Ann Surg Oncol (2011) 18:659–669
DOI 10.1245/s10434-010-1385-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Regenerative Nodular Hyperplasia of the Liver Related to Chemotherapy: Impact on Outcome of Liver Surgery for Colorectal Metastases

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ABSTRACT

Background. Regenerative nodular hyperplasia (RNH) represents the end-stage of vascular lesions of the liver induced by chemotherapy. The goal was to evaluate its incidence and impact on the outcome of patients resected for colorectal liver metastases (CLM).

Methods. Patients who underwent hepatectomy for CLM after six cycles or more of first-line chemotherapy, between January 1990 and November 2006, were included. Detailed histopathologic analysis of the nontumoral liver was performed according to a standard format.

Results. From a cohort of 856 resected patients at our institution, 771 (90%) received preoperative chemotherapy. Of these, 146 fulfilled the selection criteria and were included: 24 (16%) received 5-fluorouracil (5-FU) and leucovorin (LV) alone, 92 (63%) had 5-FU/LV and oxaliplatin, 18 (12%) had 5-FU/LV and irinotecan, and 12 (8%) were treated by 5-FU/LV, oxaliplatin, and irinotecan. RNH occurred in 22 of 146 patients (15%). Twenty of these patients (91%) received oxaliplatin, of whom six (30%) had chronomodulated therapy. Patients treated by oxaliplatin more often had RNH compared with oxaliplatin-naïve patients (22 vs. 4%). Although operative mortality was nil, the presence of RNH was associated with increased postoperative hepatic morbidity (50 vs. 29%). Elevated preoperative gamma-glutamyltransferase (GGT) (>80 U/L; >1N) and total bilirubin levels (>15 μmol/L; >1N) were independent predictors of RNH.

Conclusions. Patients with CLM who receive preoperative oxaliplatin have an increased risk of RNH and associated postoperative morbidity. Increased serum GGT and bilirubin are useful markers to predict the presence of RNH.

During recent years, the intensity of preoperative systemic chemotherapy for patients with colorectal liver metastases (CLM) has increased significantly. Patients with unresectable metastatic disease frequently receive prolonged chemotherapy treatment in an attempt to convert them to resectability. With this approach, long-term survival can be achieved when liver resection becomes feasible after tumoral downsizing.[1] In addition, neoadjuvant chemotherapy is applied for resectable liver metastases to facilitate margin-free resections, and this approach has shown recently to improve progression-free survival after hepatectomy.[2,3]

Our group and others have reported a relationship between the use of preoperative chemotherapy and histopathologic changes of the nontumoral liver with consequently an increased risk of perioperative morbidity.[3–11] This mainly concerns the prolonged use of oxaliplatin and associated vascular lesions. However, close evaluation of direct relations between specific vascular lesions and postoperative outcome

First Received: 20 April 2010;
Published Online: 26 October 2010

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remains limited (Table 1).[3,6–15] Only three studies have correlated specific chemotherapy-related vascular changes in the nontumoral liver with an increased intraoperative transfusion rate or longer hospital stay.[8–10]

Regenerative nodular hyperplasia (RNH) is considered the end-stage of vascular lesions induced by chemotherapy, but its effect on the outcome of hepatic resection for colorectal metastases remains unclear. However, with the increasing indications of preoperative chemotherapy, especially oxaliplatin, RNH is observed more frequently, necessitating an evaluation of its consequences. Furthermore, with the high incidence of recurrences observed in patients resected of CLM, repeat hepatectomies are increasingly performed.[16–18] Knowledge concerning the consequences of RNH, as well as its potential to regress, is crucial in evaluating the risks of repeat surgery with the continuing administration of chemotherapy.

In this study, we evaluated the incidence of RNH and its impact on postoperative outcome in patients resected of CLM. In addition, we assessed the evolution of RNH by analyzing the pathological specimens of patients submitted to repeat hepatectomy.

PATIENTS AND METHODS

Patients

From January 1990 to November 2006, 856 consecutive patients underwent partial hepatectomy for colorectal metastases at our institute; 771 (90%) of these patients were treated by preoperative chemotherapy, whereas 85 patients (10%) underwent hepatic resection without preoperative chemotherapy treatment. Of all 771 patients treated by preoperative chemotherapy, this study focused only on patients who received six or more cycles of first-line therapy. In addition, patients treated with preoperative intra-arterial chemotherapy were excluded.

