

## ONLINE FIRST

# Prospective Evaluation of Accuracy of Liver Biopsy Findings in the Identification of Chemotherapy-Associated Liver Injuries

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**Objective:** To evaluate the accuracy of liver biopsy findings in preoperative assessment of chemotherapy-associated liver injuries (CALIs).

**Design:** Prospective study.

**Setting:** Tertiary care referral hospital.

**Patients:** From July 1, 2007, to January 31, 2011, all patients with colorectal metastases receiving preoperative oxaliplatin- and/or irinotecan-based chemotherapy ( $\geq 4$  cycles) were considered for the present study. Patients underwent parenchymal biopsy before liver resection. Blinded CALI evaluation was performed on biopsy and resection specimens.

**Intervention:** Liver resection.

**Main Outcome Measures:** Sensitivity, specificity, and accuracy of liver biopsy in CALI evaluation.

**Results:** We included 100 patients. At specimen analysis, grade 2 or 3 steatosis was diagnosed in 30 patients; grade 2 or 3 sinusoidal dilatation, in 28; grade 2 hepatocellular ballooning, in 3; grade 2 or 3 lobular inflam-

ation, in 25; and steatohepatitis in 19. Obesity was associated with grade 3 steatosis (20.8% vs 5.3%; odds ratio [OR], 4.74 [ $P = .03$ ]) and steatohepatitis (33.3% vs 14.5%; OR, 2.96 [ $P = .04$ ]). Oxaliplatin administration was associated with higher sinusoidal dilatation grade ( $P = .049$ ). Mortality (2 cases) was increased among patients with steatohepatitis (10.5% vs 0; OR, 13.67 [ $P = .04$ ]). Biopsy findings correctly predicted steatosis (sensitivity, 88.9%; accuracy, 93.0%) but had low sensitivity and accuracy for sinusoidal dilatation (21.4% and 63.0%, respectively), hepatocellular ballooning (16.0% and 69.0%, respectively), lobular inflammation (20.0% and 78.0%, respectively), and steatohepatitis (21.1% and 79.0%, respectively). Biopsy accuracy did not improve regarding specific chemotherapy regimens or prolonged treatments.

**Conclusions:** Liver biopsy cannot be considered a reliable tool in assessing CALIs except for steatosis. The procedure should not be recommended during preoperative workup.

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**A**MONG PATIENTS WITH COLORECTAL liver metastases, preoperative chemotherapy now plays a key role. Preoperative chemotherapy allows selection of good candidates for surgery; reduction of lesion size, enabling more conservative and more radical resections; and treatment of occult disease foci.<sup>1-5</sup> A recent randomized trial conducted by the European Organisation for the Research and Treatment of Cancer demonstrated that neoadjuvant treatments even improve disease-free survival rates.<sup>6</sup>

However, chemotherapy administration has some drawbacks. First, chemotherapy-associated liver injuries (CALIs) have been reported, including steatosis, sinusoidal dilatation (SinDil), and steato-

hepatitis.<sup>7-11</sup> Recent publications have clearly demonstrated that CALIs worsen outcomes of liver resection by increasing postoperative morbidity and mortality.<sup>11-21</sup>

## See Invited Critique at end of article

Preoperative evaluation of CALIs is necessary to correctly assess liver function and operative risk and to consider procedures, such as portal vein embolization, to increase resection safety. Although results of imaging and liver function tests (LFTs)<sup>17,19,22-24</sup> can be used to perform indirect evaluations, complete preoperative assessment of CALI severity is not currently achievable, particularly with respect

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**Table 1. Histological Features and Scoring Systems**

Feature	Definition	Grade
Steatosis (low- to medium-power evaluation of parenchymal involvement), %	<5	0
	5-33	1
	33-66	2
	>66	3
Sinusoidal dilatation (centrolobular involvement, semiquantitatively graded)	None	0
	Limited to one-third of the lobular surface	1
	In two-thirds of the lobular surface	2
Lobular inflammation (overall assessment of all inflammatory foci)	Complete	3
	No foci	0
	<2 Foci per field $\times 200$	1
	2-4 Foci per field $\times 200$	2
Hepatocellular ballooning	>4 Foci per field $\times 200$	3
	None	0
	Few balloon cells	1
	Many cells/prominent ballooning	2

to steatohepatitis. Preoperative liver biopsy has been proposed,<sup>10,11</sup> although its reliability has never been confirmed in clinical trials.

