Hepatotoxicities Induced by Neoadjuvant Chemotherapy in Colorectal Cancer Liver Metastases: Distinguishing the True From the False

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ABSTRACT

BACKGROUND: Pre-operative chemotherapy for colorectal liver metastasis (CRLM) is thought to be the cause of hepatotoxicity of non-tumoural parenchyma. Studies on hepatotoxicity are contradictory. We investigated the impact of a single-line pre-operative chemotherapy on non-tumoural liver analysed by an expert hepatico-pancreatico-biliary pathologist, and the consequences on surgical outcomes.

PATIENTS AND METHODS: Patients operated for CRLM, after a pure first-line pre-operative chemotherapy, were retrospectively included. Two comparative histopathological analyses were performed for vascular toxicity and steatohepatitis.

RESULTS: Between 2003 and 2015, 147 patients were included. Chemotherapy was based on oxaliplatin (40.1%), irinotecan (55.8%), or both (4.1%). The expert pathologist described 38.8% of vascular lesions including dilation, nodular regeneration, and peliosis. In multivariate analysis, vascular lesions correlated to male sex ($P = .01$), pre-operative platelets <150 g/L ($P = .04$), and aspartate aminotransferase to platelet ratio index (APRI) score >0.36 ($P = .02$). Steatohepatitis was observed in 15 patients (10.2%), more frequently after irinotecan (14.8% vs 3.4%, $P = .01$; odds ratio [OR] = 7.3; 95% confidence interval [CI] = [1.5-34.7]), and for patients with body mass index (BMI) >25 kg/m^2 ($P = .004$; OR = 10.0; 95% CI = [2.1-47.5]). A total of 29 patients (19.7%) developed major complications with 2 risk factors: portal vein obstruction (PVO) and septic surgery. Reproducibility assessment of steatohepatitis and dilated lesions by 2 pathologists showed moderate agreement (Kappa score 0.53 and 0.54, respectively).

CONCLUSIONS: There is a probable association between non-alcoholic steatohepatitis (NASH) and irinotecan. Oxaliplatin seems to lead to higher vascular lesions. Except in the presence of pre-existent comorbidities, liver toxicities should not restrain the use of pre-operative chemotherapy prior to parenchymal-sparing surgery.

KEYWORDS: colorectal cancer, hepatic metastasis, neoadjuvant chemotherapy, vascular toxicity, steatohepatitis, hepatotoxicity

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Introduction

Liver surgery with complete resection of colorectal cancer liver metastases (CRLMs) improves long-term survival.[1,2] In primarily resectable metastases, pre-operative chemotherapy allows selecting patients with better prognosis, maximising remnant liver, and reducing local recurrence compared to surgery alone.[3] In unresectable metastases, chemotherapy reduces the disease enabling complete resectioning in 12.5% to 30% of cases.[4] Pre-operative chemotherapy based on oxaliplatin and/or irinotecan may be involved in histological damage, vascular lesions, or steatohepatitis, despite conflicting results from studies.[5,6] This hepatotoxicity could reduce liver function of the future remnant liver (FRL) and increase post-operative complications.[6,7]

Nevertheless, risk factors for steatosis and non-alcoholic steatohepatitis (NASH) exist even without any chemotherapy, for example, in obesity and diabetes. Moreover, histological assessment of sinusoidal obstruction syndrome (SOS) and steatohepatitis has limitations and requires an experienced pathologist.[8,9] In general, reports in literature on the impact of chemotherapy on non-tumoural liver and on post-operative morbidity and mortality are heterogeneous with contradictory conclusions.[10–13]

The aim of this study was to investigate the factors associated with hepatotoxicity on non-tumoural liver due to pre-operative chemotherapy. We analysed only patients who received exclusively one line of chemotherapy, operated by parenchymal-sparing surgery with 2 comparative

histopathological analyses (a routine pathological examination and an expert assessment).

