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ORIGINAL REPORT

Liver Histology and Surgical Outcomes After Preoperative Chemotherapy With Fluorouracil Plus Oxaliplatin in Colorectal Cancer Liver Metastases

Thomas Aloia, Mylène Sebagh, Marylène Plasse, Vincent Karam, Francis Lévi, Sylvie Giacchetti, Daniel Azoulay, Henri Bismuth, Denis Castaing, and René Adam

From the Departments of Hepatobiliary Surgery and Liver Transplantation, Pathology, and the Institut National de la Santé et de la Recherche Médicale, Chronotherapy Unit, Paul-Brousse Hospital, Villejuif, France; and Department of Hepatobiliary Surgery and Liver Transplantation, Hôpital St Luc, Montréal, Québec, Canada.

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Address reprint requests to René Adam, MD, PhD, Paul-Brousse Hospital, 12 Avenue Paul Vaillant Couturier, Villejuif, France 94800; e-mail: rene.adam@pbr.ap-hop-paris.fr.

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ABSTRACT

Purpose
Preoperative chemotherapy for colorectal liver metastases (CLM) can produce histologic changes in the nontumor-bearing liver (NTBL) that may impact on surgical outcomes.

Patients and Methods
From a cohort of 303 patients treated for CLM with liver resection, 92 patients (75 received preoperative chemotherapy: group C+; and 17 were chemotherapy naïve: group C−) were randomly selected for detailed pathologic analysis. Preoperative chemotherapy consisted of fluorouracil (FU)/leucovorin alone (23 patients, the majority chronomodulated) or in combination with oxaliplatin (52 patients, all chronomodulated). To determine associations between study factors, clinical and operative variables were compared with pathology data and surgical outcomes.

Results
Although clinical and operative factors were similarly distributed, C+ patients, compared with C− patients, were more likely to receive intraoperative RBC transfusions (mean units: 1.9 *v* 0.5, respectively; $P = .03$) and to have vascular abnormalities in the NTBL (52% *v* 18%, respectively; $P = .01$). Presence of the most severe forms of vascular alterations was closely associated with RBC transfusion requirements ($P = .04$). In contrast, moderate to severe steatosis was similarly distributed (C− group, 12%; C+ group, 13%). Although perioperative mortality and morbidity rates were similar in all groups, more than 12 courses of chemotherapy, compared with ≤ 12 courses, predisposed patients to reoperation (11% *v* 0%, respectively; $P = .04$) and to longer hospitalization (15 *v* 11 days, respectively; $P = .02$).

Conclusion
The main hepatic lesion induced by preoperative FU/oxaliplatin chemotherapy in patients with CLM is vascular and not steatosis. Detailed pathologic analysis determined that the most severe vascular lesions are associated with increased intraoperative transfusions. The risk for other postoperative complications is related to the duration of preoperative chemotherapy administration.

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INTRODUCTION

For patients with colorectal liver metastases (CLM), hepatic resection (HR) offers the only hope for cure, with reported posthepatectomy 5-year survival rates now reaching 58%.[1-4] Unfortunately, only 10% to 15% of patients diagnosed with CLM are candidates for curative resection because of either the distribution of metastases within the liver or the presence of simultaneous extrahepatic disease. For the remaining patients with initially unresectable disease, systemic chemotherapy without biologic agents offers median survival times of 12 to 20 months and 5-year survival rates of less than 5%.[5]

Recent advances in the efficacy of systemic therapy and the introduction of advanced surgical techniques have increased the percentage of patients with initially unresectable CLM who become candidates for curative HR.[6-10] The alliance between effective systemic chemotherapy and subsequent curative hepatectomy, with 5-year survival rates reported to be 30% to 35%,[9] has markedly increased the intensity of chemotherapy delivered to patients in an effort to convert them to resectability. In addition, neoadjuvant systemic chemotherapy is being used more frequently to treat patients who present with technically resectable disease.