The present study aimed to evaluate prospectively the accuracy of liver biopsy for the identification of CALIs and to determine whether liver biopsy should be included in the preoperative workup of patients with colorectal metastases who are scheduled for resection after preoperative chemotherapy.

## METHODS

Patients undergoing liver resection for colorectal metastases at the Mauriziano Umberto I hospital from July 1, 2007, to January 31, 2011, were prospectively considered for the present study. Inclusion criteria consisted of preoperative oxaliplatin- or irinotecan-based chemotherapy and 4 or more chemotherapy cycles. We excluded patients with unresectable disease at laparotomy. The study was approved by the local ethical committee, and informed consent was obtained from each included patient.

After a resectability assessment (complete abdominal exploration and hepatic ultrasonography), a biopsy of nontumoral parenchyma was performed using a 16-gauge Trucut needle in the future remnant liver (FRL). Ultrasonography was used to guide the puncture far away from vascular structures. Adequate samples were retained for the study, fixed in formalin, and marked with a randomly assigned numeric code.

At the end of parenchymal transection, each resected liver specimen was fixed in formalin and immediately sent to the pathology department. Hepatic parenchyma remote from the resected tumor was analyzed by 2 experienced hepatic pathologists (N.R. and M.M.) specifically trained in CALI assessment. Both pathologists were blinded to patient clinical data and preoperative chemotherapy. Biopsy samples were collected and later sent to the pathology department. Blinded evaluation of CALIs was performed by the same 2 pathologists; the only information available to them was the random numeric code.

After the enrollment of 50 consecutive patients (July 1, 2007, to February 28, 2009), collected biopsy samples were sent to the pathology department (March 2009). Patient enrollment was stopped and analysis was performed. Because the incidence of CALIs was low (9 cases of grade 2 or 3 SinDil and 7

cases of steatohepatitis), we decided to include 50 additional consecutive patients, who were enrolled from May 1, 2010, to January 31, 2011. The second group of 50 biopsy samples was collected and sent to the pathology department at the end of the study (February 2011).

## PATHOLOGICAL DATA

Tissue was fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin and Masson trichrome. Analyzed histological features included steatosis, SinDil, lobular inflammation, hepatocellular ballooning, and centrilobular and perisinusoidal fibrosis. The evaluation of CALIs was based on histological scoring systems published by Rubbia-Brandt et al<sup>9</sup> and Kleiner et al,<sup>25</sup> which are detailed in **Table 1**. Steatohepatitis was defined as a Kleiner score (unweighted sum of steatosis, lobular inflammation, and hepatocellular ballooning scores) of 4 or more according to the definition of Vauthey et al<sup>18</sup> or of 5 or more according to the definition of Kleiner et al.<sup>25</sup>

## DEFINITIONS

Major hepatectomy was defined as the resection of 3 or more Couinaud segments. Obesity was defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) of 30.0 or higher. Operative mortality was defined as death within 90 days after surgery or before discharge from the hospital. Morbidity included all postoperative complications and was defined according to the classification of Dindo et al.<sup>26</sup> Liver dysfunction was defined as a serum bilirubin level greater than 3 mg/dL (to convert to micromoles per liter, multiply by 17.104) and/or a prothrombin time (PT) less than 50% on or after postoperative day 5.<sup>27</sup>

## STATISTICAL ANALYSIS

Continuous variables were compared between groups using the Mann-Whitney test; categorical variables were compared using the  $\chi^2$  test or the Fisher exact test as appropriate.  $P < .05$  was considered statistically significant for all tests.