Preoperative Chemotherapy

Chemotherapy was most often administered before surgery for patients with initially unresectable metastases. Technical unresectability was defined as the inability to completely resect all metastases while leaving at least 30% of normal liver parenchyma, resulting from a multinodular

TABLE 1 Review of publications evaluating the effect of preoperative chemotherapy and hepatic chemotoxicity on short-term outcome after resection of colorectal liver metastases

Author	Year	No. of patients[a]	Type of chemotherapy	Related histology nontumoral liver	Short-term perioperative outcome
Studies of no effect					
Parikh[12]	2003	61	Irinotecan	Steatosis	Unaffected
Hewes[13]	2007	46	Miscellaneous[b]	None	Unaffected
Pawlik[14]	2007	153	Oxaliplatin	Sinusoidal dilatation	Unaffected
			Irinotecan	Steatosis/steatohepatitis	Unaffected
Scoggins[15]	2009	112	Miscellaneous[c]	None	Unaffected
Studies of effect—outcome related to chemotherapy					
Karoui[6]	2006	45	Miscellaneous[d]	Sinusoidal dilatation	Increased morbidity
Nordlinger[3]	2008	151	Oxaliplatin	Not analyzed	Increased morbidity
Studies of effect—outcome related to liver histology					
Vauthey[7]	2006	248	Oxaliplatin	Sinusoidal dilatation	Unaffected
			Irinotecan	Steatohepatitis	Increased 90-day mortality
Aloia[8]	2006	75	Oxaliplatin	HCN/RNH	Increased transfusion rate
Mehta[9]	2007	130	Oxaliplatin	Sinusoidal dilatation	Longer hospital stay and increased transfusion rate
Nakano[10]	2008	90	Oxaliplatin	Sinusoidal injury	Longer hospital stay and increased morbidity[e]
Kandutsch[11]	2008	50	Oxaliplatin	Fibrosis	Increased transfusion rate
				Sinusoidal dilatation	Unaffected

HCN hemorrhagic centrilobular necrosis, *RNH* regenerative nodular hyperplasia

[a] Treated with preoperative chemotherapy

[b] 5-Fluorouracil and leucovorin alone or combined with oxaliplatin

[c] 5-Fluorouracil with various combinations of other agents

[d] 5-Fluorouracil and leucovorin alone or combined with oxaliplatin, irinotecan or both

[e] In patients who underwent major hepatectomy (≥3 segments)

tumor distribution, large tumor size, or a close relationship with major vascular or biliary structures. The presence of extrahepatic metastases determined oncological unresectability. The rationale to administer preoperative chemotherapy to patients with upfront resectable metastases was to assess tumor chemoresponsiveness and to facilitate margin-negative resections.

Response to chemotherapy was evaluated in a multidisciplinary meeting with surgeons, oncologists, and radiologists, and surgery was only performed when the overall strategy could result in complete intra- and extrahepatic tumor clearance.

Liver Resection

The goal of liver surgery was to resect completely all detectable lesions. Detailed inspection, palpation, and intraoperative ultrasound of the liver were routinely performed in each patient. Local ablation, portal vein embolization, and two-stage hepatectomy were used as described before to increase the possibility of radical tumor resection.[19–21] General and local hepatic complications occurring within 2 months after surgery were recorded and classified.[22,23]

Histopathologic Examination

Detailed histopathologic assessment of the nontumoral liver was performed by a single hepatobiliary pathologist, blinded for the information regarding preoperative chemotherapy and perioperative outcome. Liver tissue was analyzed according to a standard format previously described.[8] Briefly, vascular lesions were categorized as sinusoidal alterations (vasodilatation and congestion), peliosis, hemorrhagic centrilobular necrosis (HCN), RNH, and veno-occlusive disease. The presence of macrovacuolar steatosis was graded as mild (<30% of hepatocytes), moderate (30–60%), or severe (>60%). Steatohepatitis included steatosis with signs of local inflammation and apoptotic hepatocytes. Fibrosis was divided into portal fibrosis, porto-portal fibrosis, septal fibrosis, and cirrhosis. Surgical necrosis also was noted.

Repeat Surgery

The development of recurrences was assessed by physical examination, serum CEA and CA 19.9 levels, and abdominal ultrasound at 4-month intervals after hepatectomy. CT imaging of the chest, abdomen, and pelvis was performed every 8 months. Repeat resection of intra- and/or extrahepatic recurrences was only considered if it could be macroscopically complete.[17] For patients who underwent repeat liver surgery, histopathologic examination of the nontumoral liver was performed in a similar way as described above to evaluate the evolution of initial lesions.

Statistical Analysis

All statistical analyses were performed using SPSS® software version 13.0 (SPSS Inc., Chicago, IL). Categorical data were reported as the number of patients with percentages and compared by the χ^2 test. For continuous data, reported as means ± standard deviation, the independent-samples t test was used to compare groups. Logistic regression was done to define independent predictive factors of hepatic morbidity as well as preoperative predictive factors of RNH. Factors with $P \leq 0.10$ at univariate analysis were included. P values ≤ 0.05 were considered significant.

