

Chemotherapy Regimen Predicts Steatohepatitis and an Increase in 90-Day Mortality After Surgery for Hepatic Colorectal Metastases

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ABSTRACT

Purpose

Chemotherapy before resection of hepatic colorectal metastases (CRM) may cause hepatic injury and affect postoperative outcome.

Patients and Methods

Four hundred six patients underwent hepatic resection of CRM between 1992 and 2005. Pathologic review of the nontumorous liver was performed using established criteria for steatosis, steatohepatitis, and sinusoidal injury. The effect of chemotherapy and liver injury on perioperative outcome was analyzed.

Results

One hundred fifty-eight patients (38.9%) received no preoperative chemotherapy, whereas 248 patients (61.1%) did. The median duration of chemotherapy was 16 weeks (range, 2 to 70 weeks). Chemotherapy consisted of fluoropyrimidine-based regimens (fluorouracil [FU] alone, 15.5%; irinotecan plus FU, 23.1%; and oxaliplatin plus FU, 19.5%) and other therapy (3.0%). On pathologic analysis, 36 patients (8.9%) had steatosis, 34 (8.4%) had steatohepatitis, and 22 (5.4%) had sinusoidal dilation. Oxaliplatin was associated with sinusoidal dilation compared with no chemotherapy (18.9% v 1.9%, respectively; $P < .001$; odds ratio [OR] = 8.3; 95% CI, 2.9 to 23.6). In contrast, irinotecan was associated with steatohepatitis compared with no chemotherapy (20.2% v 4.4%, respectively; $P < .001$; OR = 5.4; 95% CI, 2.2 to 13.5). Patients with steatohepatitis had an increased 90-day mortality compared with patients who did not have steatohepatitis (14.7% v 1.6%, respectively; $P = .001$; OR = 10.5; 95% CI, 2.0 to 36.4).

Conclusion

Steatohepatitis is associated with an increased 90-day mortality after hepatic surgery. In patients with hepatic CRM, the chemotherapy regimen should be carefully considered because the risk of hepatotoxicity is significant.

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INTRODUCTION

Surgical resection of hepatic metastases is the standard of care for resectable disease, with recent single and multicenter studies reporting up to a 58% 5-year survival rate.¹⁻⁴ Even after successful hepatic resection, however, the majority of patients will develop recurrent disease, either in the liver alone or in combination with extrahepatic sites.^{5,6} Therefore, systemic chemotherapy (primarily fluoropyrimidine-based regimens) has been used as adjuvant therapy in combination with resection or as part of a multimodality approach of initially unresectable hepatic colorectal metastases (CRM).⁷⁻¹¹

Although traditionally administered postoperatively, systemic chemotherapy has increasingly been used in the preoperative setting before liver resection^{7,8,12} because of several theoretical advantages. These include the potential to downsize tumor(s) preoperatively, to increase curative resection rates, and to convert some patients from having unresectable to resectable disease. Use of preoperative therapy in patients at high risk for recurrence may assist in identifying responders so that therapy can be tailored postoperatively based on preoperative response. In addition, patients with multiple tumors who progress on preoperative chemotherapy and who, therefore, may not benefit from resection can be spared nontherapeutic surgery.^{8,13}

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Although preoperative therapy has been shown to be effective and safe in other types of solid tumors, such as rectal and esophageal carcinoma,^{14,15} recent reports indicate a chemotherapy-associated increase in the incidence of steatosis,¹² steatohepatitis,¹⁶ and sinusoidal injury.¹⁷ The impact of these changes on outcome after liver resection remains uncertain. In the current study, we analyzed the histopathologic changes associated with preoperative chemotherapy and report the postoperative outcome of patients who received chemotherapy before resection of hepatic CRM.