We computed the sensitivity, specificity, positive and negative predictive values, and accuracy of liver biopsy findings in assessing CALIs. We also analyzed the usefulness of biopsy findings for identifying any relevant CALI (grade 2 or 3 SinDil, grade 2 or 3 steatosis, or Kleiner score  $\geq 4$ ). Receiver operating characteristic curves were plotted to assess the area under the curve of the liver biopsy findings for each CALI. Furthermore, we assessed the agreement between observations (specimen vs biopsy) using the  $\kappa$  coefficient that determines how much better agreement is than would occur by chance alone, where  $\kappa = 1$  indicates perfect agreement. The specimen analysis was considered the criterion standard in all cases. We performed subgroup analyses according to patient characteristics, LFTs, and chemotherapy regimen (type and number of cycles). We computed and compared the accuracy of biopsy results in the 2 halves of the series (cases 1-50 vs 51-100).

## RESULTS

### PATIENT CHARACTERISTICS AND CHEMOTHERAPY DETAILS

From July 1, 2007, to January 31, 2011, we enrolled 100 patients undergoing liver resection for colorectal liver metastases. The patient population included 69 men and 31 women with a median age of 60.5 (range, 37-81) years.

Twenty-four patients were obese, with a median body mass index of 32.4 (range, 30.4-38.8). Liver metastases were synchronous with the primary tumor in 68 patients, were multiple in 67 (>3 lesions in 37 patients), and measured more than 50 mm in 25. Major liver resection was performed in 34 patients.

Preoperative chemotherapy included oxaliplatin in 79 patients and irinotecan in 50; 29 patients underwent chemotherapy with both drugs. Fifty-three patients had associated targeted therapies, including bevacizumab (n=46) and cetuximab (n=14) (7 had both). Thirty-two patients had multiple chemotherapy lines. The median number of cycles was 12 (range, 4-32). The chemotherapy details are summarized in **Table 2**.

### CALIs ON PERITUMORAL PARENCHYMA

At specimen analysis, the prevalence of hepatic injuries was as follows: grade 2 or 3 steatosis in 30 cases, grade 2 or 3 SinDil in 28, grade 2 hepatocellular ballooning in 3, grade 2 or 3 lobular inflammation in 25, centrilobular fibrosis in 55, and perisinusoidal fibrosis in 44. Steatohepatitis (Kleiner score  $\geq 4$ ) was diagnosed in 19 patients (**Table 3**).

Higher proportions of severe steatosis (grade 3, 5 of 24 patients [20.8%] vs 4 of 76 [5.3%]; OR, 4.74 [95% CI, 1.16-19.38;  $P=.03$ ]) and steatohepatitis (8 of 24 patients [33.3%] vs 11 of 76 [14.5%]; OR, 2.96 [95% CI, 1.02-8.55;  $P=.04$ ]) were observed in obese vs nonobese patients. Patients receiving oxaliplatin had a higher grade of SinDil compared with patients who did not receive it (grade 0, 20 patients [25.3%] vs 8 [38.1%]; grade 1, 36 [45.6%] vs 8 [38.1%]; and grade 2 or 3, 23 [29.1%] vs 5 [23.8%] [ $P=.049$ ]). No other associations were observed between administered chemotherapy and CALIs. The number of cycles, number of lines, and time interval between chemotherapy and liver resection did not affect CALI occurrence. No LFT was predictive of CALIs, even considering indocyanine green retention test results, aspartate aminotransferase to platelet ratio index,<sup>28</sup> and Fibrosis-4 score (combining standard biochemical measurements of platelet and liver enzyme levels and age).<sup>29</sup>

### CALIs ON BIOPSY SAMPLES AND COMPARISON WITH PERITUMORAL TISSUE ANALYSIS

Results of the peritumoral tissue analysis compared with the biopsy results are given in **Table 4**. Grade 2 or 3 steatosis was diagnosed in 24 biopsy samples. In 63 cases, the grading of steatosis (grades 0-3) achieved by the biopsy results agreed completely with results of the peritumoral parenchyma analysis. Among 37 discordant cases, only 4 differed by more than 1 grade. Biopsy findings predicted moderate to severe steatosis (grade 2 or 3 vs 0 or 1) with mild sensitivity (66.7%) and high specificity (94.3%). Biopsy findings were better able to predict severe steatosis (grade 3 vs 0-2), with a sensitivity of 88.9% and a specificity of 93.4%.