RESULTS

Of all 771 consecutively resected patients treated by preoperative chemotherapy, 155 received six or more cycles of first-line therapy, delivered by intravenous route. Due to an insufficient amount of nontumoral liver parenchyma available for histopathological analysis, 9 patients were excluded, resulting in a cohort of 146 patients (Fig. 1).

Patient and Tumor Characteristics

Included patients had a median age of 61 (range, 34–79) years and 76% presented with synchronous liver metastases (Table 2). Most patients (54%) had >3 metastases at diagnosis with a median diameter of 40 (range, 6–160) mm. Metastases were located in both liver lobes in 70% of patients and 20 patients (14%) had concomitant extrahepatic disease.

Preoperative Chemotherapy

Chemotherapy was indicated for initially unresectable metastases in the majority of patients (72%). Unresectability was related to multinodular disease (59%), large tumor size (29%), close vascular relationship (10%), and extrahepatic disease (3%). The remaining 28% of patients received preoperative chemotherapy for resectable disease. The median number of administered cycles for the total group was 8 (range, 6–21) and chemotherapy delivery was chronomodulated in 41% of patients.[24] Twenty-four patients (16%) received 5-fluorouracil (5-FU) and leucovorin (LV) alone (9.0 ± 2.0 cycles), 92 patients (63%) had 5-FU/LV and oxaliplatin (8.6 ± 2.8 cycles), 18 patients (12%) had 5-FU/LV and irinotecan (8.9 ± 3.0 cycles), and 12 patients (8%) were treated by 5-FU/LV, oxaliplatin, and

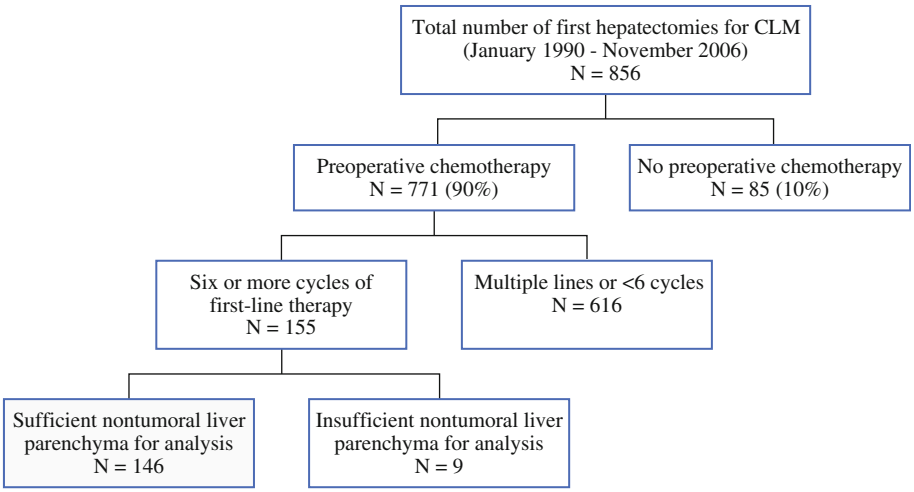

FIG. 1 Flowchart of patient selection

irinotecan (9.6 ± 3.6 cycles). The number of chemotherapy cycles did not differ between different regimens ($P = 0.70$).

Hepatectomy Characteristics

Major hepatectomies (≥3 segments) were performed in 50% of patients (Table 2). Red blood cell transfusions were required in 41% of patients, of whom 94% needed more than 1 unit of blood. Postoperative morbidity occurred in 43% of patients and one patient (1%) died within 60 days after surgery. Hepatic complications were classified as grade III or IV complications in 34% of patients. Median duration of hospital stay was 11 (range, 6–42) days.

Nontumoral Liver Parenchyma

Vascular liver lesions constituted the most frequent type of histopathological lesion and were present in 82 patients (56%; Table 2). Peliosis was most often observed (31%). RNH occurred in 22 of 146 patients (15%) and was more frequent than sinusoidal alterations (11%; Fig. 2). Of note, steatohepatitis occurred in only one patient (1%).

RNH Versus Non-RNH Patients

Patients with RNH more often presented with >3 metastases at diagnosis compared with patients without RNH (78 vs. 50%; $P = 0.03$; Table 3). Twenty RNH patients (91%) preoperatively received 5-FU/LV and oxaliplatin (9.2 ± 2.6 cycles). The two remaining patients were treated by 5-FU/LV and irinotecan (12 cycles; N = 1) and 5-FU/LV, oxaliplatin, and irinotecan (6 cycles; N = 1). Chemotherapy was chronomodulated in six patients (27%; all oxaliplatin). RNH occurred in 22% of patients treated by oxaliplatin compared with 4% of oxaliplatin-naïve patients ($P = 0.003$). The number of chemotherapy cycles was not increased in RNH patients compared with the control group (9.1 ± 2.7 vs. 8.8 ± 2.8; $P = 0.55$).

