**0.034**

4. *Predictive Value of Liver Function Tests for Liver Injury*

Comparison between preoperative laboratory values for different chemotherapy-induced liver lesions is displayed in tables 9 and 10.

Table 9. Preoperative laboratory data according to presence of SOS-related lesions (mean value and standard deviation)

	Study population (n=140)	*Sinusoidal Dilation/SOS (n=73)*	*Peliosis (n=6)*	*Fibrosis (n=34)*	*NRH (n=26)*	*Moderate to Severe SOS (n=18)*
AST (IU/L)	31.3±18.1	32.8±19.2	37.0±23.3	34.6±23.2	**38.6±19.6**[b]	34.1±17.7
ALT (IU/L)	31.3±27.1	33.3±33.3	56.5±72.0	38.1±46.0	38.0±38.4	36.0±42.3
GGT (IU/L)	102.5±150.6	115.7±183.8	345.7±337.9	167.3±241.8	144.8±210.8	**210.6±240.9**[e]
Total Bilirubin (mg/dL)	0.83±1.1	0.89±1.40	2.62±4.60	1.13±1.97	1.20±2.25	1.35±2.68
Platelets ($x10^9$/L)	209.8±66.3	207.6±70.3	199.0±108.0	199.2±67.8	214.9±82.7	213.9±74.9
INR	1.077±0.116	1.083±0.120	1.117±0.107	1.102±0.131	1.094±0.112	**1.145±0.158**[f]
AST/ALT	1.167±0.455	1.169±0.381	0.945±0.332	1.205±0.502	1.271±0.469	1.145±0.335
APRI	0.544±0.403	0.586±0.463	0.997±1.280	0.674±0.630	**0.693±0.641**[c]	0.667±0.757
Fib4	1.950±0.921	2.065±0.966	2.494±1.765	**2.273±1.143**[a]	**2.298±1.085**[d]	2.143±1.214

[a]Fib4 in patients without fibrosis of 1.848±0.819 (p=0.02)
[b]AST in patients without NRH of 29.6±17.5 IU/L (p=0.023)
[c]APRI in patients without NRH of 0.507±0.321 (p=0.037)
[d]Fib4 in patients without NRH of 1.856±0.853 (p=0.028)
[e]GGT in patients without moderate to severe SOS of 86.5±125.9 IU/L (p=0.046)
[f]INR in patients without moderate to severe SOS of 1.067±0.106 (p=0.007)

Table 10. Preoperative laboratory data according to presence of CASH-related lesions (mean value and standard deviation)

	Study population (n=140)	*Steatosis (n=47)*	*Moderate to Severe Steatosis (n=15)*	*CASH (n=23)*
AST (IU/L)	31.3±18.1	**27.73±10.9**[a]	28.2±12.8	26.7±11.5
ALT (IU/L)	31.3±27.1	30.7±18.6	38.6±23.3	30.4±21.3
GGT (IU/L)	102.5±150.6	80.6±95.6	68.0±53.3	61.6±47.6
Total Bilirubin (mg/dL)	0.83±1.1	0.73±0.60	0.70±0.45	0.75±0.52
Platelets ($x10^9$/L)	209.8±66.3	207.4±64.5	216.5±69.1	225.5±77.6
INR	1.077±0.116	**1.042±0.076**[b]	**1.006±0.464**[d]	1.052±0.82
AST/ALT	1.167±0.455	**1.028±0.276**[c]	**0.818±0.244**[e]	1.029±0.320
APRI	0.544±0.403	0.482±0.249	0.434±0.170	0.424±0.205
Fib4	1.950±0.921	1.743±0.808	**1.357±0.437**[f]	**1.579±0.779**[g]

[a]AST in patients without steatosis of 33.1±20.5 IU/L (p=0.048)
[b]INR in patients without steatosis of 1.095±0.128 (p=0.003)
[c]AST/ALT in patients without steatosis of 1.234±0.507 (p=0.002)
[d]INR in patients without moderate to severe steatosis of 1.086±0.119 (p<0.001)
[e]AST/ALT in patients without moderate to severe steatosis of 1.206±0.457 (p=0.002)
[f]Fib4 in patients without moderate to severe steatosis of 2.018±0.938 (p<0.001)
[g]Fib4 in patients without CASH of 2.021±0.932 (p=0.039)

Additionally, elevated Gamma-GT levels, above 118.5 U/L (AUC 0.768, p<0.001, sensitivity 61%, specificity 85.1%), were found to have a predictive value for the presence of moderate to severe SOS (Figure 5A).

