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Prediction of Recurrence Patterns from Hepatic Parenchymal Disease After Resection of Colorectal Liver Metastases

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Abstract

Background: Obesity and metabolic syndrome are associated with inflammatory hepatic parenchymal disease (HPD) and increased risk for recurrence after resection of colorectal liver metastases (CRLM). The independent impact of HPD on recurrence patterns has not been well-defined.

Methods: The non-alcoholic fatty liver disease activity score (NAS) was used to quantify HPD including steatosis and fibrosis for all patients with completely resected CRLM between April 2003 and March 2007. Clinicopathologic factors, perioperative history, and outcomes were compared to the NAS. Fisher's exact test examined the association between severe HPD (NAS ≥ 3) with clinical and perioperative characteristics. Kaplan-Meier methods were used to estimate recurrence-free survival (RFS). The cumulative incidence of recurrence (any intrahepatic recurrence (IHR), extrahepatic recurrence only (EHR), and death without recurrence (DWR)), were estimated using competing risks methods.

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Results: Among the 357 patients included in this study, microsteatosis was noted in 124 (35%) patients, severe HPD in 31 (9%), steatohepatitis in 14 (4%), and sinusoidal injury in 36 (10%). After a median follow-up of 127 months (range=4-175), 10-year RFS was 22% (95%CI=17-27%). Ten-year cumulative incidence for IHR, EHR, and DWR was 37%, 30%, and 12%, respectively. After controlling for confounders, NAS 3 was independently associated with higher risk of IHR (HR=1.76, 95%CI=1.07-2.90, p=0.027) and lower risk of EHR (HR=0.18, 95%CI=0.04-0.75, p=0.019) on multivariable analysis.

Conclusion: Severe HPD was associated with increased IHR risk and decreased EHR risk. Future investigation into whether improving hepatic parenchymal disease from reversible etiologies can reduce the risk for intrahepatic recurrence is warranted.

INTRODUCTION

One in five colorectal cancer (CRC) patients present with metastatic disease and most develop metastases in their lifetime.¹ Although the only curative option for patients with colorectal liver metastases (CRLM) is liver resection, 70-80% ultimately develop recurrent disease.² Several prognostic scores have been developed to aid in the prediction of recurrence risk, such as the Clinical Risk Score (CRS), and others based on tumor characteristics.³⁻⁵ Growing interest in cancer genomics has led to the identification of specific alterations that confer greater risk for recurrence as well as a novel molecular risk score to predict relapse after resection.⁶⁻⁸ Although these prognostic tools identify patients with high-risk disease, they neglect key patient risk factors that play a role in cancer development and propagation.

Hepatic steatosis or non-alcoholic fatty liver disease (NAFLD) is a known risk factor for CRC^{9,10} with rising incidence^{11,12} that will soon overtake viral hepatitis as the most common indication for liver transplantation in America.¹³ The role of hepatic steatosis in CRLM recurrence after resection is unclear, with different studies reporting increased, decreased, or no association with recurrence risk.¹⁴⁻¹⁶ These prior studies have been limited by small sample sizes and a narrow focus on steatosis or other features of hepatic parenchymal disease (HPD) in isolation. To date, no studies have comprehensively characterized the role of overall HPD (i.e., steatosis, hepatocyte ballooning, lobular inflammation, and fibrosis) in the development and pattern of recurrence after CRLM resection.

We aimed to better define the relationship between HPD and the development of recurrence after CRLM resection. Here, we report the association between composite histologic characteristics and the risk for intrahepatic and extrahepatic recurrence following resection of CRLM.