Methods

Patients

Patients operated on for CRLM, between January 2003 and May 2015, were retrospectively identified from our prospectively maintained database (Base FOI, Medlog™). Patients treated with only one line of pre-operative chemotherapy were included. Patients with chronic liver disease, treated with adjuvant chemotherapy with FOLFOX (and not 5-fluouracil alone) or 2 different lines of pre-operative chemotherapy, were excluded. Details on patient selection and surgical methods are given in Supplementary Material.

Histological analysis

Histological analysis of non-tumoural hepatic parenchyma was performed using archived material (prepared from formalin-fixed, paraffin-embedded tissue). Morphological analysis was based on haematoxylin and eosin (H&E), Masson trichrome, and reticulin stains. The pathologists were unaware of the clinical data. Patients were excluded when the slides were too close to the metastases or presented surgical hepatitis. First analysis was made by our pathologist followed by a second analysis by an expert from the university hospital. Results from the second analyses were used as reference. In the second part, we analysed inter-observer interpretation and the impact on main results. Histological features of parenchymal, stromal, and vascular changes were evaluated and graded according to Rubbia-Brandt et al[5,9] Classification. The standard scores for the evaluation of steatosis and steatohepatitis or NASH were adopted, as defined by Kleiner et al.[14]

Statistical methods

The statistical analyses were performed using SAS software Version 9.3 (Cary, NC). Categorical variables were described using their size and percentages; quantitative variables using their median and range (min-max). In univariate analysis, predictive factors of post-operative complications and of histological lesions were obtained using the chi-square or Fisher exact tests for comparing categorical variables; the Wilcoxon non-parametric test was used to compare continuous variables. A $P < .05$ was considered to be statistically significant. In multivariate analysis for post-operative complications, significant factors were introduced in a stepwise logistic regression. Weighted kappa scores were used to measure the degree of inter-observer agreement between the 2 pathologists.

Results

Patient characteristics, pre-operative treatment, and surgery

The chemotherapy regimens used every 2 weeks before surgery were as follows:

LV5FU2: folinic acid 400 mg/m² in 2 hours + 5FU 400 mg/m² in 10 minutes + 5FU 2400 mg/m² in 46 hours

with or without bevacizumab 5 mg/kg

FOLFIRI: irinotecan 180 mg/m² in 90 minutes + LV5FU2

with or without bevacizumab 5 mg/kg

with or without panitumumab 6 mg/kg

with or without cetuximab 500 mg/m² every 2 weeks

FOLFOX 4: oxaliplatin 85 mg/m² in 2 hours + LV5FU2

with or without bevacizumab 5 mg/kg

with or without panitumumab 6 mg/kg

with or without cetuximab 500 mg/m²

FOLFIRINOX: irinotecan 180 mg/m² + oxaliplatin 85 mg/m² + LV5FU2

with or without bevacizumab 5 mg/kg

with or without panitumumab 6 mg/kg

with or without cetuximab 500 mg/m²

A total of 319 patients were operated on for CRLM. In total, 153 patients did not meet chemotherapy inclusion criteria. Three had hepatitis virus infection and 76 patients were excluded on histological criteria. Finally, 147 patients matched the inclusion criteria whose clinico-pathological characteristics are given in Table 1. A major liver resection was performed in 58 (39.5%) patients. Intra-operative radiofrequency ablation and resection were performed in 67 patients (45.6% cases). Portal vein obstruction (PVO) by embolisation (by the radiologist) or by ligature plus alcoholisation (during the surgery) was used in 18 patients in whom post-hepatectomy liver failure was considered to be a threat due to a small FRL. Two-stage hepatectomies were planned in 11 cases, but the disease progressed in 4 patients prior to the second intervention, which was cancelled. An extra-hepatic procedure was performed in 66 (44.9%) patients and was potentially contaminating in 38 (25.9%) patients.

Vascular lesions: predictive and risk factors

Histological lesions in non-tumoural liver were described in 87 (59.2%) patients (Table 2). Vascular lesions, including dilation, nodular regeneration, and peliosis, were considered significant based on our definition in 57 patients (38.8%). Steatohepatitis or NASH was observed in 15 (10.2%) patients and steatosis >5% in 82 (55.8%) patients.