GGT levels above 137.5 U/L (AUC 0.853, p=0.004, sensitivity 83%, specificity of 86.5%) also predicted the presence of peliosis (Figure 5B).

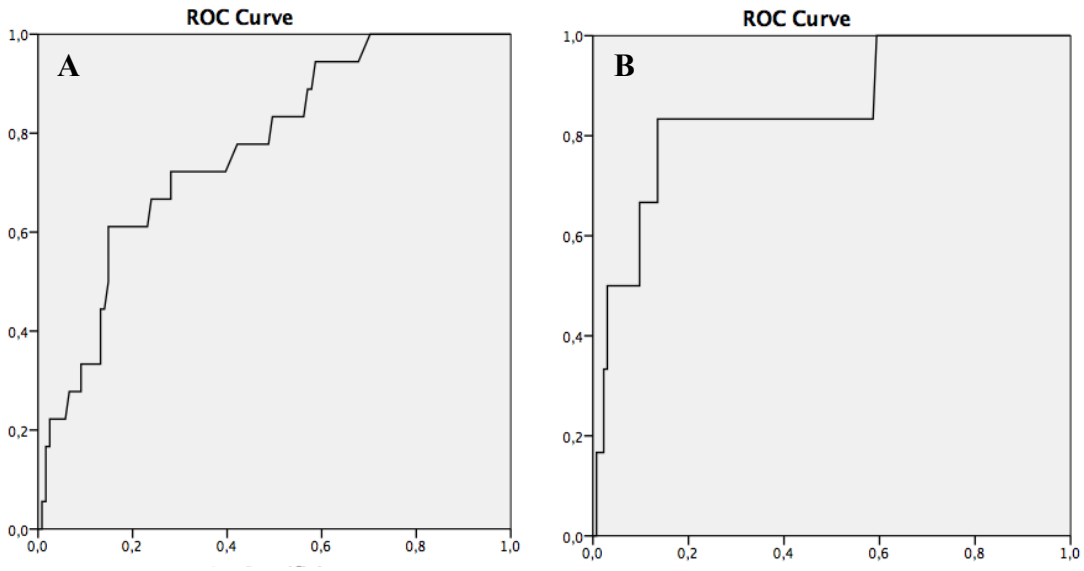

Figure 5. Predictive value of GGT for **(A)** moderate to severe SOS and **(B)** peliosis.

5. *Impact of Neoadjuvant Chemotherapy on Morbidity and Mortality*

No significant association between the administration of NCT and postoperative complications or mortality was found (Table 11). Mean LOS was also similar between the two groups (NCT group 10.9±11.8 vs. non-NCT group 10.6±10.2, p=0.855).

Table 11. Impact of NCT on postoperative morbidity and mortality

	NCT (n=70)	*No NCT (n=70)*	*OR*	*CI 95%*	*p*
Morbidity	18 (25.7%)	13 (18.6%)	1.518	0.678-3.399	0.416
Liver-specific Morbidity	15 (21.4%)	10 (14.3%)	1.636	0.679-3.944	0.378
Liver Failure	7 (10%)	2 (2.9%)	3.778	0.756-18.869	0.165
Major Morbidity	12 (17.1%)	9 (12.9%)	1.402	0.550-3.576	0.637
Mortality	4 (5.7%)	2 (2.9%)	2.061	0.365-11.633	0.681

The number of NCT cycles did not correlate either with postoperative morbidity or mortality, or with a higher LOS (<9 cycles 12.0±13.3 vs. ≥9 cycles 10.5±10.9, p=0.605).

6. *Impact of liver injury on morbidity and mortality*

Steatosis

Steatosis (Table 12) reduced the risk of postoperative complications (10.6% vs. 28%, p=0.014) and major morbidity (6.4% vs. 19.4%, p=0.047).

Table 12. Impact of steatosis on postoperative morbidity and mortality

	Steatosis (n=47)	*No Steatosis (n=93)*	*OR*	*CI 95%*	*p*
Morbidity	**5 (10.6%)**	**26 (28%)**	**0.307**	**0.109-0.861**	**0.014**
Liver-specific Morbidity	4 (8.5%)	21 (22.6%)	0.319	0.103-0.991	0.06
Liver Failure	1 (2.1%)	8 (8.6%)	0.231	0.028-1.904	0.272
Major Morbidity	**3 (6.4%)**	**18 (19.4%)**	**0.284**	**0.079-1.019**	**0.047**
Mortality	1 (2.1%)	5 (5.4%)	0.383	0.43-3.373	0.664

Moderate and severe steatosis (Table 13) related with the absence of postoperative complications (0% vs. 24.8%, p=0.019).

