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Effect of non-alcoholic liver disease on recurrence rate and liver regeneration after liver resection for colorectal liver metastases

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ABSTRACT

Background Resection of metastases is the only potential cure for patients with liver metastasis from colorectal cancer (CRC-LM). But despite an improved overall 5-year survival, the recurrence rate is still as high as 60%. Non-alcoholic fatty liver disease (NAFLD) can decrease the liver's capacity to regenerate after resection and might also affect cancer recurrence, potentially by elevating transforming growth factor β, levels of specific metalloproteinases, and oxidative stress. The objective of the present work was to determine the effect of the histologic features of NAFLD on cancer recurrence and liver regeneration.

Methods This retrospective analysis considered 60 patients who underwent an R0 hepatectomy for CRC-LM. Volumetric analysis of the liver was calculated using axial view, portovenous phase, 2.5 mm thickness, multiphasic computed tomography images taken before and after surgery. The histologic features of NAFLD (steatosis, inflammation, and ballooning) were scored using the NAFLD activity score, and the degree of fibrosis was determined.

Results The hepatic recurrence rate was 38.33%. Median overall survival duration was 56 months. Median disease-free survival duration was 14 months, and median hepatic disease-free survival duration was 56 months. Multivariate analysis revealed significant correlations of hepatic disease-free survival with hepatocyte ballooning ($p = 0.0009$), lesion diameter ($p = 0.014$), and synchronous disease ($p = 0.006$). Univariate and multivariate analyses did not reveal any correlation with degree of steatosis or recurrence rate.

Conclusions This study reveals an important potential negative effect of hepatocyte ballooning on hepatic disease-free survival.

Key Words Non-alcoholic fatty liver disease, NAFLD, CRC liver metastases, liver regeneration, liver volumetrics, liver metastasis recurrence

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INTRODUCTION

Colorectal cancer is the 3rd leading cause of cancer-related death, most commonly from uncontrolled metastasis[1]. The liver is the most common site of metastasis, with the median overall survival for patients with metastatic disease to the liver being 6–12 months in the absence of treatment[2–4]. Of all colorectal cancer patients, 50% will develop liver metastasis during the course of their disease[5], and 15%–20% will present with synchronous liver metastasis[5]. The treatment of colorectal cancer liver metastasis (CRC-LM) is chemotherapy; in a small fraction of patients in whom it is possible to remove all disease (15%–20%), liver resection (R0) is also indicated[6]. The 5-year overall survival for patients who undergo an R0 resection for CRC-LM is 25%–44%[7,8]. Of patients who undergo a liver resection for CRC-LM, 60% experience recurrence[9].

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As a result of the high recurrence rate after curative liver resection, many investigators have tried to determine predictors of such recurrences. Several studies have identified liver regeneration, with its associated growth factors and cytokines, as a potential process that can stimulate tumour growth, thus promoting recurrence[10–51].

The regenerative ability of the liver after partial liver resection can be affected by the quality of the liver, which can be affected by steatosis[52], fibrosis, and cirrhosis[53,54]. It has been suggested that the degree of liver steatosis is an important indicator of the liver's regeneration capacity[52]. Non-alcoholic fatty liver disease (NAFLD) can range from simple steatosis, to steatohepatitis, and later to fibrosis and cirrhosis. The histologic features that can be present in fatty liver are steatosis, inflammation, hepatocyte ballooning, and fibrosis. Fatty liver disease is increasing in prevalence, affecting 20%–30% of people in North America[55]. The mechanism by which steatosis affects liver regeneration is not yet clear; however, insulin resistance, defective metabolic gene expression, and abnormal expression of transforming growth factor β1 have been shown to have a role[56–60]. Steatosis and steatohepatitis have also been shown to increase the level of transforming growth factor β, specific metalloproteinases, and oxidative stress, which in turn can facilitate tumour growth and progression[61–64].

On the other hand, knowing that liver regeneration can have a stimulatory effect on tumour growth and recurrence, and that NAFLD decreases the liver's regeneration capacity, there is currently an interest in defining whether fatty liver could have a protective effect with respect to metastatic tumour recurrence—a question that remains unanswered at the present time. Here, we examine the correlations and interplay between the degree of NAFLD, liver regeneration, and tumour recurrence after hepatectomy for CRC-LM.

METHODS

Patients

After obtaining institutional review board approval, a review of our CRC-LM database for all R0 liver resections performed for CRC-LM at the McGill University Health Centre from January 2007 to January 2012 identified 215 patients. We then excluded patients who did not have, within their electronic medical record, at least 1 preoperative computed tomography (CT) exam and 1 CT exam at 12 or more weeks postoperatively; who had previously undergone portal vein embolization or staged resection; who had undergone procedures, such as liver ablation, that affect liver volume; and for whom histology blocks of the non-tumoural hepatic parenchyma were unavailable for histopathologic analysis. Application of those criteria left 60 evaluable patients, who constituted the study sample (Figure 1).