Grade 2 or 3 SinDil was evident in 21 biopsy samples. Biopsy findings disagreed with results of the peritu-

**Table 2. Chemotherapy Details<sup>a</sup>**

Variable	Data
No. of chemotherapy lines	
Median (range)	1 (1-3)
1	68 (68.0)
2	28 (28.0)
3	4 (4.0)
No. of cycles	
Median (range)	12 (4-32)
1-6	25 (25.0)
7-12	47 (47.0)
13-18	15 (15.0)
19-24	9 (9.0)
>24	4 (4.0)
Chemotherapy regimen	
Oxaliplatin	61 (61.0)
Oxaliplatin + bevacizumab	15 (15.0)
Oxaliplatin + cetuximab	3 (3.0)
Irinotecan	13 (13.0)
Irinotecan + bevacizumab	32 (32.0)
Irinotecan + cetuximab	12 (12.0)

<sup>a</sup>Includes 100 patients with 136 lines of chemotherapy. Unless otherwise indicated, data are expressed as number (percentage) of patients.

moral parenchyma analysis in 64 cases, with a difference of more than 1 grade in 26 cases. In 23 cases, the biopsy findings overestimated SinDil. Regarding the evaluation of SinDil (grade 0 or 1 vs 2 or 3), the biopsy findings exhibited low sensitivity (21.4%) and accuracy (63.0%). The results did not improve for cases of complete SinDil (grade 3 vs 0-2).

Hepatocellular ballooning was observed in 14 biopsy samples. Similar to SinDil, the biopsy findings exhibited low sensitivity (16.0%) and accuracy (69.0%) regarding ballooning (grade 0 vs 1 or 2). Biopsy findings failed to identify all patients with grade 2 hepatocellular ballooning.

The prevalence of lobular inflammation in biopsy samples was 45.0%. Agreement with the results of the peritumoral tissue analysis was poor (43.0%). The biopsy findings underestimated lobular inflammation: 20 of 25 patients with grade 2 or 3 lobular inflammation were incorrectly classified as having grade 0 or 1 injuries. The biopsy findings of lobular inflammation (grade 0 or 1 vs 2 or 3) had good specificity (97.3%) but low sensitivity (20.0%).

Although steatohepatitis was diagnosed in 10 biopsy samples, only 4 cases were confirmed by results of the specimen analysis. The biopsy findings missed 15 of 19 patients in whom the diagnosis was determined through peritumoral tissue analysis. The sensitivity and positive predictive values of the biopsy findings were extremely poor, according to the definitions of Vauthey et al<sup>18</sup> ( $\geq 4$  points, 21.1%, and 40.0%, respectively) and Kleiner et al<sup>25</sup> ( $\geq 5$  points, 0, and 0, respectively).

Centrilobular and perisinusoidal fibrosis were each poorly identified by biopsy findings. Centrilobular fibrosis was identified with 32.7% sensitivity and 54.0% accuracy, whereas perisinusoidal fibrosis was identified with 25.0% sensitivity and 63.7% accuracy.