Table 13. Impact of moderate and severe steatosis on postoperative morbidity and mortality

	Moderate and Severe Steatosis (n=15)	*Mild or No Steatosis (n=125)*	*OR*	*CI 95%*	*p*
Morbidity	**0 (0%)**	**31 (24.8%)**	**0.862**	**0.800-0.930**	**0.019**
Liver-specific Morbidity	0 (0%)	25 (20%)	0.87	0.810-0.933	0.073
Liver Failure	0 (0%)	9 (7.2%)	0.885	0.833-0.942	0.597
Major Morbidity	0 (0%)	21 (16.8%)	0.874	0.816-0.936	0.127
Mortality	0 (0%)	6 (4.8%)	0.888	0.836-0.943	1

CASH

The presence of CASH (Table 14) reduced the prevalence of overall morbidity (4.3% vs. 25.6%, p=0.016).

Table 14. Impact of CASH on postoperative morbidity and mortality

	CASH (n=23)	*No CASH (n=117)*	*OR*	*CI 95%*	*p*
Morbidity	**1 (4.3%)**	**30 (25.6%)**	**0.132**	**0.017-1.020**	**0.016**
Liver-specific Morbidity	1 (4.3%)	24 (20.5%)	0.176	0.023-1.373	0.077
Liver Failure	0 (0%)	9 (7.7%)	0.824	0.762-0.892	0.355
Major Morbidity	1 (4.3%)	20 (17%)	0.22	0.028-1.731	0.198
Mortality	0 (0%)	6 (5.1%)	0.828	0.767-0.895	0.589

Sinusoidal Dilation

The presence of sinusoidal dilation (Table 15) increased the risk of general morbidity (31.5% vs. 12%, p=0.008), liver-specific complications (26% vs. 9%, p=0.014) and major morbidity (22% vs. 7.5%, p=0.019).

Table 15. Impact of sinusoidal dilation on postoperative morbidity and mortality

	Sinusoidal Dilation (n=73)	*No Sinusoidal Dilation (n=67)*	*OR*	*CI 95%*	*p*
Morbidity	**23 (31.5%)**	**8 (12%)**	**3.393**	**1.395-8.247**	**0.008**
Liver-specific Morbidity	**19 (26%)**	**6 (9%)**	**3.577**	**1.332-9.610**	**0.014**
Liver Failure	7 (9.6%)	2 (3%)	3.447	0.690-17.216	0.169
Major Morbidity	**16 (22%)**	**5 (7.5%)**	**3.481**	**1.198-10.114**	**0.019**
Mortality	4 (5.5%)	4 (6%)	1.884	0.334-10.636	0.682

Peliosis

Peliosis (Table 16) was a risk factor for liver failure (50% vs. 4.5%, p=0.003), major morbidity (50% vs. 12.9%, p=0.003) and mortality (50% vs. 2.2%, p=0.001).

Table 16. Impact of peliosis on postoperative morbidity and mortality

	Peliosis (n=6)	*No Peliosis (n=134)*	*OR*	*CI 95%*	*p*
Morbidity	3 (50%)	28 (20.9%)	3.786	0.724-19.783	0.122
Liver-specific Morbidity	3 (50%)	22 (16.4%)	5.091	0.964-26.890	0.07
Liver Failure	**3 (50%)**	**6 (4.5%)**	**21.333**	**3.535-128.745**	**0.003**
Major Morbidity	**3 (50%)**	**18 (12.9%)**	**6.444**	**1.206-34.425**	**0.044**
Mortality	**3 (50%)**	**3 (2.2%)**	**43.667**	**6.105-312.316**	**0.001**

Fibrosis

The presence of fibrosis (Table 17) increased the prevalence of liver failure (14.7% vs. 3.8%, p=0.038), major morbidity (26.5% vs. 11.3%, p=0.05) and mortality (11.8% vs. 1.9%, p=0.031).