PATIENTS AND METHODS

A retrospective review of patients who underwent hepatic surgery for CRM with curative intent at The University of Texas M.D. Anderson Cancer Center (Houston, TX) and the Department of Surgical Oncology, Istituto per la Ricerca e la Cura del Cancro Candiolo (Torino, Italy) between June 1992 and June 2005 was undertaken. Hepatic resections were defined according to the Brisbane terminology.^{18,19} Patients were divided into the following five groups based on their preoperative chemotherapy regimen: (1) no preoperative chemotherapy; (2) fluoropyrimidine-based chemotherapy with fluorouracil (FU) and leucovorin alone; (3) fluoropyrimidine-based chemotherapy with FU plus irinotecan; (4) fluoropyrimidine-based chemotherapy with FU plus oxaliplatin; and (5) other therapy. Patients who received chemotherapy for their primary tumor within 1 year of liver resection and patients who received regional therapy were excluded. Patients who underwent preoperative portal vein embolization were also excluded because of the histopathologic changes affecting the nontumorous hepatic parenchyma.²⁰

Standard demographic data were collected on all patients including type and duration of preoperative chemotherapy; details of the resection; estimated blood loss (EBL), which was calculated as previously described²¹; characteristics of the resected tumor; and 90-day morbidity and mortality.

Four attending pathologists (T.-T.W., M.R., G.Y.L., and M.M.-K.) with hepatobiliary expertise and who were blinded to the clinical data evaluated the resected specimens. Pathologic findings of the hepatic parenchyma remote from the resected tumor were scored as follows: (1) degree of steatosis was graded as none, mild (< 30%), moderate (\geq 30% to 50%), or severe (\geq 50%); (2) steatohepatitis was graded as defined by Kleiner et al²² based on steatosis (score 0 = 5%; 1 = 5% to 33%; 2 \geq 33% to 66%; and 3 \geq 66%), lobular inflammation (score 0 = no foci; 1 = one to two foci; 2 = two to four foci; and 3 \geq four foci per \times 200 field), and ballooning (score 0 = none; 1 = few balloon cells; 2 = many cells/prominent ballooning; Fig 1); and (3) sinusoidal injury was scored based on an established grading system of sinusoidal dilation (Fig 2).¹⁷ Hepatic injury was defined as steatosis more than 30%, steatohepatitis Kleiner score \geq 4, and/or grade 2 to 3 sinusoidal dilation.

Summary statistics were obtained using the χ^2 and Fisher's exact tests for comparing categorical variables; the Kruskal-Wallis test was used to compare continuous variables among the treatment groups. The odds ratios (ORs) and the 95% CIs were estimated, and a $P < .05$ was considered to be statistically significant.

RESULTS

Table 1 lists the clinicopathologic features of the 406 patients in the study. There were 250 men and 156 women; the median patient age was 59 years (range, 18 to 86 years). Most patients had a primary colon carcinoma ($n = 310$; 76.3%) with node-positive disease ($n = 245$; 60.3%). The median number of lesions was two (range, one to 12 lesions), and the median size of the largest lesion was 3.5 cm (range, 1.1 to 9.4 cm).

The majority of patients received preoperative chemotherapy ($n = 248$; 61.1%) before surgical treatment of the hepatic metastases

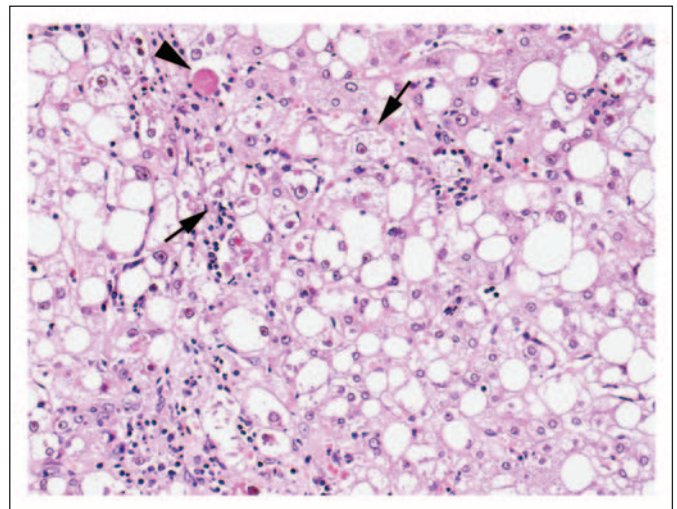


Fig 1. Example of steatohepatitis. The disorganized lobular parenchyma displays marked macrovesicular steatosis with evidence of ballooning (arrows) surrounded by scattered inflammation and apoptotic hepatocytes (arrowhead). Hematoxylin and eosin, \times 200.