METHODS

Patients Selection

Following approval from the Memorial Sloan Kettering Institutional Review Board, all patients with CRLM undergoing complete hepatectomy between April 2003 and March 2007 were identified from a prospectively-maintained clinical database. Of 506 patients

identified, 139 were excluded due to the lack of adequate tumor or hepatic parenchymal (non-tumor) tissue for pathologic analysis. Additionally, two patients that died and eight patients that were lost to follow-up within 90 days of resection were removed. The final cohort for analysis included 357 patients. This cohort was previously studied for associations between clinicopathologic factors and HPD with the exception of 27 samples (14 were specimens from repeat resections, 2 had died and 8 were lost to follow-up within 90 days, 2 lacked tumor on the resected specimen, and 1 had features suspicious for neuroendocrine tumor).¹⁷

Clinicopathologic Variables

Data on clinicopathologic characteristics, staging, perioperative chemotherapy, surgical history, postoperative outcomes, histopathology, follow-up, and survival were collected from a prospectively-maintained liver resection database. Right colon tumors were defined as those arising from the cecum to the distal transverse colon, and left colon tumors originated from the splenic flexure to the distal sigmoid colon. Any tumors arising in the rectosigmoid junction or distally were rectal in origin. Preoperative chemotherapy was defined as treatment within six months prior to hepatectomy. The CRS was prospectively calculated to estimate risk for recurrence after liver resection and is based on primary nodal status, preoperative carcinoembryonic antigen (CEA) level, largest CRLM tumor size, number of CRLM tumors, and disease-free interval (DFI) from primary resection to detection of CRLM.³

Tissue Analysis

All specimens were re-reviewed by two pathologists (FB and JS) experienced in CRLM diagnosis, grading, and staging. Both were blinded to the patients' preoperative characteristics (e.g., body mass index (BMI), diabetes status, chemotherapy exposure) and clinical outcome at the time of review, as described previously.¹⁷ Due to mass effect causing liver parenchyma immediately adjacent to an invading tumor to have associated inflammation, liver sections distant from the tumor and upstream of bile flow were analyzed. Initial specimen review for adequacy of parenchymal tissue was conducted with hematoxylin and eosin stained slides.

The degree of HPD was quantified based on the Kleiner-Brunt histologic scoring system, also known as the NAFLD activity score (NAS).¹⁸ This incorporates degree of steatosis (0-3), lobular and portal inflammation (0-3), hepatocyte ballooning degeneration (0-2), and fibrosis (0-4), including Mallory hyalinization, lipogranuloma deposition, and apoptosis. Degree of fibrosis was determined using Masson's trichrome and reticulin staining. Patients with a NAS ≥ 3 were defined to have severe HPD. Those with a steatosis score of ≥ 1 ($\geq 5\%$ fat infiltration) were considered to have microsteatosis. A NAS ≥ 4 defined steatohepatitis. Sinusoidal injury was separately defined by the Rubbia-Brandt grading system based on a score from 0 to 3;^{19,20} patients with a score of ≥ 1 were considered to have sinusoidal injury.

Statistical Analyses

Fisher's exact test was used to examine the association between severe HPD (NAS ≥ 3) with clinical and perioperative characteristics. Recurrence-free survival (RFS) was estimated

using Kaplan-Meier methods and calculated from the date of surgery to the date of recurrence or death. Patients who were alive or without recurrence at the date of last follow-up were censored. Cumulative incidence of the first recurrence – either intrahepatic recurrence with or without extrahepatic recurrence (IHR), isolated extrahepatic recurrence only (EHR), or death without recurrence noted (DWR) – was estimated using competing risks methods. Fine and Grey regression methods were used to examine the association between histologic findings as well as patterns of recurrence and adjusted for known clinical confounders, such as CRS and preoperative chemotherapy exposure.²¹ All p-values were two-sided, and $p < 0.05$ was considered statistically significant on univariate modeling and thus eligible for inclusion in multivariate models. If multiple components of the CRS were significantly associated with either recurrence pattern on univariate modeling, the CRS was included as a summative representative in multivariate modeling. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC, USA) or R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

The median age for the 357 study patients at resection was 60 years (range=28-88, Table 1) and the majority were male ($n=216$, 61%). Most had a BMI ≥ 25 ($n=237$, 66%) and few had diabetes ($n=42$, 12%). Most patients had primary node-positive ($n=206$, 58%) and low-risk (CRS=0-2) disease ($n=270$, 76%). The median largest CRLM tumor size was 2.9 cm (range=0.3-17), and the median number of CRLM tumors at resection was 2 (range=1-20). Most patients received preoperative systemic chemotherapy ($n=234$, 66%). Additionally, 28 (8%) underwent preoperative hepatic artery infusion (HAI) pump placement (prior to liver resection), 109 (31%) had adjuvant placement (at the time of resection), and 10 (3%) had salvage pump placement (after detection of IHR). On histopathologic analysis, microsteatosis was noted in 124 (35%) patients, severe HPD in 31 (9%), steatohepatitis in 14 (4%), and sinusoidal injury in 36 (10%).