Predictive factors for vascular lesions, including congestion and/or nodular lesions, are described in Table 3. In univariate analysis, male sex, pre-operative platelets <150 g/L, oxaliplatin, and aspartate aminotransferase to platelet ratio index (APRI)

Table 1. Clinico-pathological characteristics of patients (N = 147).

VARIABLE	NO. OF PATIENTS	%	NUMBER (MIN-MAX)
Median age, y			64 (34-88)
Sex			
Female	61	41.5	
Male	86	58.5	
Body mass index, kg/m²			
Median			25 (17-47)
<25	72	49	
⩾25	75	51	
⩾30	19	12.9	
Diabetes mellitus			
Present	13	8.8	
Absent	134	91.2	
Arterial hypertension			
Present	65	44.2	
Absent	82	55.8	
Dyslipidaemia			
Present	37	25.2	
Absent	110	74.8	
Primary tumour site			
Colon	120	81.6	
Rectum	27	18.4	
Hepatic metastasis			
Synchronous	111	75.5	
Metachronous	36	24.5	
Initially resectable	79	53.7	
Initially unresectable	68	46.3	

score >0.36 were correlated with the development of vascular lesions. Patients receiving oxaliplatin developed more vascular lesions than without (50% vs 30.5%; $P = .016$). Five patients had abnormally high level of bilirubin before chemotherapy and 10 patients before surgery had more vascular toxicity. In multivariate analysis, sex ($P = .01$), platelets ($P = .04$), and APRI remained correlated with vascular lesions. An APRI score >0.36 correlated to a higher incidence of vascular lesions: 57.1% vs 28.3% of patients with an APRI score ⩽0.36 ($P = .02$, 134 patients, odds ratio [OR] = 2.9; 95% confidence interval [CI] = [1.2-7.3]). Oxaliplatin and bilirubin levels were not retained as independent risk factors of vascular lesions.

Out of the 2 different types of vascular lesions, congestion lesions and non-nodular lesions tended to associate with pre-operative oxaliplatin ($P = .064$). For patients receiving oxaliplatin, bevacizumab had a protective effect on the development of vascular lesions ($P = .04$). Oxaliplatin seems to have a high impact on the development of severe vascular lesions with severe toxicity in 26.6% of patients against only 3.7% that did not ($P < .0001$). Number of chemotherapies and the time between the end of chemotherapy and liver surgery had no effect on the incidence of vascular lesions.

Steatohepatitis: predictive and risk factors

In univariate analysis, irinotecan, body mass index (BMI) >25 kg/m², dyslipidaemia, pre-operative gamma-glutamyl-transferase level >N, and bilirubin >N were related to more

Table 2. Incidence of liver injuries in non-tumoural parenchyma.

LIVER INJURY	NO. OF PATIENTS	%
Sinusoidal dilation		
No	77	52.8
Yes	69	47.2
Grade 1	44	30.1
Grade 2	17	11.6
Grade 3	8	5.5
Nodular regeneration		
No	85	58.2
Yes	61	41.8
Grade 1	38	26.0
Grade 2	13	8.9
Grade 3	10	6.8
Vascular toxicity		
No	90	61.2
Yes	57	38.8
Grade <5	126	86.3
Grade ⩾5	20	13.7
Chemotherapy-associated steatohepatitis		
No	132	89.8
Yes	15	10.2
Steatosis		
<5%	65	44.2
Of 5 at 33%	58	39.5
Of 33 at 66%	19	12.9
>66%	5	3.4
Lobular inflammation		
Absent	103	70.1
⩽2/foci	40	27.2
2-4/foci	4	2.7
⩾4/foci	0	0
Ballooning		
0	112	76.2
1	31	21.1
2	4	2.7

steatohepatitis lesions (Table 4). Multivariate analysis on 15 patients with NASH, irinotecan, and BMI >25kg/m^2 remained statistically associated with NASH. In patients treated with or without irinotecan, NASH was observed in 14.8% and 3.4%, respectively (P=.01; OR=7.3; 95% CI=[1.5-34.7]); a BMI >25 kg/m^2 was linked to more NASH (P=.004; OR=10.0; 95% CI=[2.1-47.5]). Neither the duration of chemotherapy nor the delay between surgery and the end of the chemotherapy had an impact on incidence of NASH.