(Table 2). Most of these patients ($n = 204$ of 248; 82.3%) were resectable at presentation, and chemotherapy was administered as neoadjuvant therapy. In 44 patients (17.7%), the hepatic CRM were initially unresectable, and preoperative chemotherapy resulted in tumor downsizing, thereby allowing subsequent resection. Chemotherapy consisted of fluoropyrimidine-based regimens (FU alone, 15.5%; FU plus irinotecan, 23.1%; and FU plus oxaliplatin, 19.5%) and other therapy (3.0%; capecitabine, 1.7%; floxuridine, 0.5%; and tegafur with uracil 0.8%; Table 2). In the latter part of the study, bevacizumab was combined with oxaliplatin ($n = 18$) or with irinotecan ($n = 1$); no patient received cetuximab. Of the 248 patients who received preoperative chemotherapy, the median duration of treatment was 16 weeks (range, 2 to 70 weeks).

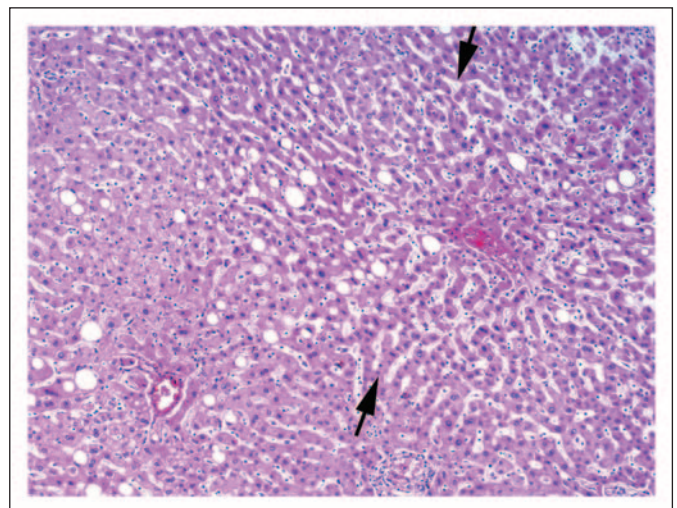


Fig 2. Moderate centrilobular sinusoidal distention in a patient who received oxaliplatin. Only scattered macrovesicular steatosis is present. Compare the zone with sinusoidal distention (arrows) to the normal parenchyma in the left lower quadrant. Hematoxylin and eosin, \times 100.

Table 1. Clinical and Pathologic Features of Patients (N = 406)

Variable	No. of Patients	%
Median age, years	59	
Sex		
Female	156	38.4
Male	250	61.6
Body mass index		
Median, kg/m ²	26.3	
< 25 kg/m ²	156	38.5
≥ 25 kg/m ²	249	61.3
Not available	1	0.2
Diabetes mellitus		
Present	50	12.3
Absent	356	87.7
Site of primary tumor		
Colon	310	76.3
Rectum	92	22.7
Not available	4	1.0
Status of primary lymph nodes		
Negative	133	32.7
Positive	245	60.3
Not available	28	7.0
Hepatic colorectal metastases		
Median	2	
Solitary	206	50.7
Multiple	200	49.3
Median tumor size, cm*	3.5	

*Calculated using the size of the largest lesion when multiple colorectal metastases were present.