Although little is known about the exact effects of preoperative chemotherapy on the nontumor-bearing liver (NTBL), chemotherapy has been associated with changes in the gross appearance of the liver (Fig 1), poor parenchymal hemostasis, and

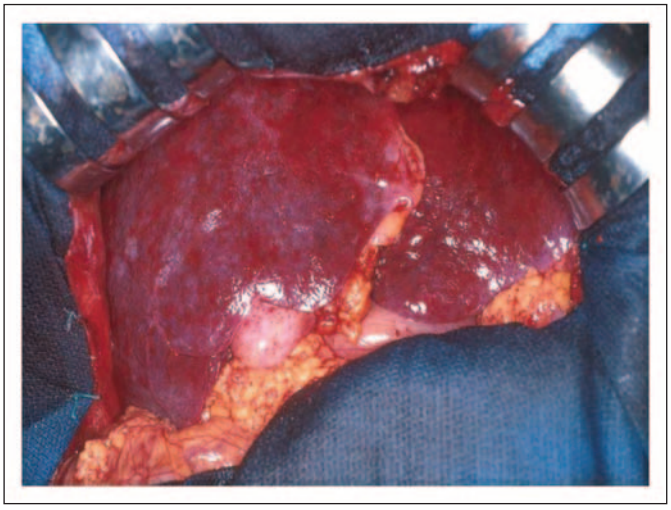

Fig 1. Intraoperative photograph demonstrating the typical appearance of the postchemotherapy liver.

defects in liver regeneration that may increase postoperative morbidity and mortality.[11,12] Initially, the phenotypic changes in the NTBL observed after systemic or regional chemotherapy were attributed to the development of hepatic steatosis.[13-16] In contrast, subsequent reports have suggested that vascular lesions are more closely associated with prehepatectomy chemotherapy administration than steatosis, particularly for oxaliplatin-containing regimens.[11,17,18] However, a detailed investigation of the spectrum of vascular lesions that are induced by preoperative chemotherapy is lacking. Moreover, the influence of chemotherapy treatment duration has not been extensively evaluated.

This study was designed to assess relationships between systemic chemotherapy, hepatotoxicity, and surgical outcomes by comparing study variables between chemotherapy-naïve patients and patients who were treated before HR with either fluorouracil (FU) and leucovorin (LV) or FU, LV, and oxaliplatin (I-OHP).

PATIENTS AND METHODS

Patients

From January 1990 to December 1995, 303 (89%) of 340 HRs for CLM performed in our center were first hepatectomies. Of these 303 HR patients, 144 patients (48%) were treated with prehepatectomy systemic chemotherapy, and 159 patients (52%) did not receive chemotherapy within 6 months of HR. Treatment sequence decisions for all patients were made by a multidisciplinary treatment planning group based on the number, size, and distribution of intrahepatic tumors. Forty-two (29%) of 144 patients treated with prehepatectomy chemotherapy were initially considered unresectable. For this group, surgery was performed as soon as tumor downsizing permitted an attempt at margin-negative resection. For the remaining 102 patients (71%) with initially resectable disease, prehepatectomy chemotherapy was used as neoadjuvant treatment.

The study was focused on patients treated with systemic FU- or FU/I-OHP–based regimens by excluding 38 of the 144 chemotherapy-treated patients (26%) who received intra-arterial chemotherapy or other miscellaneous systemic regimens. From the remaining group of 106 chemotherapy-treated patients, 75 patients (71%) were randomly selected for in-depth pathologic analysis (group C+). In addition, 17 (11%) of 159 patients without preoperative chemotherapy were randomly selected for in-depth pathologic analysis (group C–) and served as a control group. Primary tumors had been resected before hepatectomy in all study patients.

Chemotherapy: Regimen and Duration

The 75 patients in the C+ group included 23 patients who were treated with an intravenous regimen of FU/LV (FU 700 to 1,000 mg/m^2/d and LV 300 mg/m^2/d) administered continuously for 4 or 5 days every 2 to 3 weeks as previously described.[19,20] Fifty-two patients received intravenous FU/LV/I-OHP (FU 700 to 900 mg/m^2/d, LV 300 mg/m^2/d, and I-OHP 25 mg/m^2/d) administered for a duration of 4 to 5 days at 2- to 3-week intervals.[21] Chemotherapy delivery for the majority of patients in the FU/LV group and all patients in the FU/LV/I-OHP group was chronomodulated using a time/dose programmed pump (Aguettant, Lyon, France). No patients were administered erythropoietin-stimulating agents. To assess the impact of preoperative chemotherapy duration on study outcomes, patients in the C+ group were also subgrouped based on the number of preoperative chemotherapy cycles ($<$ six cycles, n = 29; six to 12 cycles, n = 28; and $>$ 12 cycles, n = 18).