Post-operative outcomes and risk factors

In total, 78 patients (53.1%) developed post-operative complications, including 29 (19.7%) major complications and 31 (21.1%) liver-related complications. Supplementary Table S1 details the post-operative complications. Ninety-day mortality rate was 0.7% (one septic shock on a post-operative bilioma). Two patients had a splenomegaly, possibly related to chemotherapy.

Risk factors of poorer post-operative outcomes were analysed and are described in Table 5. Patients' characteristics, pre-operative type of treatment, or presence of histological lesions were not correlated to more complications or more liver-related complications.

In univariate analysis, 4 surgical characteristics were related to poorer outcomes: two-stage hepatic surgeries, PVO, extra-hepatic surgery, and a potentially contaminating procedure. In multivariate analysis, only PVO and septic surgery were associated with more grade ⩾3 post-operative complications. Two-stage hepatectomies (including PVOs) and extra-hepatic surgery (P=.14) were not used in the multivariate models. Major complications were associated with a higher blood requirement and a longer time at hospital.

APRI score >0.36 did not correlate with poorer post-operative outcomes. Among the 25 patients with grade ⩾3 complications and a calculated APRI score, only 6 (24%) had a score >0.36. Time between the end of chemotherapy and surgery was not significantly different for the occurrence of post-operative complications when two-stage surgeries were excluded. Among the biological parameters, post-operative aspartate aminotransferase (AST) levels below 1.5N during the 2 days after surgery were predictive for complications: 57.1% of patients (4 of 7) with AST ⩽1.5N had severe complications vs 18% (25 of 139 patients) with AST >2N (P=.03).

Comparison of the 2 histological analyses

We compared the histologic descriptions by an expert hepatico-pancreatico-biliary pathologist to those of our general pathologist. Reproducibility was assessed using the Kappa score. For NASH, analyses' agreement was 90.5%, with a Kappa score of 0.53 (moderate agreement). Indeed, 9 patients were considered 'with NASH lesions' and 'without NASH' by our

Table 3. Predictive factors of vascular histologic lesions in non-tumoural parenchyma.

CHARACTERISTICS	VASCULAR TOXICITY (N=57)				TOTAL	*P*, UNIVARIATE ANALYSIS	*P*, MULTIVARIATE ANALYSIS	OR [95% CI]
	ABSENT		PRESENT					
	NO.	%	NO.	%				
Sex								
Male	44	51.2	42	48.8	86			
Female	45	75.0	15	25.0	60	.004	.01	0.3 [0.1-0.8]
Chemotherapy with oxaliplatin								
Yes	32	50.0	32	50.0	64			
No	57	69.5	25	30.5	82	.016	NR	
Chemotherapy with irinotecan								
Yes	59	67.0	29	33.0	88			
No	30	51.7	28	48.3	58	.06		
Number of cycles								
⩽8	46	61.3	29	38.7	75			
>8	43	60.6	28	39.4	71	.82		
Targeted therapy								
Bevacizumab	44	69.8	19	30.2	63			
None or other	45	54.2	38	45.8	83	.55		
APRI score								
⩽0.36	65	71.4	26	28.6	91			
>0.36	18	42.8	24	57.1	42	.002	.02	2.9 [1.2-7.3]
Bilirubin before chemotherapy								
⩽1N	71	69.6	31	30.4	102			
>1N	1	20	4	80	5	.038	NR	
Pre-operative bilirubin								
⩽1N	65	69.1	29	30.9	94			
>1N	4	40	6	60	10	.022	NR	
Pre-operative platelets								
⩾150 g/L	86	66.2	44	33.8	130			
<150 g/L	2	15.4	11	84.6	13	.0003	.04	10.1 [1.2-89.5]

Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; CI, confidence interval; NR, not retained at multivariate analysis; OR, odds ratio.

pathologist and the expert, respectively, and 5 patients had a NASH according to the expert and no lesion according to our pathologist, suggesting that among the 15 NASH diagnosed, only one was concordant. For steatosis measurement, comparing no steatosis or steatosis <5% vs >5% steatosis, the Kappa score was very high, 0.82 (95% CI = [0.69-0.95]). On the contrary, for inflammation and balloon lesion assessments, scoring only agreed at levels expected by chance: $r = 0.05$ and $r = -0.04$.