At the time of operation, the extent of hepatic resection was less than a hemihepatectomy in 131 patients (32.3%), a hemihepatectomy in 203 patients (50.0%), and an extended hepatectomy in 72 patients (17.7%). Resection was combined with radiofrequency ablation in 126 patients (31.0%). The median operative time was similar for patients who had received preoperative chemotherapy (173 minutes;

Table 2. Details of Chemotherapy Treatment (N = 406)

Variable	No. of Patients	%
Preoperative chemotherapy		
No	158	38.9
Yes	248	61.1
Indication for preoperative chemotherapy, n = 248		
Initially resectable disease	204	82.3
Initially unresectable disease	44	17.7
Chemotherapy type		
None	158	38.9
Fluorouracil alone	63	15.5
Fluorouracil plus irinotecan	94	23.1
Fluorouracil plus oxaliplatin	79	19.5
Other	12	3.0
Median duration of chemotherapy treatment, weeks	16.0	
Median interval duration between chemotherapy and surgery, weeks	6.4	

range, 61 to 564 minutes) compared with patients who had not received chemotherapy treatment (176 minutes; range, 60 to 577 minutes; $P = .43$). The median EBL was comparable between patients with a history of preoperative chemotherapy (250 mL; range, 0 to 3,400 mL) and patients with no history of chemotherapy (300 mL; range, 0 to 15,000 mL).

Patient characteristics and operative details were stratified according to chemotherapy regimens (Table 3). In general, tumor characteristics and surgery details were similar among all chemotherapy groups. Patients who received FU alone tended to have less major hepatectomies ($P = .06$) and had smaller tumors that were more likely to be solitary (both $P < .05$). Patients treated with FU alone also had a longer duration of chemotherapy treatment ($P = .001$). The EBL was significantly lower in patients receiving oxaliplatin, which likely reflects recent changes in operative technique.²¹

The perioperative complication rate was 20.9%. Nineteen patients (4.7%) suffered from hepatic complications including liver failure ($n = 5$), hepatic insufficiency ($n = 4$), bile leaks/biloma ($n = 4/3$), hepatic cut surface bleeding ($n = 1$), and portal vein thrombosis ($n = 2$). Nonhepatic complications occurred in 66 patients (16.2%); there were 23 pulmonary complications (5.7%; pleural effusion, $n = 5$; pneumonia, $n = 10$; atelectasis, $n = 2$; pneumothorax, $n = 2$; respiratory failure, $n = 2$; and pulmonary emboli, $n = 2$), eight cardiovascular complications (2.0%; myocardial infarction, $n = 1$; tachycardia/arrhythmias, $n = 5$; stroke, $n = 1$; and congestive heart failure, $n = 1$), one renal insufficiency (0.2%), one multiorgan failure (0.2%), four infected (1.0%) and six sterile fluid collections (1.5%), two postoperative bleedings (0.5%), seven patients with postoperative ileus (1.7%), three other infectious complications (0.7%), and 11 miscellaneous complications (2.7%). Perioperative complication rates were similar between the different chemotherapy groups ($P = .27$). The median length of stay was 7 days (range, 3 to 38 days) and did not differ between the preoperative chemotherapy (7 days) and no preoperative chemotherapy groups (7 days; $P = .92$).

On final pathologic analysis of the resected specimen, hepatic injury was present in 92 patients (22.7%). Steatosis more than 30% was identified in 36 patients (8.9%), grade 2 to 3 sinusoidal dilation was found in 22 patients (5.4%), and steatohepatitis Kleiner score ≥ 4 in 34 patients (8.4%). Specifics on hepatic injury stratified by chemotherapy regimen are listed in Table 4. No specific chemotherapy regimen was associated with steatosis. Oxaliplatin was associated with grade 2 to 3 sinusoidal dilation compared with no chemotherapy (18.9% v 1.9%, respectively; $P < .001$; OR = 8.3; 95% CI, 2.9 to 23.6). Irinotecan was associated with steatohepatitis compared with no chemotherapy (20.2% v 4.4%, $P < .001$; OR = 5.4; 95% CI, 2.2 to 13.5). Patients receiving oxaliplatin were significantly more likely to develop sinusoidal dilation compared with patients who received irinotecan (OR = 5.2; 95% CI, 1.65 to 16.3; $P = .01$). Prior irinotecan exposure was significantly more likely to be associated with steatohepatitis compared with a history of oxaliplatin treatment (OR = 3.7; 95% CI, 1.3 to 10.5; $P = .02$). In patients receiving bevacizumab in combination with oxaliplatin, the rates of sinusoidal dilation and steatohepatitis were similar to the rates seen in patients treated with oxaliplatin alone (5.5% v 22.9%, $P = .08$ and 11.1% v 4.9%, $P = .3$, respectively). When patients were stratified according to duration of chemotherapy (2 to 8, 9 to 16, 17 to 24, and > 24 weeks), the rate of hepatic injury did not seem to increase over time in patients who received oxaliplatin (grade