Table 17. Impact of fibrosis on postoperative morbidity and mortality

	Fibrosis (n=34)	*No Fibrosis (n=106)*	*OR*	*CI 95%*	*p*
Morbidity	12 (35.3%)	19 (17.9%)	2.498	1.056-5.907	0.55
Liver-specific Morbidity	10 (29.4%)	15 (14.2%)	2.528	1.009-6.330	0.69
Liver Failure	**5 (14.7%)**	**4 (3.8%)**	**4.397**	**1.108-17.440**	**0.038**
Major Morbidity	**9 (26.5%)**	**12 (11.3%)**	**2.82**	**1.069-7.441**	**0.05**
Mortality	**4 (11.8%)**	**2 (1.9%)**	**6.933**	**1.211-39.712**	**0.031**

NRH

Patients with NRH (Table 18) did not reveal any correlation with postoperative morbidity or mortality.

Table 18. Impact of moderate and severe NRH on postoperative morbidity and mortality

	NRH (n=26)	*NRH (n=113)*	*OR*	*CI 95%*	*p*
Morbidity	5 (19.2%)	25 (22.1%)	0.838	0.287-2.448	1
Liver-specific Morbidity	5 (19.2%)	10 (8.8%)	1.107	0.373-3.288	0.785
Liver Failure	4 (15.4%)	5 (4.4%)	3.927	0.976-15.806	0.63
Major Morbidity	3 (11.5%)	17 (15%)	0.737	0.199-2.727	0.766
Mortality	2 (7.7%)	4 (3.5%)	2.271	0.393-13.120	0.312

Moderate and Severe SOS

Patients with moderate and severe SOS (Table 19) had a higher prevalence of postoperative complications (44.4% vs. 18.9%, p=0.029), liver failure (27.8% vs. 3.3%, p=0.002), liver-specific morbidity (38.9% vs. 14.8%, p=0.021), major complications (33.3% vs. 12.3%, p=0.031) and mortality (16.7% vs. 2.5%, p=0.028).

Table 19. Impact of moderate and severe SOS on postoperative morbidity and mortality

	Moderate and Severe SOS (n=18)	*Mild or No SOS (n=122)*	*OR*	*CI 95%*	*p*
Morbidity	**8 (44.4%)**	**23 (18.9%)**	**3.443**	**1.224-9.689**	**0.29**
Liver-specific Morbidity	**7 (38.9%)**	**18 (14.8%)**	**3.677**	**1.259-10.736**	**0.021**
Liver Failure	**5 (27.8%)**	**4 (3.3%)**	**11.346**	**2.704-47.608**	**0.002**
Major Morbidity	**6 (33.3%)**	**15 (12.3%)**	**3.567**	**1.165-10.921**	**0.031**
Mortality	**3 (16.7%)**	**3 (2.5%)**	**7.933**	**1.467-42.909**	**0.028**

However, patients with moderate and severe SOS underwent significantly more extensive hepatectomies (p=0.003) and longer periods of hepatic pedicle clamping (p=0.021). Also the number of lesions was higher in the patients with moderate to severe SOS (Table 20).

Table 20. Intraoperative parameters in patients with and without moderate to severe SOS

	Moderate and Severe SOS (n=18)	*Mild or No SOS (n=122)*	*OR*	*CI 95%*	*p*
Lesions					
Number	4.17±3.808	2.72±2.764			0.051
Diameter (millimeters)	4.606±3.382	4.001±3.199			0.459
Type of Hepatectomy					
Major	**13 (72.2%)**	**40 (32.8%)**	**5.33**	**1.777-15.988**	**0.003**
Minor	5 (27.8%)	82 (67.2%)			
Intraoperative					
RBC Transfusion (mL)	675±1323	297±771.8			0.104
Plasma Transfusion (mL)	360±387	195±346			0.084
Pringle Maneuver (minutes)	**40.24±25.03**	**26.33±22.45**			**0.021**

7. *Multivariate analysis*

On multivariate analysis, sinusoidal dilation was found to be an independent risk factor for postoperative morbidity (Table 21), increasing almost four times the risk of overall complications (p=0.02, OR 3.884, CI 95% 1.233-12.232) and five times the risk of liver-specific complications (p=0.016, OR 4.921, CI 95% 1.346-17.995).