For the 60 identified patients, the following data were collected from the CRC-LM database: patient demographics, surgical procedure details, resection margin status, tumour characteristics, preoperative and postoperative chemotherapy regimens, number of cycles, and date of last cycle. Patient charts and follow-up imaging (CT, positron-emission tomography, and magnetic resonance) were reviewed for any evidence of recurrence. We then recorded the date and site of recurrence. We obtained overall survival duration by chart review and by retrieving death certificates from the Régie de l'assurance maladie du Québec. Any patient who proved to be alive at January 2013 was considered a survivor.

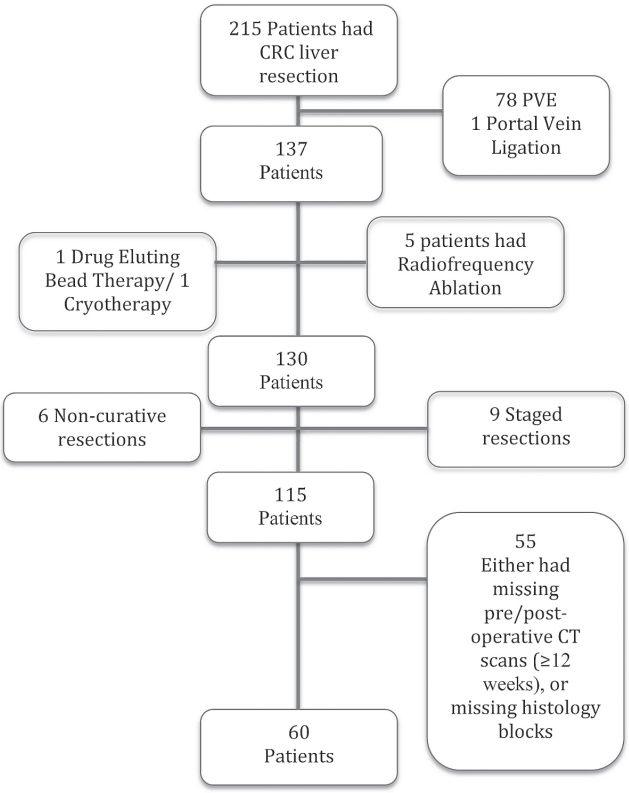

FIGURE 1 CONSORT diagram for the study sample. CRC = colorectal cancer; PVE = portal vein embolization; CT = computed tomography.

Liver Volumetrics

Preoperative and postoperative (at 12 weeks or more after surgery) CT imaging was retrieved for each patient. The 12-week time point was chosen for the follow-up imaging, because most liver regeneration had occurred by that time[65]. Volume measurements were performed on axial view, portovenous phase, 2.5 mm thickness, multiphasic CT images. The images were transferred to the Advantage Workstation 4.3 (GE Healthcare, Little Chalfont, U.K.) with dedicated three-dimensional volume calculation software.

Preoperative scans were analyzed for total liver volume before resection ($TLV_{pre\text{-}op}$), future liver remnant (FLR), and total tumour burden. To measure the $TLV_{pre\text{-}op}$, the edges of the liver were manually traced on each CT slice, excluding the vena cava, gallbladder, and liver ligaments. The volume was then automatically calculated based on the traced area and slice thickness. The total tumour burden was measured by highlighting each lesion (based on lesion density, the highlight diffuses throughout the slices to cover the whole lesion). The volume was automatically calculated after all lesions had been highlighted.

The edges of the FLR were traced according to the Couinaud classification and on the basis of the predicted

postoperative outflow anatomy. The selected area was then highlighted, and the volume was automatically calculated. The FLR of patients who underwent wedge resection was calculated differently, given that wedge resection is an operator-dependent type of resection. The weight of resected liver was retrieved from the pathology report and was then converted to a cubic volume in centimetres, assuming that liver density is the same as water density. The equation TLV minus volume of resected liver was then applied to yield the FLR[66].

Imaging was also analyzed for postoperative total liver volume ($TLV_{post\text{-}op}$). Based on image availability, $TLV_{post\text{-}op}$ was not necessarily measured using portovenous phase CT images because the measurement did not require identification of the venous blood supply. To measure the $TLV_{post\text{-}op}$, the edges of the liver were manually traced on each CT slice, excluding the vena cava, gallbladder, and liver ligaments. The volume was then automatically calculated based on the traced area and the slice thickness. We excluded postoperative fluid collections from the $TLV_{post\text{-}op}$ when present.