Table 3. Patient Characteristics and Operative Details Stratified by Chemotherapy Regimen

Characteristic	No Chemotherapy (n = 158)		Fluorouracil (n = 63)		Irinotecan (n = 94)		Oxaliplatin (n = 79)		Other Chemotherapy (n = 12)		P
	No.	%	No.	%	No.	%	No.	%	No.	%	
Site of primary tumor											
Colon	122	77.2	50	79.3	73	77.6	58	73.4	7	58.3	.52
Rectum	35	22.1	13	20.7	19	20.2	20	25.3	5	41.7	
Not available	1	0.7			2	2.1	1	1.3			
Status of primary lymph nodes											
Negative	66	41.8	19	30.1	20	21.3	23	29.1	5	41.7	
Positive	79	50.0	42	66.7	65	69.2	53	67.1	6	50.0	.09
Not available	13	8.2	2	3.2	9	9.5	3	3.8	1	8.3	
Timing of hepatic metastases											
Synchronous	79	50.0	46	73.0	70	74.5	61	77.2	10	83.3	.0001
Metachronous	79	50.0	17	27.0	24	25.5	18	22.8	2	16.7	
Surgery type											
Extended hepatectomy	24	15.1	6	9.6	22	23.4	20	25.3	0	0.0	.06
Hemihpatectomy	84	53.2	34	53.9	48	51.0	33	41.8	4	33.3	
Segmentectomy	47	29.8	17	26.9	20	21.3	19	24.0	7	58.3	
Wedge resection	3	1.9	6	9.6	4	4.3	7	8.9	1	8.4	
RFA associated with major liver resection	27	25.0	13	32.5	25	35.7	18	33.9	1	25.0	.6
RFA associated with liver resection	39	24.7	22	34.9	40	42.5	20	25.3	5	41.6	.02
No. of hepatic CRM											
Single	102	64.5	34	54.0	37	39.3	26	32.9	7	58.3	.00001
Multiple	56	35.5	29	46.0	57	60.4	53	67.1	5	41.7	
Largest hepatic CRM tumor size, cm	3.9		3.2		3.2		3.0		3.5		.02
Median body mass index, kg/m ²	26.5		26.0		26.8		25.7		25.8		.45
Median estimated blood loss, mL	300		350		300		200		250		.0007
Duration of chemotherapy, weeks											
Median			20		16		12		16		.001
Range			4-70		3-60		2-34		4-48		
Interval between chemotherapy and surgery, weeks											
Median			7.2		5.8		6.4		5.9		.45
Range			2.5-15.7		1.5-16		2.1-16		1.2-16		
Postoperative complication											
Yes	29	18.3	17	27.0	17	18.0	21	26.5	1	8.3	.27
No	129	81.7	46	73.0	77	82.0	58	73.5	11	91.7	
Major complications	15	9.5	10	15.9	10	10.6	12	15.1	0	0.0	.34

Abbreviations: CRM, colorectal metastases; RFA, radiofrequency ablation.

2 to 3 sinusoidal dilation: n = 3, 18.7%; n = 7, 20.5%; n = 4, 26.6%; and n = 1, 16.6%, respectively; *P* = .93) or irinotecan (steatohepatitis Kleiner score \geq 4: n = 3, 18.7%; n = 7, 19.4%; n = 7, 28.0%; and n = 2, 11.7%, respectively; *P* = .63).