Biochemical Variables

Liver-specific biochemical parameters were compared between the panel obtained at diagnosis of liver metastasis (before chemotherapy administration in the C+ group) and the panel drawn immediately before HR (after completion of chemotherapy in the C+ group). Recorded values included AST, ALT, alkaline phosphatase, gamma-glutamyltransferase, total bilirubin, and prothrombin time. These data were available at both time points for 86 (93%) of the 92 study patients. Preoperative hemoglobin levels and platelet counts were also compared between patients in the C+ and C– groups.

Operative and Postoperative Outcomes

Data regarding each patient's intraoperative course, including RBC and fresh frozen plasma transfusion rates, were collected from our prospective liver surgery database. Postoperative complications were classified as local or general, and the duration of postoperative inpatient hospital length of stay (LOS) was recorded. Postoperative mortality rates were measured at 2 and 6 months from hepatectomy, with follow-up data available at 6 months for all patients.

Histopathologic Examination

A hepatobiliary pathologist (M.S.) made a detailed microscopic assessment of liver tissue not involved by tumor in the resected specimens from each study patient. The NTBL analysis was independently performed from the analysis of the tumoral lesions, and the pathologist was given no information regarding preoperative chemotherapy administration or perioperative outcomes before this analysis.

NTBL tissues were analyzed according to a predetermined format to identify the following four histologic entities: fibrosis, vascular lesions, macrovacuolar steatosis, and surgical necrosis. Fibrosis was categorized as portal fibrosis, porto-portal fibrosis, septal fibrosis, and cirrhosis. Likewise, vascular lesions were categorized, in ascending order of severity, as sinusoidal vasodilatation and congestion, peliosis, hemorrhagic centrilobular necrosis (HCN), and regenerative nodular hyperplasia (RNH; Fig 2). The presence of venoocclusive lesions was also noted. Macrovacuolar steatosis was graded as mild ($<$ 30% of hepatocytes), moderate (30% to 60% of hepatocytes), or severe ($>$ 60% of hepatocytes) and reported for analysis in cases of clinically significant involvement (moderate or severe steatosis). Finally, the presence or absence of necrotic lesions induced by operative manipulation of the liver, termed surgical necrosis or surgical hepatitis, was defined by the finding of hepatocyte necrosis associated with neutrophils disseminated throughout the periportal or centrilobular areas.

Statistical Analysis

Continuous data are reported as mean ± standard deviation, and categoric data are reported as the number of patients with percentages. Quantitative variables were compared using the Student's t or analysis of variance tests, and qualitative variables were compared using χ^2 tests. Differences were considered significant when $P \leq .05$. For the univariate analysis of study variables based on the presence (n = 75) or absence (n = 17) of preoperative chemotherapy, the probability of detecting a 15% difference at $\alpha = .05$ was 33%. For the univariate analysis of study variables based on low (n = 55) versus high (n = 37) transfusion rates, the probability of detecting a 15% difference at