**Table 3. Liver Damage on Peritumoral Parenchyma Analysis**

CALI, Grade	No. (%) of Patients					Obese Patients (n = 24)
	Whole Series (N = 100)	Chemotherapy Variable			≥12 Cycles (n = 52)	
		Including Oxaliplatin (n = 79)	Including Irinotecan (n = 50)	Addition of Bevacizumab (n = 46)		
Steatosis						
1	41 (41.0)	32 (40.5)	15 (30.0)	15 (32.6)	14 (26.9)	11 (45.8)
2	21 (21.0)	17 (21.5)	13 (26.0)	13 (28.3)	12 (23.1)	7 (29.2)
3	9 (9.0)	8 (10.1)	2 (4.0)	4 (8.7)	4 (7.7)	5 (20.8)
Sinusoidal dilatation						
1	44 (44.0)	36 (45.6)	20 (40.0)	18 (39.1)	24 (46.2)	9 (37.5)
2	23 (23.0)	21 (26.6)	8 (16.0)	11 (23.9)	11 (21.2)	6 (25.0)
3	5 (5.0)	2 (2.5)	3 (6.0)	4 (8.7)	2 (3.8)	1 (4.2)
Hepatocellular ballooning						
1	22 (22.0)	18 (22.8)	12 (24.0)	10 (21.7)	13 (25.0)	5 (20.8)
2	3 (3.0)	2 (2.5)	2 (4.0)	3 (6.5)	2 (3.8)	0
Lobular inflammation						
1	42 (42.0)	35 (44.3)	22 (44.0)	17 (37.0)	25 (48.1)	11 (45.8)
2	24 (24.0)	16 (20.3)	12 (24.0)	13 (28.3)	12 (23.1)	6 (25.0)
3	1 (1.0)	1 (1.3)	0	0	1 (1.9)	1 (4.2)
Steatohepatitis (≥4 points) <sup>a</sup>	19 (19.0)	16 (20.3)	7 (14.0)	11 (23.9)	11 (21.2)	8 (33.3)
Centrilobular fibrosis	55 (55.0)	44 (55.7)	28 (56.0)	30 (65.2)	32 (61.5)	13 (54.2)
Perisinusoidal fibrosis	44 (44.0)	32 (40.5)	22 (44.0)	22 (47.8)	25 (48.1)	9 (37.5)

Abbreviation: CALI, chemotherapy-associated liver injury.

<sup>a</sup>As defined by Vauthey et al.<sup>18</sup>**Table 4. Comparison of CALI Evaluation on Biopsy Finding and Peritumoral Tissue Analysis**

	Percentage					AUC	P Value	κ Value
	Sen	Spec	PPV	NPV	Acc			
Steatosis								
Grade 0 or 1 vs 2 or 3	66.7	94.3	83.3	86.8	86.0	0.81	<.001	0.65
Grade 0-2 vs 3	88.9	93.4	57.1	98.8	93.0	0.91	<.001	0.66
Sinusoidal dilatation								
Grade 0 or 1 vs 2 or 3	21.4	79.2	28.6	72.2	63.0	0.50	.96	0.01
Grade 0-2 vs 3	20.0	92.6	12.5	95.7	89.0	0.56	.64	0.10
Hepatocellular ballooning								
Grade 0 vs 1 or 2	16.0	86.7	28.6	75.6	69.0	0.51	.84	0.03
Grade 0 or 1 vs 2	0	97.9	0	96.9	95.0	0.49	.95	-0.03
Lobular inflammation								
Grade 0 or 1 vs 2 or 3	20.0	97.3	71.4	78.5	78.0	0.59	.20	0.23
Grade 0-2 vs 3	0	99.0	0	99.0	98.0	0.50	.99	-0.01
Steatohepatitis								
≥4 Points <sup>a</sup>	21.1	92.6	40.0	83.3	79.0	0.57	.36	0.17
≥5 Points <sup>b</sup>	0	97.8	0	92.9	91.0	0.56	.59	0.17
Centrilobular fibrosis, no vs yes	32.7	80.0	66.7	49.3	54.0	0.56	.28	0.12
Perisinusoidal fibrosis, no vs yes	25.0	93.1	73.3	62.1	63.7	0.57	.22	0.16
Any relevant CALI, no vs yes <sup>c</sup>	53.9	64.6	62.2	56.4	59.0	0.59	.11	0.18

Abbreviations: Acc, accuracy; AUC, area under the curve; CALI, chemotherapy-associated liver injury; NPV, negative predictive value; PPV, positive predictive value; Sen, sensitivity; Spec, specificity.

<sup>a</sup>As defined by Vauthey et al.<sup>18</sup><sup>b</sup>As defined by Kleiner et al.<sup>25</sup><sup>c</sup>Includes grade 2 or 3 sinusoidal dilatation, grade 2 or 3 steatosis, or a Kleiner score of 4 or more.

The receiver operating characteristic curve analyses confirmed these results. The liver biopsy achieved significant areas under the curve only for evaluation of steatosis (grade 2 or 3 vs 0 or 1, 0.81 [ $P < .001$ ]; grade 3 vs 0-2, 0.91 [ $P < .001$ ]). Furthermore, disagreement between the biopsy findings and the results of the speci-

men analysis was underlined by low  $\kappa$  coefficients for all CALIs with the exception of steatosis (grade 2 or 3 vs 0 or 1,  $\kappa = 0.65$ ; grade 3 vs 0-2,  $\kappa = 0.66$ ).