Regarding vascular lesions, only dilated lesions were analysed by both pathologists. The Kappa score showed a moderate agreement (0.54). A total of 166 patients could be analysed using the routine pathologist assessment results, whereas only 147 patients by the expert analysis; the expert eliminated 19 patients (2 missed strains, 17 lack of non-tumoural liver with presence of surgical hepatitis). According to statistical analyses using our general pathologist results,

Table 4. Predictive factors of NASH in non-tumoural parenchyma.

CHARACTERISTICS	NASH (N = 15)				TOTAL	*P*, UNIVARIATE ANALYSIS	*P*, MULTIVARIATE ANALYSIS	OR [95% CI]
	ABSENT		PRESENT					
	NO.	%	NO.	%				
Dyslipidaemia								
Yes	29	78.4	8	21.6	37			
No	101	93.5	7	6.5	108	.02	NR	
Diabetes								
Yes	10	76.9	3	23.1	13			
No	121	91.0	12	9.0	133	.13		
Arterial hypertension								
Yes	56	86.2	9	13.8	65			
No	75	92.6	6	7.4	81	.20		
Body mass index								
⩽25 kg/m²	70	97.2	2	2.8	72			
>25 kg/m²	62	82.7	13	17.3	75	.004	.004	10.0 [2.1-47.5]
Chemotherapy with irinotecan								
Yes	75	85.2	13	14.8	88			
No	57	96.6	2	3.4	59	.03	.01	7.3 [1.5-34.7]
Chemotherapy with oxaliplatin								
Yes	63	96.9	2	3.1	65			
No	69	84.1	13	15.9	82	.01		
Number of cycles								
⩽8	67	88.2	9	11.8	76			
>8	65	91.5	6	8.5	71	.50		
Pre-operative GGT								
⩽1N	67	93.1	5	6.9	72			
>1N	49	86	8	14	57	.045	NR	
Pre-operative bilirubin								
⩽1N	89	93.7	6	6.3	95			
>1N	8	80	2	20	10	.033	NR	

Abbreviations: CI, confidence interval; GGT, gamma-glutamyltransferase; NASH, non-alcoholic steatohepatitis; NR, not retained at multivariate analysis; OR, odds ratio.

oxaliplatin and irinotecan were not correlated with higher rates of SOS/sinusoidal dilation and NASH, respectively. These results differ with previously described results from the expert, demonstrating an impact of irinotecan on the incidence of steatohepatitis. Body mass index was correlated with NASH in both analyses. The 2 histological analyses were in agreement to conclude that the presence of histopathological lesions did not worsen post-operative outcomes. Septic surgery was associated with more grade ⩾3 post-operative complications whatever the histological analysis, but PVO was significantly associated with more complications only with the expert results.

Table 5. Impact of clinico-pathological characteristics, pre-operative treatments, surgery protocols, and histological injuries on post-operative outcomes, in univariate analysis.

CHARACTERISTICS	POST-OPERATIVE COMPLICATIONS				TOTAL	*P*, UNIVARIATE ANALYSIS	*P*, MULTIVARIATE ANALYSIS	OR [95% CI]
	NO OR GRADE <3		GRADE ⩾3					
	NO.	%	NO.	%				
Total	118	80.3	29	19.7	147			
Chemotherapy								
Oxaliplatin	47	79.7	12	20.3	59			
Irinotecan	66	80.5	16	19.5	82			
Both	5	83.3	1	16.7	6	.90		
Number of cycles								
⩽8	69	84.1	13	15.9	82			
>8	66	78.6	18	21.4	84	.36		
Targeted therapy								
None	45	81.8	10	18.2	55			
Bevacizumab	49	77.8	14	22.2	63			
Other	24	82.8	5	17.2	29	.72		
Liver surgery extension								
Minor	71	79.8	18	20.2	89			
Major	47	81.0	11	19.0	58	.85		
Pre-operative PVO								
Yes	10	55.6	8	44.4	129			
No	108	83.7	21	16.3	18	.01	.004	5.4 [1.7-16.6]
Two-stage hepatectomy								
Yes	6	54.5	5	45.5	11			
No	112	82.4	24	17.6	136	.04		
Extra-hepatic surgery								
Yes	46	69.7	20	30.3	66			
No	72	88.9	9	11.1	81	.004	NR	
Septic surgery								
Yes	23	60.5	15	39.5	38			
No	95	87.2	14	12.4	109	.001	<.001	5.2 [2.1-13.1]
Vascular lesion								
Absence	74	83.2	15	16.8	89			
Presence	43	75.4	14	24.6	57	.25		
Absent or grade <5	101	80.2	25	19.8	126			
Grade ⩾5	16	80.0	4	20.0	20	.99		