Chemotherapy and body mass index (BMI) were further analyzed using the BMI cut point of 25 kg/m². Irinotecan was associated with steatohepatitis irrespective of BMI (BMI < 25 kg/m²: no chemotherapy, 0% v irinotecan, 12.1%; BMI \geq 25

Table 4. Liver Injury Characteristics Stratified by Chemotherapy Regimen

Regimen	Sinusoidal Dilatation* (n = 22)					Steatosis > 30% (n = 36)					Steatohepatitis† (n = 34)				
	Yes		No		<i>P</i> ‡	Yes		No		<i>P</i> ‡	Yes		No		<i>P</i> ‡
	No.	%	No.	%		No.	%	No.	%		No.	%	No.	%	
No CTx	3	1.9	155	98.1		14	8.9	144	91.1		7	4.4	151	95.6	
FU	0	0	63	100	NS	9	16.6	54	83.4	NS	3	4.8	60	95.2	NS
IRI	4	4.3	90	95.7	NS	9	10.6	85	89.4	NS	19	20.2	75	79.8	.0001
OX	15	18.9	64	81.1	.00001	3	3.8	76	96.2	NS	5	6.3	74	93.6	NS
Other	0	0	12	100	NS	1	8.3	11	91.7	NS	0	0	12	100	NS

Abbreviations: CTx, chemotherapy; FU, fluorouracil; IRI, irinotecan; OX, oxaliplatin; NS, not significant.

*Rubbia-Brandt grade 2 or 3.

†Kleiner score \geq 4.

‡Presence of liver injury characteristic; comparison of each chemotherapy group v no chemotherapy.

kg/m²: no chemotherapy, 7.1% *v* irinotecan, 24.6%; both $P < .01$; Table 5).

Eleven patients died within 90 days of surgery, for a perioperative mortality rate of 2.7%. The median EBL for patients who died within 90 days was 550 mL compared with 275 mL for patients who did not die ($P = .041$). There were six deaths (6.5%) in 92 patients with hepatic injury (three from liver failure, of which two were associated with bile leak; one from acute respiratory distress syndrome; one from cerebrovascular accident; and one from unknown cause) compared with five deaths (1.6%) in 314 patients without hepatic injury (two from liver failure, of which one was associated with bile leak; one from myocardial infarction; one from coagulopathy; and one from bile leak and sepsis; $P = .01$). Of the patients with hepatic injury, no deaths occurred in the 22 patients with sinusoidal injury. Rather, the six patients with hepatic injury who died had either steatosis more than 30% ($n = 1$) or steatohepatitis (Kleiner score ≥ 4 ; $n = 5$). Patients with steatohepatitis had an increased 90-day mortality rate compared with patients who did not have steatohepatitis (14.7% *v* 1.6%, respectively; $P = .001$; OR = 10.5; 95% CI, 2.0 to 36.4). Patients with steatohepatitis ($n = 34$) also had a higher risk of death specifically from postoperative liver failure (5.8%) versus all other patients (0.8%; $P = .01$; OR = 7.7; 95% CI, 1.24 to 47.7). All five patients with steatohepatitis who died postoperatively underwent resection (hemihepatectomy, $n = 4$; wedge resection, $n = 1$) combined with radiofrequency ablation of one lesion (median diameter, 1.5 cm) in the remnant liver. However, resection combined with ablation was not associated with increased mortality in patients without steatohepatitis (resection plus radiofrequency ablation, 1.8% *v* resection alone, 1.5%; $P = .8$).

DISCUSSION

To our knowledge, the current study is the first to systematically analyze the association between chemotherapy, histopathologic changes of the liver, and postoperative outcome in a large cohort of patients who underwent liver resection for hepatic CRM. We report that preoperative chemotherapy may be associated with pathologic changes of the liver parenchyma, which may translate into adverse clinical outcomes after hepatic surgery. Specifically, oxaliplatin was associated with an increase in sinusoidal injury but no increase in

perioperative morbidity or mortality. Preoperative treatment with irinotecan was associated with an increased risk of steatohepatitis. In turn, steatohepatitis was associated with an increased overall postoperative mortality and, specifically, death from postoperative liver failure. Although previous studies^{16,23} had suggested an increased likelihood of adverse events in patients treated preoperatively with chemotherapy, the current study is the first not only to quantify this risk, but also to identify chemotherapy-specific toxicity associated with an increase in postoperative mortality.