The biopsy findings did not improve with regard to the presence of any relevant CALI (grade 2 or 3 SinDil, grade 2 or 3 steatosis, or Kleiner score  $\geq 4$ ).

**Table 5. CALI Evaluation According to Chemotherapy Regimen and Patient Characteristics**

CALI	Percentage				
	Chemotherapy Variable				Obese Patients (n = 24)
	Including Oxaliplatin (n = 79)	Including Irinotecan (n = 50)	Addition of Bevacizumab (n = 46)	≥12 Cycles (n = 52)	
Steatosis (grade 0 or 1 vs 2 or 3)					
Sen	64.4	60.0	58.8	50.0	83.3
Spec	94.4	94.3	89.7	91.7	83.3
Acc	84.8	84.0	78.3	78.8	83.3
Sinusoidal dilatation (grade 0 or 1 vs 2 or 3)					
Sen	17.4	18.2	13.3	23.1	0
Spec	78.6	84.6	87.1	82.1	100.0
Acc	60.8	70.0	63.0	67.3	70.8
Hepatocellular ballooning (grade 0 vs 1 or 2)					
Sen	15.0	21.4	15.4	26.7	0
Spec	86.4	80.6	84.9	86.5	89.5
Acc	68.4	64.0	65.2	69.2	70.8
Lobular inflammation (grade 0 or 1 vs 2 or 3)					
Sen	17.7	16.7	15.4	15.4	28.6
Spec	98.4	97.4	97.0	100.0	100.0
Acc	81.0	78.0	73.9	78.8	79.2
Steatohepatitis (<4 vs ≥4 points) <sup>a</sup>					
Sen	18.8	14.3	18.2	9.1	50.0
Spec	93.7	90.7	91.4	90.2	93.8
Acc	78.5	80.0	73.9	73.1	79.2
Any relevant CALI <sup>b</sup>					
Sen	52.4	50.0	50.0	46.2	68.8
Spec	64.9	69.2	72.2	61.5	87.5
Acc	58.2	60.0	58.7	53.9	75.5

Abbreviations: Acc, accuracy; CALI, chemotherapy-associated liver injuries; Sen, sensitivity; Spec, specificity.

<sup>a</sup>Defined by Vauthey et al.<sup>18</sup>

<sup>b</sup>Includes grade 2 or 3 sinusoidal dilatation, grade 2 or 3 steatosis, or a Kleiner score of 4 or more.

### BIOPSY FINDINGS ACCORDING TO CHEMOTHERAPY REGIMEN AND PATIENT CHARACTERISTICS

Biopsy accuracy did not improve with respect to chemotherapy-related specific injuries, such as SinDil in patients receiving oxaliplatin and steatohepatitis in patients receiving irinotecan, or prolonged treatments (≥12 cycles). In obese patients, biopsy findings exhibited a slight improvement in identifying steatohepatitis, reaching 50.0% sensitivity and 79.2% accuracy (**Table 5**).

We compared the 2 halves of the study (cases 1-50 and 51-100). Biopsy results did not change between the first and last 50 patients except for a lower sensitivity in steatosis evaluation in the second group (83.3% vs 55.6% [ $P = .25$ ]).

### POSTOPERATIVE OUTCOMES

No biopsy-related complications occurred. Two patients died, for a postoperative mortality rate of 2.0%. The first case was a 48-year-old woman undergoing right-sided trisectionectomy extended to segment 1 associated with bile duct confluence resection for recurrent metastases. Before surgery, this patient received 12 cycles of irinotecan and bevacizumab and 5 cycles of irinotecan and cetuximab chemotherapy. The FRL was 36.2%. The patient had postoperative liver dysfunction associated with persistent bile leakage and sepsis, which led to death on postopera-