(Continued)

Table 5. (Continued)

CHARACTERISTICS	POST-OPERATIVE COMPLICATIONS				TOTAL	*P*, UNIVARIATE ANALYSIS	*P*, MULTIVARIATE ANALYSIS	OR [95% CI]
	NO OR GRADE <3		GRADE ⩾3					
	NO.	%	NO.	%				
NASH								
Absence	105	79.6	27	20.4	132			
Presence	13	86.7	2	13.3	15	.74		
APRI score								
⩽0.36	73	79.3	19	20.7				
>0.36	36	85.7	6	14.3		.38		

Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; CI, confidence interval; NASH, non-alcoholic associated steatohepatitis; NR, not retained in multivariate analysis; OR, odds ratio; PVO: portal vein obstruction.

Discussion

The aim of this study was to investigate the predisposing factors for hepatotoxicity due to pure first-line pre-operative chemotherapy on the non-tumoural liver, analysed by an expert hepatico-pancreatico-biliary pathologist, and the consequences on surgical outcomes in a series of parenchymal-sparing surgeries. Nevertheless, the main limitation of our work is the lack of a histological assessment of cancer-free liver before chemotherapy.

After 10 years and many studies, results are still heterogeneous, including patients with different and incomparable chemotherapies, without essential and exhaustive histological analysis.[10,12–17] Our study is interesting as the patients received only one line of chemotherapy, giving us pertinent and homogeneous results on the impact of chemotherapy on liver. The study by Rubbia-Brandt et al[9] did not show any impact of sex, contrary to our results.

Probable association between oxaliplatin and vascular lesions

Rubbia-Brandt et al[5,9] reported high rates (51%) of vascular lesions after pre-operative chemotherapy with oxaliplatin or irinotecan. In our study, oxaliplatin tended to have an impact on the development of vascular lesions. However, other chemotherapies may also have an effect: 30% of patients receiving no oxaliplatin had vascular lesions. We observed lower incidence of vascular lesions and less severe lesions, probably because of the limited number of pre-operative chemotherapies (only 8 cycles).[7] In our results, bevacizumab seems to have a protective effect against vascular toxicity when associated with oxaliplatin, in agreement with previous studies.[9,18] Biological predictive factors of vascular lesions were statistically significant: low pre-operative platelets and an APRI score >0.36. These factors could be useful to select patients with a high risk of vascular toxicity, which should lead to a prudent parenchymal saving surgery.[14,18]

Supplementary Table S2 lists some of the publications on pre-operative chemotherapy and its impact on non-tumoural liver, with some conflicting results.[12,15] These differences could be a result of difficulty in diagnosing and assessing vascular lesions, confirming the importance of an expert analysis.[9,11] These results are consistent with intra- and inter-observer variations published by Pilgrim et al[10] where in the Spearman correlation coefficients were weak, 0.52 and 0.53, respectively.