We defined postoperative mortality as any death occurring within 90 days of the operative procedure. The reason for using 90-day mortality was to account for the broad spectrum of complications and deaths that can occur late in the postoperative course of patients having undergone a liver resection. Although postoperative technical complications are reflected in the early postoperative morbidity and mortality and have been minimized even after extended liver resection,²⁴ it has become evident that outcome after hospital discharge or 30 days underestimates morbidity and mortality after hepatic resection. A recent study reporting on resection of hepatocellular carcinoma in patients with chronic liver disease revealed postoperative mortality that occurred beyond the hospital stay and the traditional 30-day postoperative period.²⁵ As such, 90-day mortality may better define the subset of patients who die from progressive liver failure related to impaired hepatic regeneration. In the present study, three of the five deaths in the subset of patients with steatohepatitis occurred after discharge and more than 30 days after hepatic resection. In some patients, the development of liver failure may be associated with an adverse physiologic event such as a bile leak, abscess, or septic event. Typically, these patients succumb to a late postoperative death from progressive intrahepatic cholestasis often with minimal other associated signs of liver failure.^{26,27}

The effect of chemotherapy on perioperative outcome has been controversial. New chemotherapy regimens for CRM, such as FU plus irinotecan or oxaliplatin,²⁸⁻³⁰ have response rates up to 56%,³⁰ but there have been reported cases of severe histopathologic changes in the resected liver of patients treated with these regimens.^{16,17} Rubbia-Brandt et al¹⁷ reported an increased rate of sinusoidal dilation in patients who had received chemotherapy, most of whom (78%) had received preoperative oxaliplatin. In 21 (48%) of these 44 patients, perisinusoidal and occlusive fibrosis were noted, whereas diffuse

Table 5. Rate of Steatohepatitis* Stratified by BMI and Chemotherapy Regimen† (steatohepatitis present, $n = 34$ *v* steatohepatitis absent, $n = 371$)

Regimen	Patients With Steatohepatitis										
	BMI < 25 kg/m ² ($n = 155$)					<i>P</i> ‡	BMI ≥ 25 kg/m ² ($n = 250$)				
	Yes		No		Yes		No				
No.	%	No.	%	No.	%	No.	%	No.	%	<i>P</i> ‡	
No CTx	0	0	58	100		7	7.1	92	92.9		
FU	1	4.2	23	95.6	NS	2	5.1	37	94.9	NS	
IRI	4	12.1	29	87.9	.006	15	24.6	46	75.4	.002	
OX	0	0	35	100	NS	5	11.4	39	88.6	NS	
Other	0	0	5	100	NS	0	0	7	100	NS	

Abbreviations: BMI, body mass index; CTx, chemotherapy; FU, fluorouracil; IRI, irinotecan; OX, oxaliplatin; NS, not significant.

*Kleiner score ≥ 4 .

†BMI missing for one patient without steatohepatitis.

‡Comparison of each group *v* no chemotherapy.

nodular regenerative hyperplasia was present in seven patients.¹⁷ In the current study, oxaliplatin was also shown to be significantly associated with an increased risk of sinusoidal dilation.

Prior research has shown that camptothecin derivatives, such as irinotecan, are directly toxic to primary hepatocytes *in vitro*.³¹ Fernandez et al¹⁶ suggested an association between preoperative chemotherapy for hepatic CRM and steatohepatitis. In their study, 10 of the 14 patients who developed steatohepatitis had received preoperative irinotecan-containing fluoropyrimidine chemotherapy. Our data confirmed this presumed association of irinotecan with steatohepatitis in patients receiving preoperative chemotherapy for CRM. Traditionally, steatohepatitis has been associated with certain patient factors such as hyperglycemia and obesity.^{32,33} In our study, irinotecan was associated with an increased risk of steatohepatitis irrespective of BMI, but the effect was more pronounced in patients with a higher BMI (BMI < 25 kg/m², 12.1% v BMI ≥ 25 kg/m², 24.6%; *P* = .01; Table 5).