RNH patients had lower platelet counts at hospital admission (≤150 × 10^3/μL: 48 vs. 17%; $P = 0.002$). Mean alkaline phosphatase, gamma-glutamyltransferase (GGT), and total bilirubin levels before surgery were higher in RNH patients (Table 3).

Major hepatectomies were performed in a similar percentage of patients with and without RNH (55 vs. 49%, respectively; $P = 0.64$; Table 3). None of the RNH patients died within 60 days postoperatively. However, hepatic complications occurred in 50% of RNH patients compared with 29% of patients without RNH ($P = 0.05$). This difference was mainly caused by an increased incidence of biliary leaks (27 vs. 0%).

Uni- and Multivariate Analysis of Hepatic Morbidity

Seven factors, including RNH, were associated with hepatic morbidity at univariate analysis (Table 4). However, only four factors were independent predictors at multivariate analysis: a preoperative platelet count of <150 × 10^3/μL, major hepatectomy, two-stage hepatectomy, and intraoperative red blood cell transfusion.

Predictive Factors of RNH

Multivariate logistic regression analysis identified elevated preoperative GGT (>80 U/L; >1N) and total bilirubin levels (>15 μmol/L; >1N) as independent factors predictive for the presence of RNH. Risk ratios were 6.6 (95% confidence interval (CI), 2–21.4) for GGT ($P = 0.002$) and 3.3 (95% CI, 1.1–10.0) for total bilirubin ($P = 0.04$).

TABLE 2 Characteristics of 146 included patients

	Chemotherapy group (N = 146)
Patients	
Mean age ± SD (yr)	59.1 ± 9.5
Male/female ratio	85 (58%)/61 (42%)
Mean body mass index ± SD (kg/m^2)	24.1 ± 3.6
Diabetes mellitus	8 (6%)
Primary tumor	
Colon/rectum	114 (79%)/31 (21%)
T stage	
1/2	19 (17%)
3/4	92 (83%)
N stage	
0	43 (38%)
1/2	70 (62%)
Liver metastases diagnosis	
Synchronous[a]	111 (76%)
Number	
≤3	62 (46%)
>3	73 (54%)
Mean maximum size ± SD (mm)	45.2 ± 28.6
Bilobar	102 (70%)
Mean CEA ± SD (ng/mL)	293.2 ± 643.1
Concomitant extrahepatic disease	20 (14%)
Extrahepatic resection	11 (58%)
Hepatectomy	
Major resection (≥3 segments)	73 (50%)
Resection type	
Anatomical	47 (32%)
Nonanatomical	34 (23%)
Both	65 (45%)
Vascular occlusion	
No	21 (15%)
Total pedicular	73 (54%)
Vascular exclusion	20 (15%)
Selective	22 (16%)
Combined local ablation	
No	129 (88%)
Radiofrequency ablation	10 (7%)
Cryotherapy	7 (5%)
Portal vein embolization	18 (12%)
Two-stage hepatectomy	10 (7%)
Red blood cell transfusions	
No	78 (59%)
Yes	54 (41%)
Postoperative outcome	
Mortality (≤60 days)	1 (1%)
Morbidity	63 (43%)
General complications[b]	43 (30%)
Hepatic complications	47 (32%)
Biliary leak	3 (6%)
Hemorrhage	2 (4%)
Infected collection	5 (11%)
Noninfected collection	21 (45%)
Liver insufficiency[23]	8 (17%)
Combination	8 (17%)
Relaparotomy	5 (3%)
Drainage	14 (10%)
Mean hospital stay ± SD (days)	12.9 ± 5.9
Nontumoral liver	
Macrovacuolar steatosis (≥30%)	12 (8%)
Steatohepatitis	1 (1%)
Fibrosis	69 (47%)
Portal	57 (83%)
Porto-portal	11 (16%)
Septal	0 (0%)
Cirrhosis	1 (1%)
Vascular lesions[c]	82 (56%)
Sinusoidal alterations[d]	16 (11%)
Peliosis	45 (31%)
HCN	36 (25%)
RNH	22 (15%)
Veno-occlusive disease	18 (14%)
Surgical necrosis	8 (6%)

SD standard deviation, *CEA* carcinoembryonic antigen, *HCN* hemorrhagic centrilobular necrosis, *RNH* regenerative nodular hyperplasia

[a] Synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor

[b] As general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic) and iatrogenic complications

[c] Patients with one or more individual vascular changes

[d] Vasodilatation or congestion

Evolution of RNH Within Time

Fifteen of 82 patients (18%) with vascular changes of the nontumoral liver at first hepatectomy underwent repeat liver surgery. This included 2 of 22 patients (9%) with RNH at first hepatectomy.