Probable association between irinotecan and NASH

Irinotecan was implicated by Vauthey et al[6] in the incidence of chemotherapy-associated steatohepatitis (CASH) (20.2%). There have been reports on the association between other chemotherapies (5-FU alone, FOLFIRI, or FOLFOX) and CASH.[10,19] On the contrary, confounding factors such as BMI or diabetes could influence the development of CASH.[8,12,20] The absence of histological differences between pre-existent NASH and CASH may impede understanding the role of irinotecan in the development of steatohepatitis. Of note, NASH is observed in around 5.7% to 17% of the general population.[21]

Our results are relevant to these studies as NASH and CASH are similar histological lesions with the same pathogenic mechanism. Hence, the risk factors such as BMI, dyslipidaemia, diabetes, and chemotherapy influenced the development of steatohepatitis (Supplementary Table S2). Furthermore, one limitation of our study is the absence of a control group without pre-operative chemotherapy, which we deemed not necessary as this was not the aim of our study. Nevertheless, our population represents the general population, matching on the sex and age proportions, different parameters of metabolic syndrome: diabetes, arterial hypertension, dyslipidaemia, and BMI. Therefore, we can conclude that patients receiving oxaliplatin and not irinotecan have a similar incidence of NASH compared to the general population.[22] Our results are consistent with Pilgrim et al,[10] with the Spearman

correlation coefficients good for steatosis, but not favourable for ballooning and inflammation lesions, as a consequence of steatohepatitis. Moreover, lesions have a heterogeneous distribution inside the liver.[23]

Correlation between type of neoadjuvant chemotherapy, surgical methods, histological lesions, and post-operative outcomes

Most of the reports on outcomes impacted by chemotherapies have used non-parenchymal-sparing strategies, where in the quantity of normal parenchyma retrieved at each procedure was possibly more than in our series. Nakano et al[7] found that SOS was correlated with an increased risk of post-operative complications but only if a major resection was practised. Sinusoidal lesions have been associated with an increased blood requirement and higher post-operative liver failure,[20,24] but no poorer outcomes in other studies.[6,12,25–28] The extent of liver resection, and hence the FRL, is a determinant factor for complications.[11,29,30] The negative impact of chemotherapy on post-operative outcomes has been suggested by Nordlinger et al,[3] but lacked non-tumoural liver analysis. Hepatotoxicity could reduce liver function of the FRL which should not measure below 30% to 40% of liver.[6,7] The type and number of chemotherapies may influence these complications with 6 or 8 cycles showing an augmentation of risks.[31,32]

Potential septic surgery is also known to cause higher post-operative complications.[13,28,30] As often in extensive surgeries, PVO was correlated with higher post-operative complications. In the literature, PVO seems to improve liver volume and function,[33] but is associated with more post-operative complications (blood loss) and may stimulate the growth of the remaining metastases.[34] Rubbia-Brandt et al[9] found no impact of PVO on histological non-tumoural liver lesions. On the whole, PVO has to be restricted to the patients having a clear risk of post-hepatectomy liver failure and only if one-stage treatment is not possible.[35]

Our data have not shown an association between liver injury and outcome. Nevertheless, this retrospective study of 147 patients over a 12-year period is underpowered to demonstrate any association between histological lesions (vascular lesions or steatohepatitis) and post-operative outcomes. Indeed, Vauthey et al[6] have demonstrated a 10-fold higher post-operative mortality in the presence of steatohepatitis in a cohort of over 400 patients. Other larger studies on the same topic also conflict with our conclusions.[6,10,20,21]

Conclusions

The results of our study are in agreement with the literature and show a probable association between the development of NASH and irinotecan and suggest that pre-existent comorbidities may influence this outcome. We also conclude that oxaliplatin seems to lead to higher vascular lesions. Except in specific cases, liver toxicities cannot be used as an argument to proscribe or restrain the use of pre-operative chemotherapy as it is particularly useful in parenchymal-sparing surgery. Nevertheless, our data are underpowered to demonstrate an association between liver injury and outcome.

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Author Contributions

DB contributed to study concepts. MD contributed to study design. BB contributed to data acquisition. VB contributed to statistical analysis. MD, BLB, GD, MF, YB, SE, and DB contributed to data analysis and interpretation. MD, MF, SE, and DB contributed to manuscript preparation, editing, and review.

Ethics and Consent

The institutional review board waived the need for ethics and consent due to retrospective nature of the study.

Supplemental material

Supplemental material for this article is available online.

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