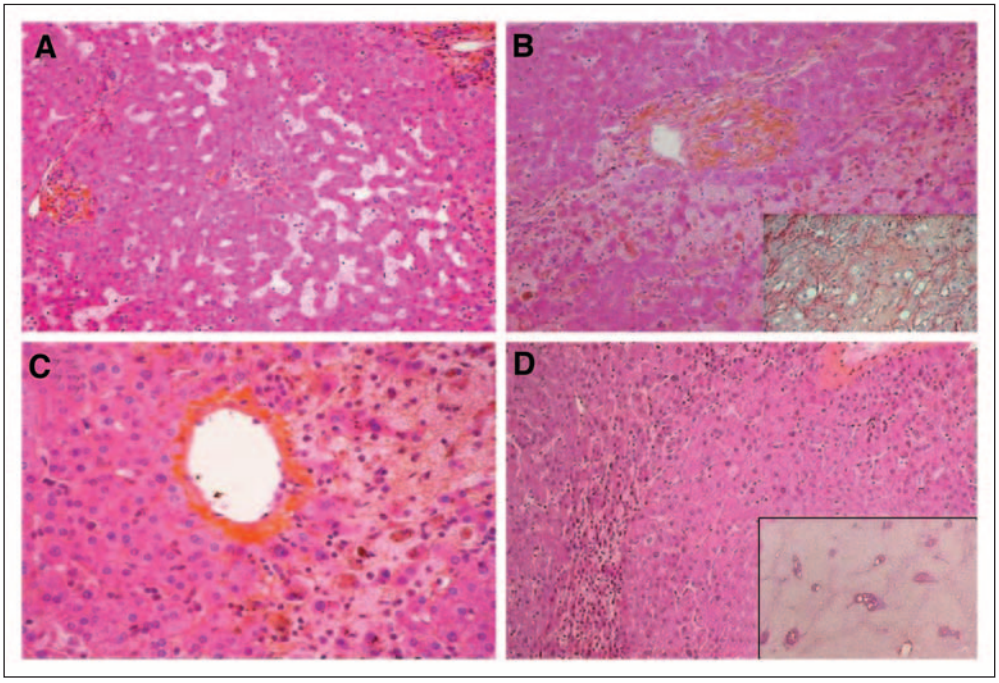

Fig 2. Illustration of the different vascular changes observed in the nontumor-bearing liver after systemic chemotherapy. (A) Vasodilation and congestion (Hematoxylin-eosin [HES]; ×10); (B) peliosis (HES ×10; inset: picrosirius stain, ×10); (C) hemorrhagic centrilobular necrosis (HES, ×40); (D) nodular regenerative hyperplasia (HES ×20; inset: picrosirius stain, ×2.5).

$\alpha = .05$ was 64%. To determine which study factors were associated with adverse perioperative outcome (ie, increased intraoperative transfusion rates), binomial logistic regression was used. All statistical calculations were made with SPSS 12.0 software (SPSS Inc, Chicago, IL).

RESULTS

Comparisons Based on Presence of Preoperative Chemotherapy

Analysis of clinical variables. The 92 study patients were characterized by a male to female ratio of 54:38 and a mean age of 57.9 years (range, 27.9 to 84.9 years). The distributions of patient sex, patient age, and the maximal diameter of the largest metastasis were similar in the C+ (41 ± 27 mm) and C– (39 ± 11 mm) patients ($P = .75$; Table 1). However, the mean number of tumors resected in the C+ group (3.5 ± 3.2 tumors) was higher than the mean number in C– group (2.1 ± 1.5 tumors; $P = .07$).

Analysis of biochemical variables. At diagnosis, patients in the C+ group had higher mean serum gamma-glutamyltransferase levels (36.7 ± 19.2 IU/L) than patients in the C– group (69.2 ± 51.3 IU/L; $P = .04$). Otherwise, the initial biochemical profile for patients in each group was similar. Immediately before HR, no difference in liver function was observed in the C+ patients compared with the C– patients. Analysis of preoperative hematology profiles in the C+ and C– groups determined that hemoglobin levels (12.4 ± 1.6 *v* 13.2 ± 1.3 g/dL, respectively; $P = .28$) and platelet counts (224 ± 67 *v* 270 ± 71 × $10^3/\mu$L, respectively; $P = .53$) were similar.

Analysis of operative variables. C+ and C– patients had a similar rate of major resection (67% *v* 59%, respectively; $P = .54$) and similar mean number of liver segments resected (3.1 *v* 2.9 segments, respectively; $P = .59$). Likewise, the use of hepatic pedicle clamping was similar between groups. In contrast, the mean transfusion rate for packed RBCs (PRBCs) was four-fold higher in the C+ group (1.9 ± 2.6 units) compared with the C– group (0.5 ± 1.0 units; $P = .03$). Transfusion rates for fresh frozen plasma were similar between the study groups.

During postoperative recovery, the prevalence of local complications (C+ group, 20%; C– group, 6%; $P = .17$) and general complications (C+ group, 13%; C– group, 6%; $P = .39$) was higher in the C+ group than in the C– group. However, mean LOS was similar between study groups (C+ group, 12.5 ± 4.5 days; C– group, 12.0 ± 2.7 days; $P = .68$). Two patients in the C+ group (3%) required reoperation as a result of hemorrhagic complications. No study patients died within 60 days of hepatectomy; however, two patients died between 2 and 6 months after hepatectomy. Both patients had experienced immediate postoperative complications. One patient died from sepsis and multiorgan failure 2.5 months after hepatectomy, and one patient, who had a lung recurrence, died from pulmonary embolus 5 months after hepatectomy.