RNH was replaced by HCN at second hepatectomy in both patients following interruption of oxaliplatin and subsequent treatment with irinotecan. These patients received 11 and 12 cycles of irinotecan-based chemotherapy between both hepatectomies, respectively. No new cases of RNH were found at repeat hepatectomy in the remaining cases.

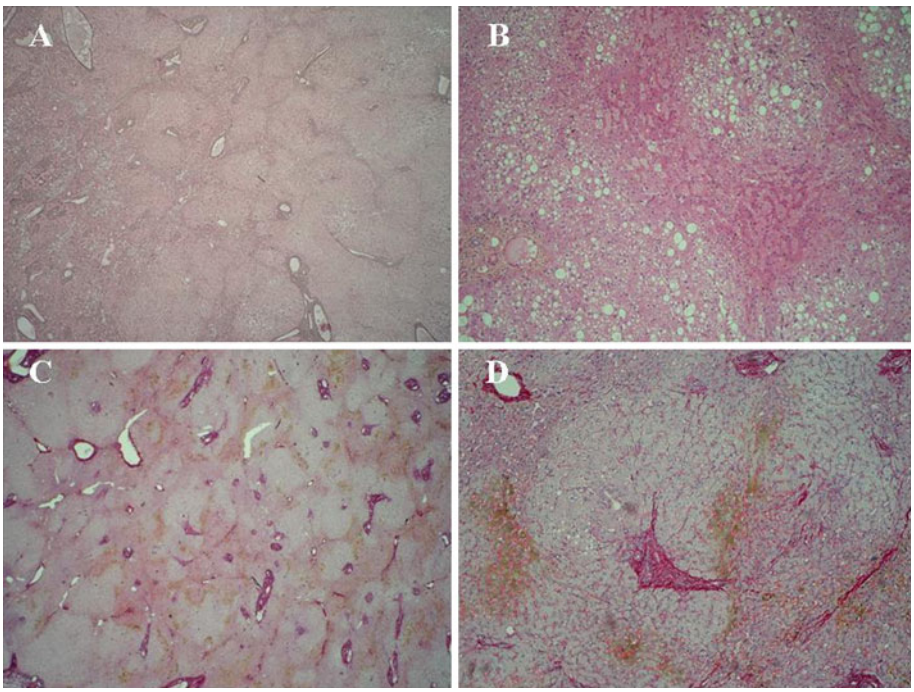

FIG. 2 Example of regenerative nodular hyperplasia. Nodules of hyperplastic hepatocytes replace the normal liver parenchyma and are surrounded by atrophic plates without evidence of fibrosis (note the hemorrhagic changes close to atrophic plates). **a** Gordon and Sweet stain (×20); **b** Hematoxylin-eosin stain (×10); **c** Picrosirius stain (×20); **d** Picrosirius stain (×10)

TABLE 3 Characteristics of patients with and without RNH

	No RNH (N = 124)	RNH (N = 22)	*P*
Patients			
Mean age ± SD (yr)	59.1 ± 9.9	59.1 ± 7.6	0.99
Male/female ratio	73 (59%)/ 51 (41%)	12 (55%)/ 10 (46%)	0.71
Mean body mass index ± SD (kg/m^2)	24.0 ± 3.5	24.4 ± 4	0.6
Diabetes mellitus	6 (5%)	2 (10%)	0.43
Liver metastases diagnosis			
Synchronous[a]	91 (73%)	20 (91%)	0.08
Number			
≤3	58 (50%)	4 (22%)	**0.03**
>3	59 (50%)	14 (78%)	
Mean maximum size ± SD (mm)	44.5 ± 28.4	49 ± 30.2	0.52
Bilobar	84 (68%)	18 (82%)	0.19
Preoperative chemotherapy			
Chronotherapy	53 (43%)	6 (27%)	0.16
Mean number of cycles ± SD	8.8 ± 2.8	9.1 ± 2.7	0.55
≤9	75 (63%)	12 (55%)	0.45
>9	44 (37%)	10 (46%)	
Regimen			
5-FU/LV and oxaliplatin	72 (58%)	20 (91%)	**0.003**
Other	52 (42%)	2 (9%)	
Preoperative biochemical variables			
Mean ICG-R15 ± SD (%)	15 ± 7.3	13 ± 5.7	0.35
Mean hemoglobin level ± SD (g/dL)	12.3 ± 1.5	11.9 ± 1.5	0.27
Mean platelet count ± SD (10^3/μL)	217.8 ± 74.7	158.7 ± 63.3	**0.001**
≤150	19 (17%)	10 (48%)	**0.002**
>150	92 (83%)	11 (52%)	
Mean prothrombin time ± SD (%)	90.2 ± 12.2	91.8 ± 8.9	0.59
Mean AST ± SD (U/L)	48 ± 64.7	58.6 ± 36.2	0.46
Mean ALT ± SD (U/L)	46.9 ± 81	60.2 ± 49.6	0.46
Mean AP ± SD (U/L)	133.6 ± 124.7	208.8 ± 154.5	**0.03**
≤100	52 (52%)	2 (12%)	**0.002**
>100	49 (49%)	15 (88%)	
Mean GGT ± SD (U/L)	96.1 ± 125.2	235.2 ± 284.8	**<0.001**
≤80	75 (65%)	4 (20%)	**<0.001**
>80	40 (35%)	16 (80%)	
Mean total bilirubin ± SD (μmol/L)	11.8 ± 10.1	15 ± 8.5	0.17
≤15	100 (86%)	14 (64%)	**0.01**
>15	16 (14%)	8 (36%)	
Hepatectomy			
Major resection (≥3 segments)	61 (49%)	12 (55%)	0.64
Vascular occlusion			
No	20 (17%)	1 (5%)	0.47
Total pedicular	60 (52%)	13 (62%)	