Survival and Recurrence Patterns and Histologic Liver Appearance

The median follow-up for survivors was 127 months (range=4-175). Five and ten-year RFS were 30% (95%CI=25-35%) and 22% (95%CI=17-27%), respectively. The ten-year cumulative incidences for IHR, EHR, and DWR were 37%, 30%, and 12%, respectively (Figure 1).

On univariate analysis, patients with severe HPD were more at risk for any IHR (with or without EHR) compared to patients without HPD (HR=1.93, 95%CI=1.19-3.12, $p=0.008$, Figure 2). Other factors significantly associated with increased risk for any IHR included preoperative chemotherapy exposure (HR=1.58, 95%CI=1.07-2.32, $p=0.019$) and multifocal CRLM (HR=1.44, 95%CI=1.00-2.07, $p=0.049$, Table 2). Lower risk for any IHR was associated with DFI less than 12 months (HR=0.60, 95%CI=0.41-0.86, $p=0.006$). In contrast, patients with severe HPD had a reduced risk of EHR only compared to patients without severe HPD (HR=0.17, 95%CI=0.04-0.71, $p=0.015$, Figure 3). Factors significantly associated with EHR only on univariate analysis included high-risk CRS (HR=1.59,

95%CI=1.01-2.49, $p=0.046$) and CRLM measuring 5 cm or larger (HR=1.82, 95%CI=1.16-2.85, $p=0.009$). Notably, a significant association was not detected between microsteatosis, steatohepatitis, and sinusoidal injury with any IHR or EHR only. In multivariable models, the overall CRS was included rather than its individual components. After controlling for confounders, severe HPD (HR=1.76, 95%CI=1.07-2.90, $p=0.027$) and preoperative chemotherapy exposure (HR=1.50, 95%CI=1.02-2.22, $p=0.042$) were independently associated with any IHR, whereas severe HPD (HR=0.18, 95%CI=0.04-0.75, $p=0.019$) and high CRS (HR=1.70, 95%CI=1.07-2.70, $p=0.024$) were independently associated with EHR only.

DISCUSSION

The liver is the most common site of metastasis and recurrence for CRC patients.² Despite the rising incidence of NAFLD, soon to be the most common indication for liver transplantation in the US,^{11,13,22} little is known about the role of this inflammatory state in driving recurrence after hepatic resection for CRLM. Our findings suggest that severe HPD is an independent predictor of increased risk of any IHR and decreased risk of EHR only following complete resection of CRLM.

Prior studies note conflicting findings on the role of hepatic steatosis and its association with liver recurrence after CRLM resection. Hamady et al. found that steatosis was associated with poor hepatic disease-free survival (HDFS) in resected CRLM patients.¹⁵ A propensity score matched analysis comparing 902 patients with steatosis and 902 control patients without found that steatosis was associated with worse HDFS (OR=1.27, 95%CI=1.09-1.48, $p=0.002$) and postoperative liver failure (OR=2.31, 95%CI=1.32-4.02, $p=0.001$). In the Hamady et al. study, steatosis was “assessed semi-quantitatively” as fat droplets involving over 5% of hepatocytes. Molla et al. used NAS to detect a similar incidence of hepatic recurrence (38%) and an association between hepatocyte ballooning and shorter HDFS in resected CRLM patients.¹⁶ Steatosis, lobular inflammation, and fibrosis were not separately associated with HDFS; however, this study of 60 patients may have been underpowered to detect an association. In contrast, a third study of primary CRC patients from all stages following complete resection reported that hepatic steatosis was associated with longer RFS and hepatic RFS, but not extrahepatic RFS.¹⁴ Additionally, the absence of hepatic steatosis was an independent risk factor for shorter hepatic RFS; however, only 75 patients in this study had stage IV disease of which, only four had hepatic steatosis. Importantly, none of these three reports examined HPD globally or used the overall NAS.