The formula used to calculate the percentage of estimated liver regeneration (%ELR)[67] was

$$\%ELR = (TLV_{post\ op} - FLR) \ / \ FLR \times 100.$$

Degree of NAFLD

Hematoxylin and eosin–stained slides of the non-tumoural hepatic parenchyma were retrieved for each patient and were scored, under the supervision of a liver pathologist, for liver steatosis, lobular inflammation, ballooning and fibrosis per the Kleiner *et al.*[68] NAFLD activity score (Table I). We also studied trichrome-stained slides to score the degree of fibrosis: 0, no fibrosis; 1, peri-sinusoidal, or peri-portal or portal (1a: mild peri-sinusoidal; 1b, moderate peri-sinusoidal; 1c, peri-portal or portal); 2, peri-sinusoidal and peri-portal or portal; 3, bridging fibrosis; 4, cirrhosis. For the present study, we treated 1a, 1b, and 1c as 1 because of the limited variability of the patients.

TABLE I Evaluation tools: non-alcoholic fatty liver disease (NAFLD) activity score and fibrosis staging

Tool	Item	Criterion	Score
NAFLD activity score			
	Steatosis	<5%	0
		5%–33%	1
		>33%–66%	2
		>66%	3
	Lobular inflammation	No foci	0
	(at 200× magnification)	<2 foci	1
		2–4 foci	2
		>4 foci	3
	Hepatocyte ballooning	None	0
		Few ballooned cells	1
		Many cells or prominent ballooning	2
Fibrosis stage			
	Fibrosis	None	0
		Perisinusoidal or periportal	1
		Mild, zone 3, perisinusoidal	1a
		Moderate, zone 3, perisinusoidal	1b
		Portal or periportal	1c
		Perisinusoidal and portal or periportal	2
		Bridging fibrosis	3
		Cirrhosis	4

Statistical Analysis

Statistical analyses were performed using the JMP software application (version 10.0: SAS Institute, Cary, NC, U.S.A.). Normally distributed data are expressed as means and standard deviations; otherwise, medians and ranges are used. Nominal data are expressed as percentages. The Kaplan–Meier method was used to plot curves for time-to-event outcomes (for example, hepatic disease-free survival, overall survival). Cox proportional hazards regression models were used to examine the association between %ELR (and other numerical variables) and hepatic disease-free survival and overall survival. The log-rank chi-square test was used with nominal data. The associations between %ELR and other variables were examined using regression analyses (linear fit for numerical variables and one-way analysis of variance for nominal variables). Levels of significance were set at 5% for all tests unless otherwise specified. We included age and body mass index (BMI) with cut-offs (>70 years and >30) to all multivariate analysis. On multivariate analysis, only significant variables ($p < 0.05$), in addition to age and BMI, were tested using proportional hazards.

We tested these variables against hepatic disease-free and overall survival:

- Liver volumetrics: TLV, FLR, $TLV_{post\text{-}op}$, and %ELR
- Control variables: age, sex, BMI
- Cancer characteristics: TNM stage; serum carcinoembryonic antigen; lesion size, number, and distribution
- Resection characteristics: type of resection, disease-free margin
  - NAFLD score (steatosis, hepatocyte ballooning, lobular inflammation) and fibrosis score

RESULTS

Patient Characteristics

Of the 60 patients eligible for the study (Figure 1), 36 were men (60%) and 24 were women (40%). Table II presents the demographic characteristics and surgical details for the patients. Median age in the cohort was 68.5 years (range: 40–81 years), and the median BMI was 26.5. Disease was unilateral in 44 patients (73.33%) and bilateral in 16 patients (26.66%). Of the 59 patients for whom