TABLE 3 continued

	No RNH (N = 124)	RNH (N = 22)	*P*
Vascular exclusion	16 (14%)	4 (19%)	
Selective	19 (17%)	3 (14%)	
Portal vein embolization	13 (11%)	5 (23%)	0.11
Two-stage hepatectomy	7 (6%)	3 (14%)	0.17
Mean red blood cell transfusions ± SD (units)	1.5 ± 2.4	1.4 ± 1.5	0.9
No	68 (61%)	10 (48%)	0.24
Yes	43 (39%)	11 (52%)	
Postoperative outcome			
Mortality (≤60 days)	1 (1%)	0 (0%)	0.67
Morbidity	50 (40%)	13 (59%)	0.1
General complications[b]	35 (28%)	8 (36%)	0.44
Hepatic complications	36 (29%)	11 (50%)	**0.05**
Biliary leak	0 (0%)	3 (27%)	**0.04**
Hemorrhage	2 (6%)	0 (0%)	
Infected collection	4 (11%)	1 (9%)	
Noninfected collection	18 (50%)	3 (27%)	
Liver insufficiency[23]	6 (17%)	2 (18%)	
Combination	6 (17%)	2 (18%)	
Relaparotomy	5 (4%)	0 (0%)	0.34
Drainage	11 (9%)	3 (14%)	0.48
Mean hospital stay ± SD (days)	12.7 ± 5.7	13.9 ± 7.3	0.36
Nontumoral liver			
Sinusoidal alterations[c]	13 (11%)	3 (14%)	0.66
Peliosis	38 (31%)	7 (32%)	0.91
HCN	30 (24%)	6 (27%)	0.77

RNH regenerative nodular hyperplasia, *SD* standard deviation, *ICG-R15* indocyanine green retention rate at 15 minutes, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AP* alkaline phosphatase, *GGT* gamma-glutamyltransferase, *HCN* hemorrhagic centrilobular necrosis

[a] Synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor

[b] As general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic) and iatrogenic complications

[c] Vasodilatation or congestion

DISCUSSION

Although previous reports have correlated preoperative chemotherapy for CLM with increased postoperative complications, evidence for a direct relation between specific nontumoral liver lesions and postoperative morbidity remains preliminary.[7–10,25,26] With the increasing use of preoperative chemotherapy, especially oxaliplatin, it is nevertheless important to know the incidence and impact of different vascular lesions on postoperative outcome and to know how these lesions can be predicted to adjust patient monitoring and to identify patients at risk of increased morbidity.

Our present study shows that RNH may occur in 15% of patients treated with preoperative chemotherapy. RNH is associated with increased hepatic morbidity and occurs most frequently in patients receiving oxaliplatin. Interestingly, its presence can be predicted preoperatively by elevated levels of GGT and total bilirubin.

The fact that RNH was related with increased postoperative hepatic morbidity was an important finding of our study. However, only a preoperative platelet count of $<150 \times 10^3/\mu L$, major hepatectomy, two-stage hepatectomy, and intraoperative red blood cell transfusion were independent predictors of hepatic morbidity at multivariate analysis in the total study population. Major hepatectomy, two-stage hepatectomy, and intraoperative red blood cell transfusions were equally distributed between RNH and non-RNH patients. However, RNH patients had relatively low platelet counts compared with non-RNH patients. We may assume that a low platelet count was related to splenomegaly due to portal hypertension caused by RNH, with subsequent platelet trapping. These results all strengthen the association of RNH with increased hepatic morbidity observed in our study.

In a recent study, sinusoidal liver injury was related with increased morbidity after major hepatectomy for CLM after preoperative chemotherapy.[10] Our inclusion of both minor and major hepatectomies confirms the importance of recognizing RNH in all patients scheduled for hepatectomy after preoperative chemotherapy treatment. Furthermore, our result was independent of the number of chemotherapy cycles.