Whether chemotherapy-induced histopathologic changes of the liver result in adverse postoperative outcomes has not previously been adequately addressed. Behrns et al³⁴ reported a nonsignificant increase in the likelihood of complications and liver failure in seven patients with moderate to severe steatosis among 135 patients who underwent liver resection for CRM in the era predating irinotecan and oxaliplatin. Belghiti et al³⁵ similarly reported an increased morbidity in 37 patients with steatosis compared with patients without underlying liver disease. Kooby et al²³ reported an increase in surgical complications and an association between marked steatosis, chemotherapy, and BMI. However, all of these studies analyzed steatosis only, whereas steatohepatitis and the effect of preoperative chemotherapy regimens were not specifically examined.

In the current study, preoperative chemotherapy with oxaliplatin, although associated with sinusoidal injury, was not associated with increased morbidity or mortality rates. In fact, of the patients with hepatic injury, no deaths occurred in the 22 patients with sinusoidal injury despite similar rates of major hepatectomy between groups (77.2% in patients with sinusoidal dilation, 61.7% in patients with steatohepatitis, and 58.3% in patients with steatosis > 30%; *P* = .45). This finding is consistent with a preliminary report from a randomized study showing no increase in mortality in 174 patients who received continuous infusion FU and leucovorin plus oxaliplatin (FOLFOX4) chemotherapy before hepatic resection.⁹ Similarly, Adam et al⁷ reported no increase in the morbidity or mortality of patients treated preoperatively with chronomodulated systemic chem-

otherapy with FU, leucovorin, and oxaliplatin for a median of 20 weeks before the patients underwent hepatic resection. Although a recent study reported an association between duration of preoperative chemotherapy and perioperative morbidity,³⁶ our study indicated no increase in the rate of hepatic injury over time. However, the effect of prolonged chemotherapy deserves further investigation because the current study included mostly patients presenting with resectable disease (82.3%) and the median durations of treatment with oxaliplatin and irinotecan were only 12 and 16 weeks, respectively.

Perhaps the most important finding of the current study was the association of irinotecan with steatohepatitis and subsequent postoperative mortality after hepatic surgery. Although steatohepatitis is generally a benign condition, the presence of steatohepatitis has been associated with an increased risk of liver disease and liver failure in some patients.³⁷⁻³⁹ Steatohepatitis of the liver may cause defective cell proliferation through alterations of the nuclear factor-kappa B pathway, which is crucial for the priming phase of liver regeneration.⁴⁰⁻⁴³ Fernandez et al¹⁶ reported an index case of a patient with steatohepatitis who died from liver failure, possibly as a result of chemotherapy-associated hepatic injury. Our data confirm the presumptive association between steatohepatitis and increased risk for mortality after hepatic surgery.

In conclusion, preoperative chemotherapy can induce regimen-specific histopathologic hepatic changes. In the case of oxaliplatin, the chemotherapy-associated liver injury was not associated with an increased risk of perioperative morbidity or mortality. In contrast, steatohepatitis was associated with irinotecan and with an increased perioperative risk of death, especially in patients undergoing a major resection combined with radiofrequency ablation. Some have recommended liver biopsy to evaluate for steatosis or steatohepatitis¹⁶; however, given the problems associated with sampling error as well as intra- and interobserver variation in the evaluation of steatosis,⁴⁴ we do not advocate this approach. Rather, laparoscopy before laparotomy in patients with preoperative imaging studies that suggest steatosis should be considered to directly evaluate the liver.⁴⁵ The extent of resection and type of chemotherapy regimen should be carefully considered and individualized, including a consideration for BMI and related comorbid factors. In patients who require major hepatic surgery and have proven hepatic injury, preoperative portal vein embolization may be considered based on prior experience with major hepatectomy in cirrhosis,^{46,47} although the specific indications for this approach remain to be defined.

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