TABLE II Baseline characteristics of the study patients

Characteristic	Value	Correlation with survival			
		Hepatic disease-free		Overall	
		Months	*p* Value	Months	*p* Value
Patients (*n*)	120				
Age (years)					
Median	68.5	RR: 0.97	0.12	RR: –0.01	0.35
Range	40–81				
BMI					
Median	26.5	RR: 1.06	0.29	RR: –0.05	0.4
Range	19.3–36.8				
Sex [*n* (%)]					
Men	36 (60)	56	0.25	58	0.34
Women	24 (40)	48		56	
Disease laterality [*n* (%)]					
Unilateral	44 (73.33)	56	0.1	63	0.39
Bilateral	16 (26.66)	14		56	
Lesions (*n*)					
Median	1	RR: 1.18	0.17	RR: 0.13	0.17
Range	0–9				
Median TNM staging (*N*=69)					
T Stage	3	RR: 2.03	0.06	RR: 0.81	0.08
N Stage	1	RR: 1.09	0.79	RR: 0.53	0.25
Carcinoembryonic antigen [*n* (%), *N*=83]					
≤200 ng/mL	54 (94.73)	48	0.56	56	0.8
>200 ng/mL	3 (5.26)	14		—	
Lesion size [*n* (%)]					
≤5 cm	52 (86.66)	56	0.04	56	0.99
>5 cm	8 (13.33)	11.5		—	
Positive nodes of the primary [*n* (%), *N*=41]					
≤5	34 (82.92)	48	0.82	63	0.11
>5	7 (17.07)	—		—	
Primary metastases [*n* (%), *N*=59]					
Synchronous	28 (47.45)	23	0.03	46	0.08
Metachronous	31 (52.54)	—		56	
Surgery [*n* (%)]					
Right hepatectomy	32 (53.33)	56	0.03	58	0.19
Left lateral hepatectomy	10 (16.66)	16		—	
Left hepatectomy	9 (15)	—		46	
Right trisegmentectomy	3 (5)	14		—	
Wedge resection	1 (1.66)	7		42	
1-Segment resection	2 (3.33)	—		27.5	
2-Segment resection	3 (5)	—		—	
Resection type [*n* (%)]					
Major	44 (73.33)	56	0.72	65	0.86
Minor	16 (26.66)	—		—	
Resected segments (*n*)					
Median	4	RR: 0.9	0.6	RR: –0.15	0.43
Range	1–6				
Margins [*n* (%)]					
Free	52 (86.66)	56	0.41		
Positive	8 (13.33)	35			

RR = risk ratio.

synchronicity was known, disease was synchronous in 28 (47.45%) and metachronous in 31 (52.54%). Median TNM staging was T3N1M1. Lesions were larger than 5 cm in 8 patients (13.33%).

In this cohort, 32 patients underwent right hepatectomy (53.33%), 9 underwent left hepatectomy (15%), 10 underwent left lateral hepatectomy (16.66%), and only 3 patients underwent right tri-segmentectomy. The rest either underwent wedge resection, single segmentectomy, or bi-segmentectomy (Table II).

Table III summarizes the liver volumetrics. The median estimated liver regeneration was 74.57% (range: –9.95% to as high as 324.32%).

The median percentage of total steatosis was 12.5% (range: 0%–85%), the median percentage of micro-steatosis was 5% (range: 0%–50%), and the median percentage of macro-steatosis was 7.5% (range: 0%–75%). Table IV summarizes the NAFLD and fibrosis scores.

Complete data on preoperative chemotherapy were available for 59 patients. Of those 59 patients, 46 received preoperative therapy. The type of preoperative chemotherapy was identified for 41 patients. The median number of preoperative chemotherapy cycles was 6. The median interval between the last preoperative chemotherapy cycle and surgery was 7 weeks.

The median length of follow-up in the cohort was 27.5 months. The hepatic recurrence rate was 38.33%. Hepatic disease-free survival at 5 years was 48%, and the median survival duration was 56 months. Overall survival at 5 years was 39%, and the median survival duration was 56 months (Table V). Figure 2 shows the Kaplan–Meier curves for hepatic disease-free and overall survival.

Predictors of Hepatic Disease-Free Survival

Univariate analysis of the study cohort revealed that a higher degree of hepatocyte ballooning was associated with an increased risk of hepatic recurrence and significantly decreased hepatic disease-free survival (risk ratio: 3.31; $p = 0.003$; Figure 3). It also showed that lesions of 5 cm or larger ($p = 0.043$) and synchronous disease ($p = 0.025$) were associated with an increased risk of hepatic recurrence. The type of resection was also significantly associated with hepatic disease-free survival ($p = 0.03$), such that disease-free survival was best after right hepatectomy (median survival duration: 56 months) and worst after wedge resection (median survival duration: 7 months). On the other hand, the degree of steatosis had no significant association with risk ($p = 0.68$), and other histopathologic features, including lobular inflammation and fibrosis, had no significant association with hepatic disease-free survival (Table IV).