Interestingly, we identified preoperative elevated levels of GGT and total bilirubin as predictive factors of RNH. A recent study also found that high levels of GGT predicted the presence of sinusoidal lesions.[27] Surprisingly, mean ICG-R15 values, known to be more sensitive and reliable for hepatic injury, were not altered in our patients with RNH. For patients at risk for RNH, efforts should be made to reduce the risks of liver surgery. Techniques, such as portal vein embolization and two-stage hepatectomy, may be helpful to spare the highest amount of liver parenchyma as possible, thereby maximizing the chances of an uneventful postoperative course.

In relation with the increased risk of hepatic morbidity and the enlarging number of patients who undergo repeat hepatectomy with perioperative chemotherapy, it is important to consider the evolution of RNH within time. RNH may have deleterious long-term consequences related to the development of portal hypertension. One case study reported the development of RNH and portal hypertension in three patients treated with oxaliplatin that finally

TABLE 4 Univariate and multivariate analysis of hepatic morbidity

Variable	N	Hepatic morbidity				
		Yes (N = 47)	No (N = 99)	UV *P*	MV *P*	RR (95% CI)
Patient factors						
Gender						
Male	85	25 (53%)	60 (61%)	0.4	–	–
Female	61	22 (47%)	39 (39%)			
Age at hepatectomy (yr)						
≤60	78	22 (47%)	56 (57%)	0.27	–	–
>60	68	25 (53%)	43 (43%)			
Liver metastases						
Synchronous[a]						
No	35	7 (15%)	28 (28%)	0.08	NS	–
Yes	111	40 (85%)	71 (72%)			
Number						
≤3	62	17 (43%)	45 (47%)	0.6	–	–
>3	73	23 (58%)	50 (53%)			
Maximum size (mm)						
≤30	50	17 (40%)	33 (38%)	0.9	–	–
>30	79	26 (61%)	53 (62%)			
Localization						
Unilobar	44	13 (28%)	31 (31%)	0.65	–	–
Bilobar	102	34 (72%)	68 (69%)			
Initial resectability						
No	105	36 (77%)	69 (70%)	0.39	–	–
Yes	41	11 (23%)	30 (30%)			
Concomitant extrahepatic disease						
No	125	40 (87%)	85 (86%)	0.86	–	–
Yes	20	6 (13%)	14 (14%)			
Preoperative chemotherapy						
No. of cycles						
≤9	87	26 (57%)	61 (64%)	0.38	–	–
>9	54	20 (44%)	34 (36%)			
Regimen						
5-FU/LV and oxaliplatin	92	33 (70%)	59 (60%)	0.21	–	–
Other	54	14 (30%)	40 (40%)			
Preoperative biochemical variables						
ICG-R15 (%)						
≤10	22	10 (35%)	12 (21%)	0.19	–	–
>10	63	19 (66%)	44 (79%)			
Platelet count[a] (10^3/μL)						
≤150	29	13 (33%)	16 (17%)	0.05	0.01	3.5 (1.3–9.2)
>150	103	27 (68%)	76 (83%)			
Prothrombin time (%)						
≤90	50	18 (41%)	32 (36%)	0.58	–	–
>90	83	26 (59%)	57 (64%)			
AST[a] (U/L)						
≤30	63	16 (36%)	47 (51%)	0.10	NS	–
>30	75	29 (64%)	46 (50%)			

TABLE 4 continued

Variable	N	Hepatic morbidity				
		Yes (N = 47)	No (N = 99)	UV *P*	MV *P*	RR (95% CI)
ALT (U/L)						
≤30	76	23 (51%)	53 (57%)	0.52	–	–
>30	62	22 (49%)	40 (43%)			
AP (U/L)						
≤100	54	19 (48%)	35 (45%)	0.79	–	–
>100	64	21 (53%)	43 (55%)			
GGT (U/L)						
≤80	79	28 (64%)	51 (56%)	0.4	–	–
>80	56	16 (36%)	40 (44%)			
Total bilirubin (μmol/L)						
≤15	114	35 (78%)	79 (85%)	0.3	–	–
>15	24	10 (22%)	14 (15%)			
Hepatectomy						
Major resection[a] (≥3 segments)						
No	73	17 (36%)	56 (57%)	0.02	0.05	2.6 (1–6.4)
Yes	73	30 (64%)	43 (43%)			
Pedicular clamping						
No	43	10 (23%)	33 (36%)	0.12	–	–
Yes	93	34 (77%)	59 (64%)			
Combined local treatment						
No	129	43 (92%)	86 (87%)	0.42	–	–
Yes	17	4 (9%)	13 (13%)			
Portal vein embolization						
No	128	40 (85%)	88 (89%)	0.52	–	–
Yes	18	7 (15%)	11 (11%)			
Two-stage hepatectomy[a]						
No	136	41 (87%)	95 (96%)	0.05	0.03	5.7 (1.2–27.2)
Yes	10	6 (13%)	4 (4%)			
Intraoperative RBC transfusion[a]						
No	78	19 (43%)	59 (67%)	0.01	0.03	2.6 (1.1–6.1)
Yes	54	25 (57%)	29 (33%)			
Nontumoral liver						
Macrovacuolar steatosis (≤30%)						
No	134	44 (94%)	90 (91%)	0.58	–	–
Yes	12	3 (6%)	9 (9%)			
Fibrosis						
No	77	28 (60%)	49 (50%)	0.25	–	–
Yes	69	19 (40%)	50 (51%)			
Sinusoidal alterations						
No	130	43 (92%)	87 (88%)	0.51	–	–
Yes	16	4 (9%)	12 (12%)			
Peliosis						
No	101	31 (66%)	70 (71%)	0.56	–	–
Yes	45	16 (34%)	29 (29%)			
HCN						
No	109	37 (79%)	72 (74%)	0.49	–	–
Yes	36	10 (21%)	26 (27%)			