We sought to improve upon prior work through the use of an objective composite metric of HPD (NAS). We found that severe HPD was independently associated with a nearly two-fold increased risk for IHR on multivariable analysis after accounting for CRS and preoperative chemotherapy exposure. These findings suggest that steatosis in the setting of inflammation is related to liver recurrence risk, consistent with reports linking fatty acid metabolism and CRC tumor growth. Notably, fatty acid synthase (the central enzyme required for oxidation and metabolism of fatty acid) is expressed at higher levels in colorectal carcinomas compared to normal human tissue,²³ enhances cellular respiration of colon cancer cells,²⁴ promotes tumor growth and survival,²⁵⁻²⁷ and likely plays a role in the

establishment of CRLM.²⁸ Co culture experiments have demonstrated free fatty acid transfer from adipocytes to colon cancer cells, enabling tumor growth and survival in a nutrient-deprived environment.²⁹ Additionally, multiple studies report that inhibition of fatty acid synthase leads to DNA replication suppression, apoptosis, and tumor volume reduction.²⁵⁻²⁷ Despite this evidence supporting a role for steatosis in the propagation of CRLM, the findings of the present study indicate that microsteatosis alone may be insufficient to promote any IHR. In support of this, severe HPD was independently associated with reduced risk for EHR only. It is possible that increased fatty acid metabolism in the setting of severe HPD or inflammation may create a more favorable milieu for recurrent CRLM growth, discouraging extrahepatic metastasis where a steatotic environment is not accessible, like the lungs. Our data is unfortunately too limited to define this phenomenon further as only a minority of patients had preoperative extrahepatic disease and were therefore at relatively similar risk for developing IHR or EHR. Thus, severe HPD may represent a state incorporating fat-infiltration and an inflammatory driver to promote recurrence after CRLM resection, but this hypothesis needs further exploration.

We also found that preoperative chemotherapy exposure was independently associated with increased risk for any IHR on multivariable analysis. Prior work demonstrated associations between preoperative chemotherapy exposure and the development of HPD, including microsteatosis, steatohepatitis, and sinusoidal injury.^{17,19,30-34} Although preoperative chemotherapy exposure was included as a risk factor in the multivariable model, the decision to treat resectable CRLM patients with chemotherapy preoperatively is subjective and may reflect an unmeasured bias by the clinician to consider these patients at higher risk for recurrence, as has been noted in multiple prior reports.³⁵⁻³⁷ While this bias may present a potential confounder, inclusion of preoperative chemotherapy exposure in a multivariable model with severe HPD indicates that these variables have independent roles in conferring risk for recurrence. Furthermore, an association between preoperative chemotherapy exposure and EHR only was not detected. Of note, HAI chemotherapy treatment prior to or after liver resection was not associated with risk for any IHR in this study. However, adjuvant HAI chemotherapy has been noted to improve hepatic RFS in previous reports.³⁸⁻⁴⁰ This discrepancy may be due to the inclusion of patients with concurrent extrahepatic recurrence in the any IHR group or from higher risk patients getting selected for HAI chemotherapy.

Several limitations to this study merit mention. Inherent to its retrospective design, selection biases could result from studying a heterogeneous sample. Additionally, small sample sizes among the histopathologic groups could create or blunt differences observed in recurrence patterns. Moreover, inflammatory changes in the liver related to preoperative comorbidities (e.g., high BMI, diabetes) may result in different patterns of HPD as compared to changes from systemic or HAI chemotherapy. A similar difference is suspected for acute (potentially reversible) liver changes compared to chronic changes. Some inflammatory hepatic features are likely more amenable to resolution with preoperative dieting than others. A recent report from Barth et al. noted that in addition to reducing intraoperative hemorrhage, preoperative dieting could reduce hepatocyte glycogen stores but not the degree of hepatic steatosis.⁴¹ Furthermore, differences in the location of inflammatory liver changes, such as local to the

tumor as opposed to throughout the hepatic parenchyma, may drive different patterns of recurrence. Future investigations will be necessary to separate such effects.