Analysis of histologic lesions. Hepatic vascular lesions were more frequent in the C+ group than in the C– group (52% *v* 18%, respectively; $P = .01$). Each type of vascular lesion was more commonly identified in C+ patients than in C– patients, including a higher incidence of sinusoidal vasodilatation and congestion (23% *v* 12%, respectively), peliosis (31% *v* 6%, respectively), HCN (25% *v* 6%, respectively), and RNH (3% *v* 0%, respectively). Veno-occlusive disease was never observed.

In contrast, the incidence of steatosis was similar between the study groups. Two patients (12%) in the C– group and 10 patients (13%) in the C+ group demonstrated clinically significant levels of steatosis ($P = .86$). Surgical necrosis (surgical hepatitis) was observed in 35% of C+ patients and in 12% of C– patients ($P = .06$).

Comparisons Based on Intraoperative Transfusions

Study factors were compared between patients with low transfusion requirements (≤ 1 unit of intraoperative RBC transfusion, n = 55) and patients with high transfusion requirements (> 1 unit of intraoperative RBC transfusion, n = 37; Table 2). Both the high and

Table 1. Comparison of the Distribution of Study Factors for Chemotherapy-Naïve Patients, Patients Treated With Preoperative FU/LV, and Patients Treated With Preoperative FU/LV/l-OHP

Factor	Preoperative Chemotherapy: None (n = 17) No. of Patients	%	FU/LV (n = 23) No. of Patients	%	FU/LV/l-OHP (n = 52) No. of Patients	%	*P*
Clinical							
Age, years							.70
Mean	60.0		59.2		56.7		
SD	11.9		12.2		11.8		
Sex							.35
Male	8	47	16	70	30	58	
Female	9	53	7	30	22	42	
No. of metastases							.06
Mean	2.1		3.7		3.4		
SD	1.5		2.9		3.3		
Size of largest metastasis, mm							.11
Mean	39		33		45		
SD	11		21		28		
Hemoglobin < 11g/dL*	1	6	3	14	5	10	.33
Platelet count < $150 \times 10^3/\mu$L†	1	6	2	10	4	9	.45
Operative							
Major resection	10	59	15	65	35	67	.82
No. of resected segments							.56
Mean	2.9		3.0		3.3		
SD	1.1		1.1		1.4		
Pedicle clamping	10	59	14	61	29	56	.91
Duration of pedicle clamping, min							.38
Mean	30.0		39.6		39.1		
SD	19.8		24.1		20.0		
Intraoperative transfusions							
Packed red blood cells, units							.04
Mean	0.5		1.5		2.0		
SD	1.0		2.0		2.8		
Fresh frozen plasma, units							.07
Mean	0		0		0.4		
SD	0		0		1.4		
Postoperative							
Local complications	1	6	6	26	9	17	.25
General complications	1	6	5	22	5	10	.23
Reoperation	0	0	0	0	2	4	.46
Length of hospital stay, days							.99
Mean	12.0		12.4		12.5		
SD	2.7		2.7		4.7		
Operative mortality							
≤ 2 months	0	0	0	0	0	0	NS
≤ 6 months	0	0	0	0	2	4	.46
Histopathologic							
Steatosis	2	12	6	26	4	8	.09
Moderate	2	12	5	22	4	8	.22
Severe	0	0	1	4	0	0	.22
Fibrosis	6	35	19	83	25	48	.005
Portal	6	35	17	74	22	42	.02
Porto-portal	0	0	2	9	2	4	.40
Septal	0	0	0	0	0	0	NS
Cirrhosis	0	0	0	0	1	2	.68
Surgical necrosis	2	12	12	52	14	27	.02
Vascular lesions‡	3	18	11	48	28	54	.03
Sinusoidal alterations§	2	12	7	30	10	19	.33
Peliosis	1	6	7	30	16	31	.11
Hemorrhagic centrilobular necrosis	1	6	1	4	18	35	.003
Regenerative nodular hyperplasia	0	0	0	0	2	4	.46

Abbreviations: FU, fluorouracil; LV, leucovorin; l-OHP, oxaliplatin; SD, standard deviation; NS, not significant.
*Hemoglobin values available for 87 patients.
†Platelet count values available for 81 patients.
‡Vascular lesions include patients with one or more of the listed individual vascular changes.
§Sinusoidal alterations include vasodilatation and congestion.