On multivariate analysis (whose variables included hepatocyte ballooning, lesion diameter, synchronous disease, and type of resection, plus age and BMI), only hepatocyte ballooning ($p = 0.0009$), maximum lesion diameter ($p = 0.014$), and synchronous disease ($p = 0.006$) proved to be significantly correlated with survival, with ballooning having the strongest correlations (Tables III–V)

The Severity of NAFLD and %ELR

On univariate analysis, a significant correlation was observed between %ELR and lobular inflammation. The higher the degree of lobular inflammation, the lower the liver capacity to regenerate (estimate: –54.31; $p = 0.003$). Results for stage of fibrosis were similar (estimate: –39.9; $p < 0.001$). Other factors that significantly correlated with liver regeneration included FLR (estimate: –0.14; $p < 0.0001$), number of segments resected (estimate: 40.80; $p < 0.0001$), major resection (mean: 114.75%; range: 93.65%–135%; $p < 0.001$), and number of lesions (estimate: 17.27; $p = 0.01$). Neither hepatocyte ballooning nor steatosis significantly correlated with regeneration capacity of the liver ($p = 0.70$ and $p = 0.35$ respectively, Figure 4).

Multivariate analysis of the significant variables (including degree of lobular inflammation, stage of fibroses, major resection, number of lobes resected, FLR, and number of lesions, plus age greater than 70 years and BMI greater than 30), showed that only FLR is a statistically significant predictor of liver regeneration ($p < 0.01$).

DISCUSSION

In the present study, we investigated the relationships of severity of NAFLD (based on histologic features) with risk of recurrence and with the regeneration capacity of the liver after hepatectomy for patients with CRC-LM. The study showed that hepatocyte ballooning is associated with an increased risk of CRC-LM recurrence. And yet the degree of steatosis did not predict the risk of recurrence nor the capacity of the liver to regenerate.

TABLE III Liver volumetrics

Variable	Median	Range	Correlation with survival			
			Hepatic disease-free		Overall	
			Estimate	*p* Value	Estimate	*p* Value
$TLV_{pre\text{-}op}$	1495.87	822.44 to 2702.28	1.0007	0.18	0.0003	0.5
TTV	6.64	0 to 601.30	1.002	0.19	0.003	0.22
FLR	770.73	285.22 to 2286.04	1.0003	0.51	0.0005	0.33
$TLV_{post\text{-}op}$	1281.61	778.30 to 3140.03	1.0003	0.54	0.0004	0.52
ELR (%)	74.57	–9.95 to 324.32	0.99	0.74	–0.003	0.18

TLV = total livervolume; TTV = total tumour volume; FLR = future liver remnant; ELR = estimated liver regeneration.

TABLE IV Histologic features of non-alcoholic fatty liver disease

Variable	Median	Range	Correlation with survival			
			Hepatic disease-free		Overall	
			Risk ratio	*p* Value[a]	Risk ratio	*p* Value[a]
Steatosis						
Total (%)	12.5	0–85	1.002	0.76	–0.008	0.48
Macro (%)	7.5	0–75	1.004	0.67	–0.01	0.5
Micro (%)	5	0–50	0.99	0.84	–0.02	0.54
Score (*n*)	1	0–3	1.09	0.68	–0.18	0.49
Score group [*n* (%)]						
0	19 (31.6)					
1	27 (45)					
2	10 (16.6)					
3	4 (6.6)					
Lobular inflammation score (*n*)	3	1–3	1.44	0.32	0.66	0.74
Score group [*n* (%)]						
1	3 (5)					
2	13 (21.7)					
3	44 (73.3)					
Hepatocyte ballooning score (*n*)	2	0–2	3.31	**0.003**	1.21	**0.01**
Score group [*n* (%)]						
0	4 (6.7)					
1	20 (33.3)					
2	36 (60)					
Tissue fibrosis score (*n*, *N*=56)	1	0–3	1.072	0.74	0.22	0.37
Score group [*n* (%)]						
0	27 (48)					
1	11 (20)					
2	16 (28.5)					
3	2 (3.5)					

[a] Significant values shown in boldface type.

TABLE V Survival results

Variable	Value
Follow up duration (months)	
Median	27.5
Range	4–73
Recurrence [n (%)]	
All	37 (61.66)
Hepatic	23 (38.33)
Extrahepatic	31 (51.66)
Disease-free survival (months)	
All	
Median	14
Mean	27.87±3.23
Hepatic	
Median	56
Mean	37.47±3.14
Overall survival	
Median	56
Mean	40±2.76

We also examined the effect on tumour recurrence of each NAFLD histologic feature separately and looked into the effect of micro- and macro-steatosis. Hamady *et al.*[69] concluded that liver steatosis is an independent predictor for disease recurrence. On the other hand, Murono *et al.*[70] found that CRC-LM occurs less frequently in fatty livers after resection, suggesting that steatosis might provide an unfavourable environment for metastasis in liver. However, in the present study, we found that steatosis does not predict hepatic disease-free survival. That discrepancy could reflect the fact that Hamady *et al.* and Murono *et al.* divided patients into two groups (steatosis and no steatosis) and did not consider the severity of steatosis. In contrast, we considered the steatosis score as well as the percentages of total steatosis, micro-steatosis, and macro-steatosis. The other two studies assessed steatosis using different methods: Hamady *et al.* used histologic assessment, and Murono *et al.* used radiologic liver density and liver-to-spleen density ratio. In our cohort, the only NAFLD histologic feature that was associated with decreased hepatic disease free-survival was hepatocyte ballooning.