Table 21. Multivariate analysis for selected hepatic lesions and postoperative morbidity and mortality

	Morbidity	*Liver-specific Morbidity*	*Liver Failure*	*Major Morbidity*	*Mortality*
Sinusoidal Dilation					
p	**0.020**	**0.016**	0.811	0.056	0.497
OR	**3.884**	**4.921**	0.751	3.690	0.383
CI 95%	**1.233-12.232**	**1.346-17.995**	0.072-7.838	0.968-14.072	0.024-6.084
Fibrosis					
p	0.317	0.254	0.606	0.423	0.199
OR	1.808	2.046	1.613	1.731	4.626
CI 95%	0.567-5.736	0.599-6.991	0.262-9.946	0.453-6.620	0.447-47.850
NRH					
p	0.143	0.249	0.227	0.102	0.876
OR	0.373	0.454	3.235	0.248	1.234
CI 95%	0.099-1.398	0.119-1.736	0.482-21.720	0.047-1.321	0.087-17.458
Moderate and Severe SOS					
p	0.848	0.753	0.141	0.975	0.586
OR	1.145	0.791	4.859	0.975	2.191
CI 95%	0.286-4.592	0.184-3.409	0.593-39.817	0.200-4.767	0.130-37.005
Steatosis					
p	0.393	0.282	0.915	0.447	0.965
OR	0.521	0.377	1.145	0.499	0.942
CI 95%	0.117-2.325	0.064-2.229	0.095-13.753	0.083-2.997	0.065-13.589
CASH					
p	0.307	0.604	0.998	0.651	0.998
OR	0.272	0.494	-	0.539	-
CI 95%	0.022-3.301	0.034-7.122	-	0.037-7.875	-
Hepatic Pedicle Clamping					
p	0.967	0.894	0.626	0.513	0.903
OR	0.976	0.920	0.636	1.604	1.162
CI 95%	0.315-3.023	0.270-3.130	0.103-3.923	0.389-6.624	0.105-12.874
Major Hepatectomy					
p	0.268	0.093	0.184	0.086	0.208
OR	1.747	2.511	3.333	2.786	4.541
CI 95%	0.652-4.685	0.859-7.345	0.565-19.663	0.863-8.992	0.431-47.818

Discussion

The aim of this study was to evaluate the impact of neoadjuvant chemotherapy for CRLM on liver parenchyma and the associated postoperative morbidity and mortality. Some studies already established the association between NCT and liver lesions such as SOS and CASH. (10–14) However, the impact of both the chemotherapy itself and the drug-induced liver lesions on postoperative morbidity remains controversial.

Our study population had a very high number of NCT cycles. Although this has been associated with an increase in liver injury (9) and postoperative morbidity (9,15), our results fail to confirm it. Nevertheless, there is a potential benefit in reducing the number of chemotherapy cycles prior to hepatectomy, not only to reduce its toxicity, but also to avoid complete radiologic response and subsequent "missing" liver metastases.

Vauthey et al (11) reported a correlation between irinotecan-based chemotherapy and SH, as well as an increase in postoperative mortality in patients with SH. Reissfelder et al (23) further confirmed this, but the type of NCT was not differentiated. Although our study population was heavily treated with NCT, especially irinotecan-based, no correlation with SH was found. Furthermore, SH did not increase postoperative mortality. In fact, both steatosis and CASH were associated with less postoperative morbidity, even though the multivariate analysis did not confirm it. The reason may be a more conservative intraoperative approach by the surgeon (such as less aggressive hepatectomy, reduced hepatic pedicle clamping or shorter intervals between clamping), as it is possible to macroscopically recognize the presence of liver steatosis. On the other hand, patients with steatosis had better preoperative biochemical parameters of liver function (lower INR and Fib4). Likewise, some particularities

of the Portuguese population, such as a possible protective effect of the Mediterranean diet on liver-specific and cardiovascular complications, have to be considered.

In our series, as previously reported, (11,12) the administration of NCT did not increase either postoperative complications or LOS. Univariate analysis revealed that patients undergoing NCT had a higher prevalence of sinusoidal dilation (p=0.09), peliosis (p=0.028), NRH (p=0.049) and moderate and severe SOS (p=0.004). However, the chemotherapy regimens did not statistically correlate with any specific lesion. Nevertheless, patients that had bevacizumab added to their NCT-protocol had a lower incidence of moderate and severe SOS (p=0.045). This protective effect of bevacizumab was first reported by Rubbia-Brandt et al (13) and was later confirmed in other studies. (9,14)

Surprisingly, in our study, diabetic patients had lower incidence of sinusoidal dilation (p=0.034). To our knowledge, only one study has reported this finding before. (24) A possible cause may be a protective role from oral antidiabetic medication. If confirmed, it could provide a clue to the pathogenesis of SOS.