Table 2. Comparison of the Distribution of Study Factors for Patients With ≤ 1 Unit of Intraoperative RBC Transfusion Versus Patients With More Than 1 Unit

Factor	No. of PRBC Transfusions: ≤ 1 Unit (n = 55) No. of Patients	%	> 1 Unit (n = 37) No. of Patients	%	*P*
Clinical					
No. of metastases					.58
Mean		3.1		3.5	
SD		2.7		3.3	
Size of largest metastasis, mm					.75
Mean		39		40	
SD		11		24	
Preoperative chemotherapy regimen					.03
None	15	27	2	5	
FU/LV	13	24	10	27	
FU/LV/l-OHP	27	49	25	68	
Chemotherapy duration					.64
< 6 cycles	17	43	12	34	
6-12 cycles	15	38	13	37	
> 12 cycles	8	19	10	29	
Preoperative hemoglobin, g/dL					.33
Mean		12.6		12.2	
SD		1.5		1.8	
Preoperative platelet count, $\times 10^3/\mu$L					.72
Mean		235		229	
SD		64		78	
Operative					
Major resection	34	62	26	70	.40
No. of resected segments					.15
Mean		3.0		3.4	
SD		1.2		1.3	
Pedicle clamping	31	56	22	60	.77
Duration of pedicle clamping, min					.10
Mean		33.5		43.2	
SD		17.7		24.2	
Postoperative					
Reoperation	0	0	2	5	.08
Length of hospital stay, days					.0001
Mean		11.1		14.2	
SD		2.6		5.3	
Operative mortality					
≤ 2 months	0	0	0	0	NS
≤ 6 months	0	0	2	5	.08
Histopathologic					
Steatosis	5	9	7	19	.17
Moderate	4	7	7	19	.09
Severe	1	2	0	0	.41
Fibrosis	32	58	18	49	.37
Portal	28	51	17	46	.64
Porto-portal	3	6	1	3	.53
Septal	0	0	0	0	NS
Cirrhosis	1	2	0	0	.41
Surgical necrosis	12	22	16	43	.03
Vascular lesions*	22	40	20	54	.19
Sinusoidal alterations†	12	22	7	19	.74
Peliosis	12	22	12	32	.26
HCN	9	16	11	30	.13
RNH	0	0	2	5	.08
HCN + RNH	9	16	13	35	.04

Abbreviations: PRBC, packed RBC; SD, standard deviation; FU, fluorouracil; LV, leucovorin; l-OHP, oxaliplatin; NS, not significant; HCN, hemorrhagic centrilobular hyperplasia; RNH, regenerative nodular hyperplasia.

*Vascular lesions include patients with one or more of the listed individual vascular changes.

†Sinusoidal alterations include vasodilatation and congestion.

low transfusion requirement groups had a similar mean number of resected metastases (3.5 ± 3.3 *v* 3.1 ± 2.7 metastases, respectively; $P = .58$), mean size of the largest metastasis (40 ± 24 *v* 39 ± 11 mm, respectively; $P = .75$), major resection rate (70% *v* 62%, respectively; $P = .40$), and mean number of resected segments (3.4 ± 1.3 *v* 3.0 ± 1.2, respectively; $P = .15$).

Multivariate analysis of all study factors potentially contributing to increased intraoperative transfusion rates determined that preoperative chemotherapy was the only independent prognostic factor ($P = .005$; Table 3). Patients who received preoperative chemotherapy were 2.26 times more likely to require more than 1 unit of intraoperative RBC transfusion (95% CI, 1.99 to 4.32). Other study factors with close, although not statistically significant, association with increased intraoperative RBC transfusions were preoperative chemotherapy with I-OHP ($P = .083$) and preoperative chemotherapy for more than six cycles ($P = .056$).

Patients in the high intraoperative transfusion group also experienced a more difficult recovery. Both of the patients who required reoperation were in this group. In addition, the mean postoperative LOS for patients who received more than 1 unit of PRBC was longer (14.2 ± 5.3 days) than for patients requiring ≤ 1 unit of intraoperative PRBC transfusion (11.1 ± 2.6 days; $P = .0001$)

In histopathologic analysis, fibrosis and steatosis were similarly distributed between transfusion groups. In contrast, vascular lesions were more common in the high transfusion group (54%) compared with the low transfusion group (40%; $P = .19$). These differences were particularly marked when the more severe vascular changes were analyzed. Compared with low transfusion group patients, patients with high transfusion requirements had higher rates of HCN (30% *v* 16%, respectively; $P = .13$) and RNH (5% *v* 0%, respectively; $P = .08$). When the incidence of these two severe vascular changes was combined, the difference in the incidence of severe vascular lesions between high (35%) and low (16%) transfusion groups achieved statistical significance ($P = .04$).