TABLE 4 continued

Variable	N	Hepatic morbidity				
		Yes (N = 47)	No (N = 99)	UV *P*	MV *P*	RR (95% CI)
RNH[a]						
No	124	36 (77%)	88 (89%)	0.05	NS	–
Yes	22	11 (23%)	11 (11%)			

UV univariate, *MV* multivariate, *RR* risk ratio, *CI* confidence interval, *NS* not significant, *5-FU/LV* 5-fluorouracil/leucovorin, *ICG-R15* indocyanine green retention rate at 15 minutes, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AP* alkaline phosphatase, *GGT* gamma-glutamyltransferase, *RBC* red blood cell, *HCN* hemorrhagic centrilobular necrosis, *RNH* regenerative nodular hyperplasia

[a] Variables entered in Cox regression model

contraindicated curative liver surgery.[28] Recently, the development of portal hypertension in patients with RNH with deleterious postoperative complications and even death was reported by another group.[29] Other reports on RNH as a result of preoperative chemotherapy are rare.[30] When we evaluated the evolution of vascular lesions in patients that underwent repeat hepatectomy, previously diagnosed RNH was replaced by HCN in two patients. Because RNH is distributed throughout the liver in a regular pattern, sample variation is unlikely to cause the absence of RNH at subsequent hepatectomies.[31] Furthermore, all nontumoral liver specimens were evaluated by the same hepatobiliary pathologist. The natural history of RNH remains largely unknown.[28] However, because it is a noncirrhotic liver disease without fibrosis, RNH can theoretically regress, as was demonstrated in our study.[27]

Interestingly, in both patients in whom RNH disappeared, oxaliplatin was stopped and irinotecan was administered before the second hepatectomy. This may suggest that irinotecan may be a good alternative of oxaliplatin to treat these patients. Previously, RNH had already been associated with the use of oxaliplatin.[4] Recently, different authors have suggested a protective effect of bevacizumab on the development of vascular toxicity.[32–34] Therefore, its addition to conventional chemotherapy may reduce the risk of RNH and associated morbidity. However, this issue lies beyond the scope of the present study and needs further evaluation. Conclusions on the evolution of vascular lesions other than RNH into less or more severe types at repeat hepatectomy are difficult because of their irregular distribution throughout the liver with the subsequent risk of sample variation.

Our study represents a selected patient group that received only one line of chemotherapy. By this way, we were able to correlate RNH with different chemotherapy regimens most accurately. However, with the large amount of patients receiving multiple chemotherapy regimens before surgery, RNH may be even more frequent in daily practice. The potential negative effect of portal hypertension related to RNH on patient outcome should not be underestimated.

A final interesting remark of our study is that we observed only one patient with steatohepatitis, who received oxaliplatin before hepatectomy. Previous large series have associated steatohepatitis mainly with irinotecan, one of whom even found that steatohepatitis was related with an increased 90-day mortality rate.[7,14] The low incidence of obese patients and patients with diabetes probably is one of the reasons for the low frequency of steatohepatitis in our current study. The precise causes and consequences of this entity should nevertheless be investigated more extensively.

CONCLUSIONS

An increasing number of patients with CLM currently receive oxaliplatin-based chemotherapy, including adjuvant treatment after stage III colon cancer, induction therapy to convert extensive metastases to resectability, or perioperative treatment in patients with resectable metastases.[1,3,35] RNH may occur in one of five patients, with an increased risk of postoperative morbidity after hepatectomy. Elevated serum GGT and bilirubin are useful markers to detect RNH that does not contraindicate hepatic resection. Clinical recommendations regarding preoperative chemotherapy treatment based on these results should be evaluated further, taking into account the availability and consequences of new biological agents.

CONFLICT OF INTEREST None.

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