Hepatic disease-free survival was also inferior in the presence of synchronous disease compared with

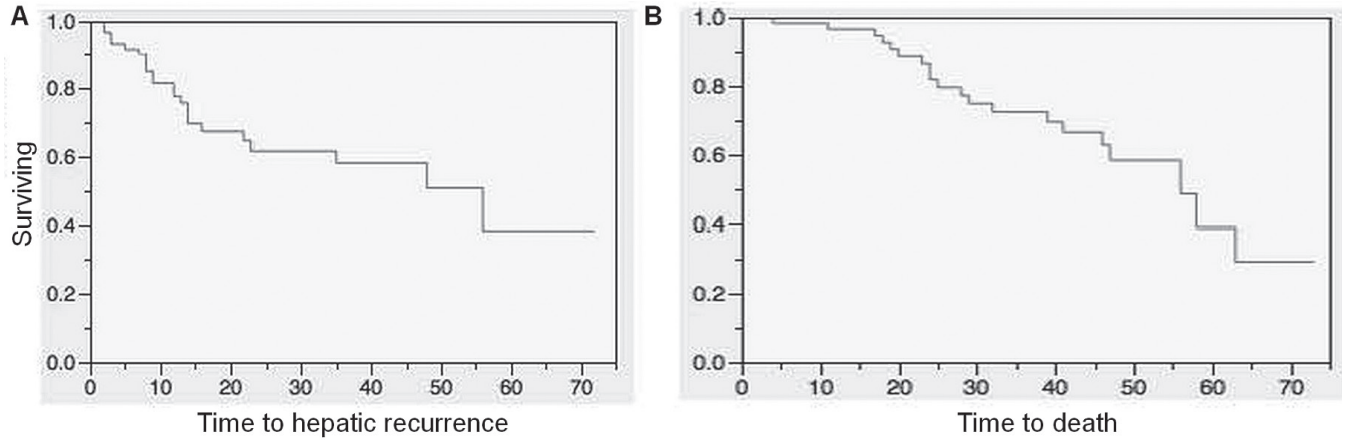

FIGURE 2 Kaplan–Meier survival curves for patients eligible to test the secondary hypothesis. (A) Hepatic disease-free survival was 78% at 1 year, 58% at 3 years, and 48% at 5 years. Median survival duration was 56 months. (B) Overall survival was 98% at 1 year, 62% at 3 years, and 39% at 5 years. Median survival duration was 56 months.