It was also noticed that almost every SOS-related lesion significantly increased postoperative morbidity, in accordance with multiples studies. (25,26) We caution for a potential bias, as patients with moderate and severe SOS had higher tumor load, underwent major hepatectomies more often and had longer periods of hepatic pedicle clamping. However, the multivariate analysis confirmed sinusoidal dilation as an independent major risk factor for overall morbidity (p=0.02) and liver-specific complications (p=0.016).

Rubbia-Brandt et al (10) were the first to report an association between oxaliplatin-based NCT and sinusoidal dilation and to describe what was later named SOS. Ever since, other studies have confirmed this correlation between NCT (particularly with oxaliplatin) and SOS lesions (11–14) However, there is still no consensual classification for SOS, as several lesions, such as sinusoidal dilation, perisinusoidal hemorrhage, fibrosis and NRH, are included in this broad spectrum. SOS usually increases perioperative bleeding, (12) postoperative morbidity, (11,12,25) and LOS, (11,12) and decreases tolerance to hepatic pedicle clamping. (27) It also lowers regenerative capacity and increases risk of postoperative liver failure. (26)

Advances in pharmacogenomics will allow targeted selection of chemotherapeutic agents, maximizing its effect without the underlying toxicity. Meanwhile, preoperative identification of patients at risk of developing SOS is paramount. Spleen size (14), platelet count and other liver function ratios, such as Fib4 and APRI, (14,16) could help identify such patients. In our series, GGT predicted moderate and severe SOS with reasonable specificity and sensitivity ($p<0.001$). We propose that it could be included in a preoperative normogram to predict SOS. Other tools, such as indocyanine green retention rate (28) and transient elastography, (29,30) could be useful for detecting chemotherapy-associated liver injury.

Conclusion

NCT is a powerful tool for the multidisciplinary management of CRLM. However, it can also severely injure the liver parenchyma. In our series, steatosis and steatohepatitis were not associated with increased morbidity. As widely reported, SOS was the prevalent histologic pattern and was associated with increased morbidity. It can be predicted by preoperative GGT values and partially prevented by bevacizumab. Pathophysiology of SOS, however, remains elusive. Further studies are needed to address this issue.

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Bibliography

1. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical Score for Predicting Recurrence After Hepatic Resection for Metastatic Colorectal Cancer. Ann Surg [Internet]. 1999 Sep [cited 2014 Dec 24];230(3):309. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1420876&tool=pmcentrez&rendertype=abstract

2. Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncologist [Internet]. 2012 Jan [cited 2014 Dec 30];17(10):1225–39. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3481888&tool=pmcentrez&rendertype=abstract

3. Nordlinger B, Van Cutsem E, Rougier P, Köhne C-H, Ychou M, Sobrero A, et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. Eur J Cancer [Internet]. 2007 Sep [cited 2014 Dec 4];43(14):2037–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17766104

4. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004;240(4):644–57; discussion 657–8.

5. Viganò L, Capussotti L, Barroso E, Nuzzo G, Laurent C, Ijzermans JNM, et al. Progression while Receiving Preoperative Chemotherapy Should Not Be an Absolute Contraindication to Liver Resection for Colorectal Metastases. Annals of Surgical Oncology. 2012. p. 2786–96.

6. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009;27(22):3677–83.

7. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet [Internet]. 2008 Mar 22 [cited 2014 Dec 7];371(9617):1007–16. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2277487&tool=pmcentrez&rendertype=abstract

8. Blazer DG, Kishi Y, Maru DM, Kopetz S, Chun YS, Overman MJ, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol [Internet]. 2008 Nov 20 [cited 2015 Jan 11];26(33):5344–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18936472

9. Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol. 2010;17:2870–6.

10. Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol [Internet]. 2004 Mar 1 [cited 2015 Jan 11];15(3):460–6. Available from: http://annonc.oupjournals.org/cgi/doi/10.1093/annonc/mdh095

11. Vauthey J-N, Pawlik TM, Ribero D, Wu T-T, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol [Internet]. 2006 May 1 [cited 2014 Dec 10];24(13):2065–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16648507

12. Aloia T, Sebagh M, Plasse M, Karam V, Lévi F, Giacchetti S, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol [Internet]. 2006 Nov 1 [cited 2014 Dec 24];24(31):4983–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17075116

13. Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology [Internet]. 2010 Mar [cited 2014 Dec 24];56(4):430–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20459550

14. Hubert C, Sempoux C, Humblet Y, Van Den Eynde M, Zech F, Leclercq I, et al. Sinusoidal obstruction syndrome (SOS) related to chemotherapy for colorectal liver metastases: Factors predictive of severe SOS lesions and protective effect of bevacizumab. HPB. 2013;15:858–64.

15. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg [Internet]. 2006 Jan [cited 2014 Dec 24];243(1):1–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1449955&tool=pmcentrez&rendertype=abstract

16. Ratti F, Cipriani F, Catena M, Paganelli M, Aldrighetti L. Liver failure in patients treated with chemotherapy for colorectal liver metastases: Role of chronic disease scores in patients undergoing major liver surgery. A case-matched analysis. Eur J Surg Oncol [Internet]. Elsevier Ltd; 2014;40(11):1550–6. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0748798314005010

17. Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg [Internet]. 2004 Aug [cited 2014 Nov 6];240(2):205–13. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1360123&tool=pmcentrez&rendertype=abstract

18. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg [Internet]. 2005 Dec [cited 2014 Dec 27];242(6):824–8, discussion 828–9. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000658-200512000-00009

19. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery [Internet]. 2011 May [cited 2014 Nov 13];149(5):713–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21236455

20. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: A definition and grading of severity by the International Study Group of Liver Surgery. Surgery. 2011;149:680–8.

21. Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: A report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology. 1990;11:787–97.

22. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology [Internet]. 2005 Jun [cited 2015 Jan 2];41(6):1313–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15915461

23. Reissfelder C, Brand K, Sobiegalla J, Rahbari NN, Bork U, Schirmacher P, et al. Chemotherapy-associated liver injury and its influence on outcome after resection of colorectal liver metastases.

Surgery [Internet]. 2014 Feb [cited 2014 Dec 24];155(2):245–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24314883

24. Pilgrim CHC, Satgunaseelan L, Pham A, Murray W, Link E, Smith M, et al. Correlations between histopathological diagnosis of chemotherapy-induced hepatic injury, clinical features, and perioperative morbidity. HPB Off J Int Hepato-Pancreato-Biliary Assoc [Internet]. 2012 May [cited 2014 Dec 24];14(5):333–40. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3384853&tool=pmcentrez&rendertype=abstract

25. Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu M-P, Dufour P, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg [Internet]. 2008 Jan [cited 2015 Jan 11];247(1):118–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18156931

26. Narita M, Oussoultzoglou E, Chenard MP, Rosso E, Casnedi S, Pessaux P, et al. Sinusoidal obstruction syndrome compromises liver regeneration in patients undergoing two-stage hepatectomy with portal vein embolization. Surgery Today. 2011. p. 7–17.

27. Narita M, Oussoultzoglou E, Fuchshuber P, Chenard M-P, Rosso E, Yamamoto K, et al. Prolonged portal triad clamping increases postoperative sepsis after major hepatectomy in patients with sinusoidal obstruction syndrome and/or steatohepatitis. World J Surg [Internet]. 2012 Aug [cited 2014 Dec 24];36(8):1848–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22456802

28. Takamoto T, Hashimoto T, Sano K, Maruyama Y, Inoue K, Ogata S, et al. Recovery of liver function after the cessation of preoperative chemotherapy for colorectal liver metastasis. Ann Surg Oncol [Internet]. 2010;17:2747–55. Available from: papers://fb79e715-13ff-49fd-a3e5-7f0e37b34256/Paper/p3567

29. Fontanilla T, Hernando CG, Claros JC, Bautista G, Minaya J, Del V C, et al. Acoustic radiation force impulse elastography and contrast-enhanced sonography of sinusoidal obstructive syndrome (Veno-occlusive Disease): preliminary results. JUltrasound Med. 2011;30:1593–8.

30. Fung J, Poon RTP, Yu WC, Chan SC, Chan ACY, Chok KSH, et al. Use of Liver Stiffness Measurement for Liver Resection Surgery: Correlation with Indocyanine Green Clearance Testing and Post-Operative Outcome. PLoS One. 2013;8(8):1–6.