Comparisons Based on Chemotherapy Regimen and Duration

Analysis of regimen. Analysis according to the type of chemotherapy demonstrated a higher, but not statistically significant, RBC transfusion rate in the FU/LV/I-OHP group compared with the FU/LV group (2.0 ± 2.8 *v* 1.5 ± 2.0 units, respectively; $P = .41$). Patients in the FU/LV group compared with the FU/LV/I-OHP group had a higher incidence of steatosis (26% *v* 8%, respectively; $P = .03$) and fibrosis (83% *v* 48%, respectively; $P = .005$), whereas patients in the FU/LV/I-OHP group had a higher incidence of HCN compared with the FU/LV group (35% *v* 4%, respectively; $P = .005$).

Analysis of duration. All study variables were similarly distributed between groups of patients who received less than six, six to 12, and more than 12 cycles of chemotherapy, with the exception that patients who received more than 12 cycles versus ≤ 12 cycles had a higher reoperation rate (11% *v* 0%, respectively; $P = .04$) and a longer LOS (14.9 ± 7.0 *v* 11.2 ± 2.9 days, respectively; $P = .02$). In pathologic analysis, HCN was more frequent in patients treated with more than 12 courses of chemotherapy compared with patients treated with six to 12 or less than six courses (50% *v* 25% *v* 10%, respectively; $P = .01$).

Table 3. Multivariate Analysis of Factors Potentially Contributing to Increased Intraoperative Transfusion Rates (> 1 unit of packed RBCs) in Study Patients With Colorectal Liver Metastases Treated With and Without Preoperative Chemotherapy

Factor	*P*	Odds Ratio	95% CI
Any preoperative chemotherapy	.005	2.26	1.99 to 4.32
Preoperative chemotherapy with oxaliplatin	.083	—	—
Preoperative chemotherapy cycles > 6	.056	—	—
Preoperative chemotherapy cycles > 12	.23	—	—
Preoperative hemoglobin level < 11 g/dL	.42	—	—
Preoperative platelet count < 150 × $10^3/\mu L$	.18	—	—
> 3 tumors	.45	—	—
Maximal tumor size > 5 cm	.17	—	—
> 3 resected segments	.62	—	—

DISCUSSION

The hypothesis that systemic chemotherapy before HR can adversely affect the liver parenchyma is strongly suggested by the commonly noted heterogeneous appearance of livers subjected to preoperative chemotherapy and by the increased fragility of the liver parenchyma observed during hepatic surgery. However, little is known about the relationship between systemic chemotherapy and histologic changes in the NTBL that may be responsible for the postchemotherapy liver. In addition, concordance between preoperative chemotherapy with FU/I-OHP, hepatic toxicity, and poor postoperative outcomes has not been established.

Through a detailed histopathologic analysis of the NTBL, this study aimed to identify specific chemotherapy-induced liver lesions, their relationship to the type and duration of chemotherapy, and their impact on perioperative outcomes. Study patients were randomly selected from a cohort treated with either FU/LV or FU/LV/I-OHP, allowing for comparison of the effects of a current standard regimen with a previously used regimen.

The major finding of the histopathologic analysis was a higher incidence of vascular hepatic lesions observed in patients who received preoperative chemotherapy. These results are in agreement with those recently published by other groups. In 2004, Rubbia-Brandt et al[17] reported a 51% incidence of sinusoidal dilation and peliosis in 87 patients treated with preoperative systemic chemotherapy compared with 0% of 66 patients without systemic treatment. However, unlike the study by Rubbia-Brandt et al,[17] veno-occlusive lesions were not observed in our patients. In 2006, Karoui et al[18] reported that 49% of 45 patients treated with preoperative chemotherapy demonstrated sinusoidal dilation, atrophy of hepatocytes, and/or hepatocyte necrosis. Most recently, Vauthey et al[11] have also reported an association between prehepatectomy chemotherapy with FU/LV/I-OHP and sinusoidal dilation.