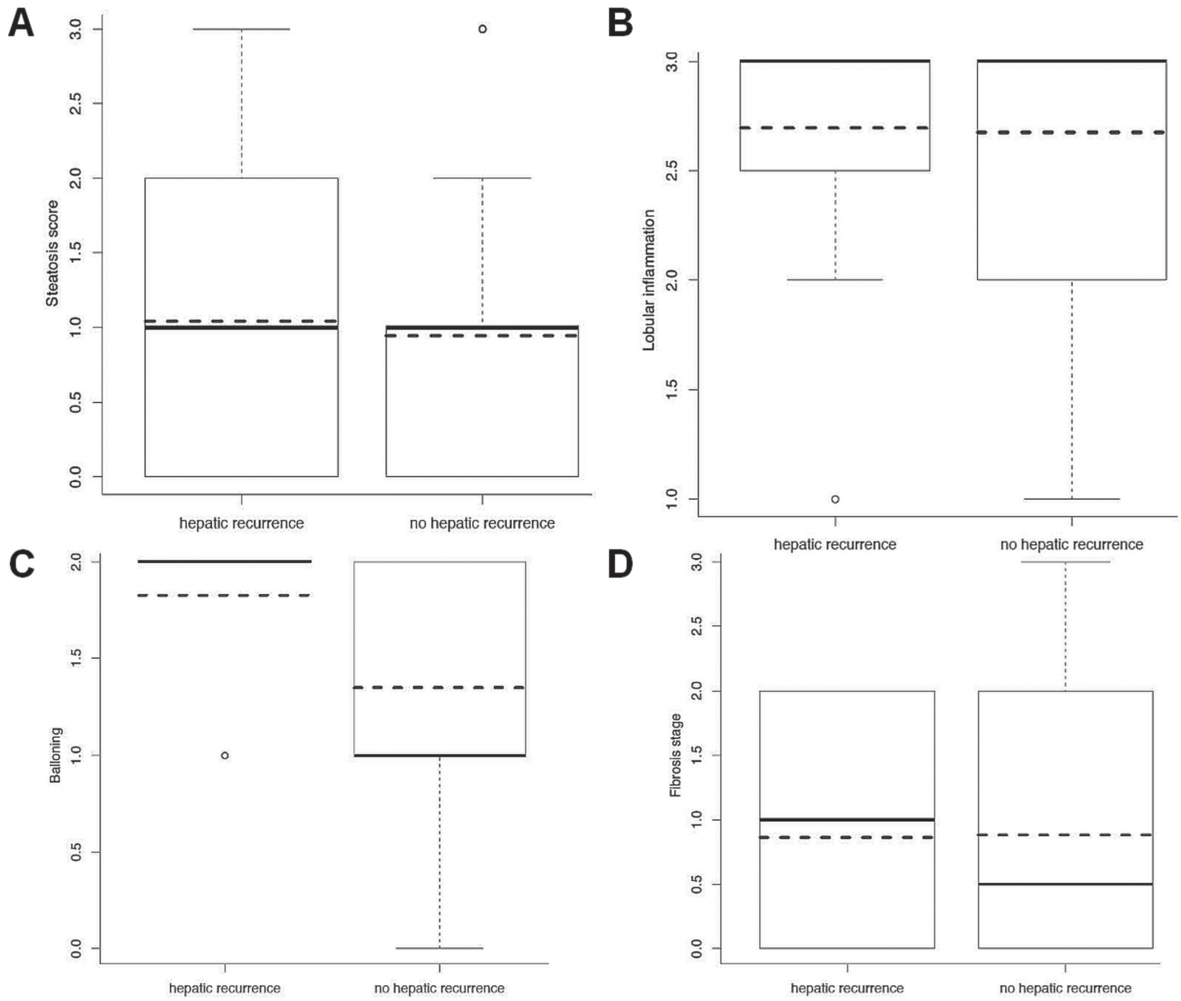

FIGURE 3 Univariate analysis evaluating the severity of histologic features of non-alcoholic fatty liver disease with respect to hepatic disease-free survival in patients eligible to test the secondary hypothesis. Correlations with lobular inflammation severity ($p = 0.32$) and fibrosis stage ($p = 0.74$) were nonsignificant. Severity of hepatocyte ballooning was significantly associated with decreased hepatic disease-free survival ($p = 0.003$). Solid line = median; dotted line = mean.