tive day 48. At final pathological examination, grade 3 SinDil and steatohepatitis (Kleiner score, 4) were demonstrated, whereas biopsy findings showed grade 2 SinDil and a Kleiner score of 0. The second patient was a 59-year-old obese man (body mass index, 31.1) undergoing right hepatectomy associated with lymph node dissection of the hepatic pedicle, celiac trunk, and retropancreatic area. He received 6 cycles of irinotecan and bevacizumab chemotherapy before surgery. The FRL was 34.0%. The patient had postoperative liver dysfunction associated with ischemic necrosis of the common hepatic duct (treated by percutaneous transhepatic biliary drainage) and sepsis, which led to death on postoperative day 101. At final pathological examination, grade 1 SinDil and steatohepatitis (Kleiner score, 4) were demonstrated, in agreement with the biopsy finding (SinDil grade, 0 and Kleiner score, 6).

Thirty-three patients (33.0%) experienced postoperative morbidity. Thirteen cases (13.0%) were classified as Clavien grades 3 to 5 with liver dysfunction in 6 (6.0%) cases, including associated sepsis in 3 (2 deceased); renal dysfunction in 2 (2.0%; associated with liver dysfunction in 1); colonic anastomosis leakage in 2 (2.0%); abdominal collection in 2 (2.0%); and bile leakage requiring endoscopic retrograde cholangiography in 2 (2.0%). Blood transfusions were required in 7 patients (7.0%), and the median hospital stay was 9 (range, 5-101) days.

The liver dysfunction rate was increased among obese patients (4 of 24 patients [16.7%] vs 2 of 76 [2.6%]; OR,

7.40 [95% CI, 1.26-43.35;  $P = .03$ ]) and among those undergoing major hepatectomy (5 of 34 patients [14.7%] vs 1 of 66 [1.5%]; OR, 11.21 [95% CI, 1.25-100.23;  $P = .02$ ]). The proportion of liver dysfunction was higher among patients with grade 2 or 3 steatosis (3 of 30 patients [10.0%] vs 3 of 70 [4.3%]; OR, 2.48 [95% CI, 0.47-13.07]), grade 2 or 3 SinDil (3 of 28 patients [10.7%] vs 3 of 72 [4.2%]; OR, 2.76 [95% CI, 0.52-14.58]), or steatohepatitis (3 of 19 patients [15.8%] vs 3 of 81 [3.7%]; OR, 4.87 [95% CI, 0.90-26.37]), although the differences were not significant ( $P = .36$ ,  $P = .35$ , and  $P = .08$ , respectively). The liver dysfunction rate was not related to any specific chemotherapy regimen or to prolonged treatments. The operative mortality rate was increased among patients with steatohepatitis (2 of 19 patients [10.5%] vs 0 of 81 [0%]; OR, 13.67 [95% CI, 1.34-139.07;  $P = .04$ ]). No other variables correlated with mortality.

## COMMENT

Evaluation of CALIs should be part of the preoperative workup in patients scheduled for liver resection after chemotherapy to correctly assess liver function and operative risk. Noninvasive studies, such as imaging and LFTs, are unreliable, especially regarding steatohepatitis. Although liver biopsy was thought to be helpful,<sup>10,11</sup> our findings indicate otherwise. The present study has clearly demonstrated that biopsy findings may predict steatosis but are inadequate to evaluate SinDil and steatohepatitis, likely because of the nonhomogeneous distribution of these CALIs.

The prevalence of moderate to severe CALIs (grade 2 or 3 SinDil, grade 2 or 3 steatosis, and steatohepatitis) ranges from 15% to 40%.<sup>9,11,15-18</sup> In the present series, 30.0% of patients had grade 2 or 3 steatosis, 28.0% had grade 2 or 3 SinDil, and 19.0% had steatohepatitis. The importance of CALIs has increased because CALIs have been associated with impaired liver function and worse postoperative outcomes.<sup>12-21</sup> Steatohepatitis has even been associated with increased 90-day mortality.<sup>18</sup> The present series observes similar findings; the rate of liver dysfunction is high (approximately 10%) among patients with moderate to severe CALIs, as is the mortality rate in patients with steatohepatitis (10.5% vs 0.0% in those without it).