None of these previously reported studies identified a specific postoperative outcome associated with histologic changes induced by FU/LV/I-OHP chemotherapy. This may be because these studies limited the examination of vascular pathologic changes to mild forms (sinusoidal dilation and peliosis). Our study, which examined a spectrum of vascular changes, was able to correlate the presence of the two most severe forms of vascular lesions (HCN and RNH) with intraoperative RBC transfusion requirements. This finding represents the first instance where a preoperative chemotherapy-induced liver toxicity

related to FU/LV/I-OHP has been associated with a specific perioperative outcome in patients with CLM.

Regarding the postoperative course, overall morbidity rates tended to be higher in the C+ group. This finding is concordant with the initial results of the European Organisation for Research and Treatment of Cancer 40983 trial, which indicated that complication rates were higher in initially resectable patients randomly assigned to chemotherapy with six cycles of infusional FU, LV, and I-OHP before hepatectomy (24.5%) compared with patients treated with surgery as primary therapy (13.3%).[12] Despite the apparent increase in postoperative complication rates after chemotherapy, we detected no difference in postoperative LOS. This finding is similar to three previous studies that also found no difference in LOS for chemotherapy-treated and non–chemotherapy-treated patients.[11,15,16]

Although we did not identify an adverse impact of prehepatectomy chemotherapy on overall postoperative LOS, the analysis of outcomes based on duration of preoperative chemotherapy determined that treatment with more than 12 courses of chemotherapy resulted in a higher reoperation rate and a longer LOS. This important finding is concordant with the outcomes data recently reported by Karoui et al,[18] who found that patients treated with ≥ six cycles of chemotherapy experienced a 54% complication rate compared with a rate of 19% in patients receiving less than six cycles.

As with any study involving patients who did and did not receive preoperative chemotherapy, the comparability of the two cohorts must be carefully examined. Tumor number was the most frequent criteria used by our group to select patients for preoperative chemotherapy, and therefore, the number of hepatic metastases per patient was higher in the C+ group than the C– group. However, the size of metastases, number of segments resected, and the percentage of patients who required major hepatectomy were similarly distributed between the groups. Furthermore, multivariate analysis determined that the only independent factor associated with intraoperative RBC transfusions was the presence of preoperative chemotherapy, supporting the conclusion that preoperative chemotherapy accounted for the observed differences in histopathologic analysis and perioperative outcomes.

The general presence of vascular lesions after chemotherapy has not been associated with statistical differences in postoperative mortality, postoperative morbidity, or the length of postoperative inpatient hospitalization.[11,17,18] Given these data, it seems that the risk of inducing histologic alterations in the NTBL with preoperative FU/LV/I-OHP chemotherapy does not justify altering the rationale to administer chemotherapy to patients with metastatic colorectal cancer or to combine it with HR in patients with initially unresectable liver metastases.[9]

However, our data indicating that patients with the severest forms of vascular lesions may experience poorer short-term outcomes have practical relevance for all patients considering prehepatectomy chemotherapy. For patients with initially unresectable disease, the data indicate that liver surgery is indicated as soon as chemotherapy-induced tumor downsizing permits margin-negative resection. For patients with initially resectable disease, short courses of chemotherapy may be appropriate, pending the results of the European Organisation for Research and Treatment of Cancer trial 40983, but the potential development of severe chemotherapy-induced vascular lesions should now be taken into consideration, and long courses of chemotherapy for this indication should be avoided.

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Authors' Disclosures of Potential Conflicts of Interest

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Author Contributions

Conception and design: Thomas Aloia, Mylène Sebagh, Francis Lévi, Henri Bismuth, Denis Castaing, René Adam
Provision of study materials or patients: Francis Lévi, Sylvie Giacchetti, Daniel Azoulay, Denis Castaing, René Adam
Collection and assembly of data: Thomas Aloia, Mylène Sebagh, Marylène Plasse, Vincent Karam
Data analysis and interpretation: Thomas Aloia, Marylène Plasse, Vincent Karam, Francis Lévi, Sylvie Giacchetti, Daniel Azoulay, Henri Bismuth, René Adam
Manuscript writing: Thomas Aloia, Mylène Sebagh, Marylène Plasse, Francis Lévi, Daniel Azoulay, René Adam
Final approval of manuscript: Thomas Aloia, Mylène Sebagh, Francis Lévi, Daniel Azoulay, Henri Bismuth, René Adam