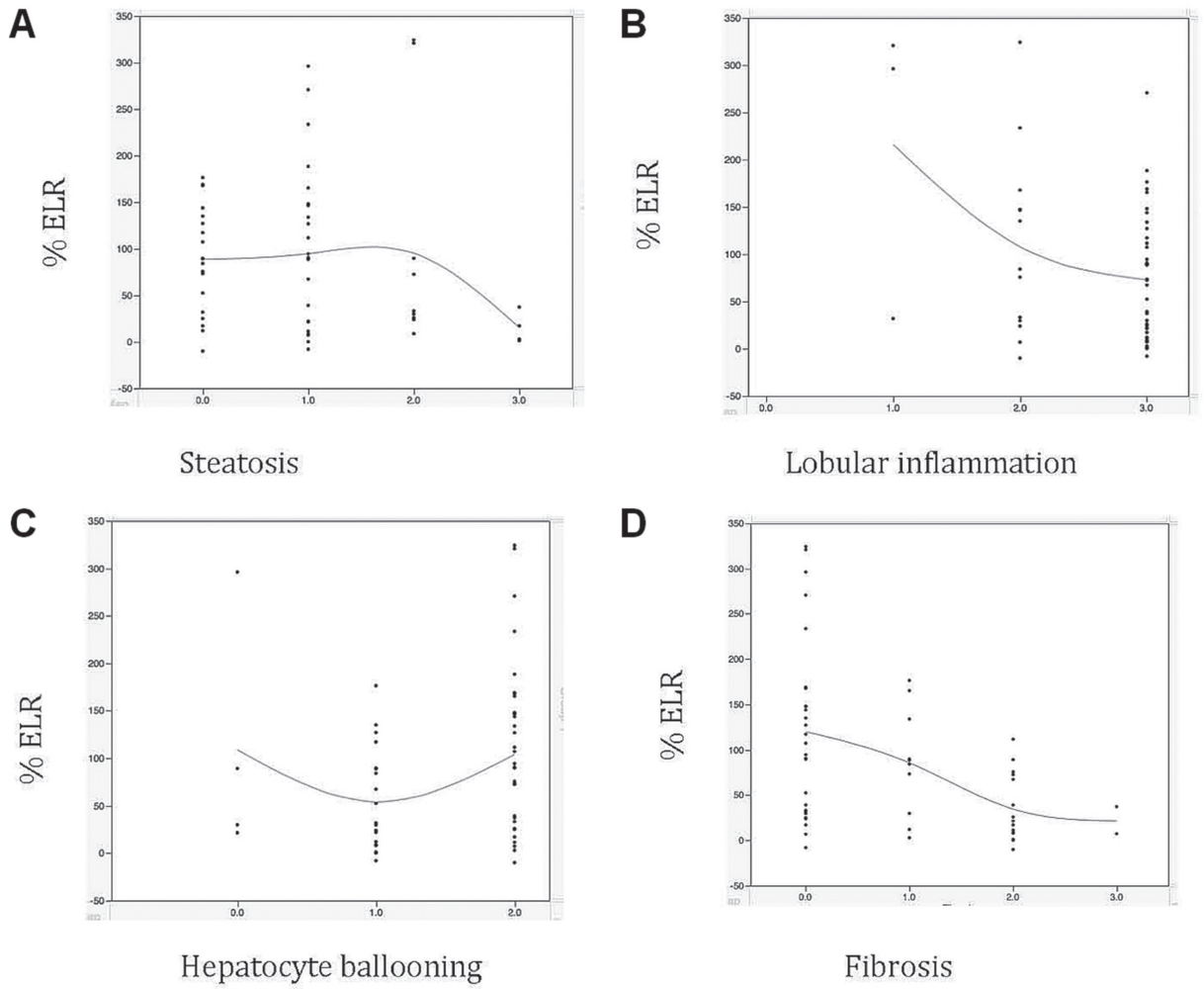

FIGURE 4 Regression analysis evaluating the severity of histologic features of non-alcoholic fatty liver disease with respect to the percentage estimated liver regeneration (%ELR) in patients eligible to test the secondary hypothesis. (A) The %ELR did not significantly correlate with severity of steatosis ($p = 0.35$). (B) The %ELR was significantly decreased with severity of lobular inflammation on univariate analysis ($p = 0.003$), but not on multivariate analysis ($p = 0.21$). (C) The %ELR did not significantly correlate with severity of hepatocyte ballooning ($p = 0.7$). (D) The %ELR was significantly decreased with severity of fibrosis on univariate analysis ($p = 0.0004$), but not on multivariate analysis ($p = 0.89$).

metachronous disease (69% at 1 year and 25% at 5 years vs. 85% at 1 year and 75% at 5 years), a result that accords with the reports of Yamada *el al.*[71] and Fong *et al.*[72]. Hepatic disease-free survival in our cohort was inferior for lesions 5 cm in diameter or larger than for smaller lesions (50% at 1 year and 33% at 5 years vs. 81% at 1 year and 40% at 5 years), a result that also accords with the literature[71,72]. However, in contrast to the results reported by Yamada *el at.*[71], we found no correlation of preoperative serum carcinoembryonic antigen, diameter of the largest nodule, number of positive lymph nodes, or bilateral disease involvement with disease-free survival.

Our study revealed interesting trends. Each histologic feature of NAFLD appears to have different effects on %ELR. Severity of steatosis (steatosis score and the percentages of total steatosis, of micro-steatosis, and of macro-steatosis), lobular inflammation, and stage of fibrosis tended to be associated with decreased liver regeneration capacity; however, only the latter two features reached the level of significance on univariate analysis. On the other hand, hepatocyte ballooning showed a trend toward association with increased liver regeneration capacity, but that trend did not reach the level of significance.

We also found that major resection, a larger number of resected segments, and a larger number of lesions were associated with increased %ELR. Those results are consistent with our findings in a different patient cohort from the same centre[73]. Higher %ELR is seen with trisegmentectomy, and the lowest %ELR with wedge resection. The 2 patients who underwent single-segment resection actually had minor liver regeneration; smaller resections provide less of a growth stimulus.

Even though our study was carefully prepared, it has several limitations that should be taken into account. First, the sample size was small because of the exclusions based the availability of CT imaging at appropriate time points.

Second, the retrospective nature of the study limited our access to some information, resulting in missing data such as the number of positive lymph nodes associated with the primary disease. Third, the limited variability in the degree of ballooning, such that only 4 of the 60 included patients showed grade 0 ballooning, could have biased the results. Nevertheless, the study raises an important concern about the effect of ballooning on liver disease.

CONCLUSIONS

In our patient population, hepatocyte ballooning might have had a negative effect on hepatic disease-free survival; however, the degree of liver steatosis did not correlate with the hepatic recurrence rate or liver regeneration capacity.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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