Preoperative CALI evaluation is theoretically mandatory; however, limited tools are available. Some data may derive from imaging,<sup>22-24</sup> and 2 recent reports demonstrated that SinDil can be predicted by LFT values.<sup>17,19</sup> However, all these findings must be validated in separate series, and no preoperative protocols have been codified. In the present study, no correlation was demonstrated between LFT results and CALIs.

Liver biopsy has been proposed<sup>10,11</sup> in this context of uncertainty; however, its reliability has never been validated. To our knowledge, this study is the first to focus specifically on this issue. Recent reports have analyzed the role of biopsy in staging liver damage in morbidly obese patients or in those with nonalcoholic fatty liver disease.<sup>30-32</sup> These reports compared paired biopsy samples. Agreement between the 2 samples was excellent for steatosis, moderate for fibrosis, and extremely low

for hepatocellular ballooning and lobular inflammation. These results have been related to the nonhomogeneous distribution of liver damage within the liver. The present study differs from previous studies in at least the following 3 ways: first, we focus on CALIs, including SinDil; second, we compared biopsy samples with the resected specimen (larger sample); and finally, the quality of the sample was extremely high because it was obtained during laparotomy, regularly checked for length and integrity, and (if needed) easily repeated.

Despite these differences and the large (16 gauge) needle caliber, results were similar. Biopsy findings had high accuracy in staging steatosis and improved regarding severe disease (grade 3). By contrast, biopsy findings were disappointing in other CALI evaluation. Sensitivity values were extremely low, even considering more severe damages. The poor value of biopsy in CALI assessment is exemplified by steatohepatitis, for which 15 of 19 cases were missed. These results are likely related to the nonhomogeneous distribution of the injuries throughout the liver.<sup>30-32</sup> Regarding SinDil, the sensitivity and the positive predictive value of biopsy results were poor. This finding is likely related to tissue distortion after biopsy, which can lead to overestimation of dilatation.

Improved results could be expected for patients with higher prevalence of CALIs, such as those with more toxic chemotherapy regimens, prolonged treatments, or obesity. Even for these subgroups, biopsy results did not improve. In addition, results did not change between the first and last 50 cases, which demonstrates that the unreliability of biopsy findings did not depend on pathologist experience and excluded any learning curve effect.

Some limitations of the present study could be argued. First, we compared the parenchyma of the FRL with the peritumoral tissue. However, no differences in CALI occurrence are expected, and studies with paired biopsy samples reported similar results for punctures performed in the same or in different lobes.<sup>31</sup> In addition, to assess postoperative liver dysfunction risk, evaluation of the FRL is theoretically more adequate than that of peritumoral tissue. Second, the present CALI assessment did not include nodular regenerative hyperplasia.<sup>20,33</sup> This liver injury has recently been associated with chemotherapy and represents an evolution of vascular lesions, such as SinDil. Therefore, we would not expect biopsy findings to perform differently in the context of nodular regenerative hyperplasia. Third, the low CALI prevalence might underestimate biopsy findings. Although larger studies are needed, the percentage of CALIs in the present cohort was similar to that reported in the literature, and subgroup analyses failed to demonstrate any difference of biopsy findings with respect to CALI prevalence. Finally, interobserver variation of CALI evaluation was not analyzed. We performed a single-center study in which CALI analysis has been standardized. The 2 observers worked jointly in classifying CALIs on the peritumoral tissue and biopsy samples. Comparison with the findings of external pathologists would be necessary to clarify this aspect.

According to present results, biopsy should not be included in the preoperative workup of patients with colorectal metastases scheduled for liver resection. Although multiple biopsy samples or laparoscopic large paren-

chyma sampling could be proposed, we believe that non-invasive tools will represent the solution to CALI assessment. Meanwhile, the best way to manage CALIs is to prevent them by reducing the number of preoperative chemotherapy cycles and to perform radical but parenchyma-sparing resections to limit the risk of liver failure.

In conclusion, preoperative liver biopsy is not a reliable tool with which to evaluate CALIs. Only steatosis can be correctly graded, whereas SinDil and steatohepatitis are often misdiagnosed, likely because of the small sample size and the nonhomogeneous intrahepatic distribution of injuries. Liver biopsy should not be included in the preoperative workup.

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