CONCLUSIONS

Severe hepatic parenchymal disease as assessed by NAS was independently associated with a greater risk of any IHR and reduced risk of EHR only following complete resection of CRLM. Future investigations should seek to define the association between gross inflammatory liver changes and recurrence patterns. Additionally, it is necessary to determine how different factors that contribute to inflammatory liver changes, such as preoperative comorbidities or chemotoxicity, influence recurrence patterns. Such studies will be necessary to define preoperative optimization strategies that can mitigate inflammatory changes in the liver as a means to potentially alter recurrence patterns following CRLM resection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SYNOPSIS

Inflammatory changes in the liver are common but their impact on recurrence after resection of colorectal liver metastases is unknown. Scored hepatic parenchymal disease adjacent to resected tumor specimens was found to be associated with higher rates of intrahepatic recurrence.

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Cumulative Incidence for Recurrence and Death After Liver Resection.

Figure 1:
Cumulative Incidence for Recurrence and Death After Liver Resection.

Figure 2:
Cumulative Incidence for Any Intrahepatic Recurrence After Liver Resection by Presence of Severe Hepatic Parenchymal Disease at Time of Resection.

Figure 3:
Cumulative Incidence for Only Extrahepatic Recurrence After Liver Resection by Presence of Severe Hepatic Parenchymal Disease at Time of Resection.

Table 1:

Demographic and Clinicopathologic Characteristics.

		All patients (n=357)
Age at surgery (years)	Median (range)	60 (28-88)
Gender		
	Male	216 (60.5)
	Female	141 (39.5)
Preoperative Comorbidities		
	Cardiac	173 (48.5)
	Pulmonary	19 (5.3)
	Diabetes	42 (11.8)
Smoking Status		
	Never	169 (47.3)
	Former	166 (46.5)
	Current	22 (6.2)
BMI (kg/m ²)		
	< 25	120 (33.6)
	≥ 25	237 (66.4)
Primary Tumor Location *		
	Right	99 (27.7)
	Left	147 (41.2)
	Rectum	107 (30)
	Bilateral	3 (0.8)
Primary T-Stage		
	T0-T2	58 (16.2)
	T3-T4	299 (83.8)
Primary Node Status		
	N-	151 (42.3)
	N+	206 (57.7)
Preoperative CEA (ng/dL)	Median (range)	7.1 (0.6-2554.0)
Largest CRLM Size (cm)	Median (range)	2.9 (0.3-17)
Number of CRLM	Median (range)	2 (1-20)
Clinical Risk Score **		
	Low (0-2)	270 (75.6)
	High (3-5)	72 (20.2)
Extrahepatic Disease		
	Yes	31 (8.7)
	No	326 (91.3)
Preoperative Chemotherapy		
	All	234 (65.5)
	5-FU	24 (6.7)

		All patients (n=357)
HAI-FUDR	FOLFOX	107 (30)
	FOLFIRI	54 (15.1)
	FOLFIRINOX	49 (13.7)
	Preoperative	28 (7.8)
	Adjuvant	109 (30.5)
	Salvage	10 (2.8)

Data are given as n (%) unless otherwise noted. Abbreviations: BMI=Body-mass index, N-=Node-negative, N+=Node-positive, CEA=Carcinoembryonic antigen, FU=fluorouracil, FOLFOX=5-FU+oxaliplatin, FOLFIRI=5-FU+irinotecan, FOLFIRINOX=5-FU+oxaliplatin+irinotecan, HAI-UDR=Hepatic artery infusion-floxuridine.

*

Primary tumor location was unknown for 1 patient.

**

Preoperative CEA was unknown for 15 patients, rendering Clinical Risk Score incalculable.

Table 2:

Risk Factors Associated with Recurrence Patterns After Liver Resection.

Univariate Analysis					
		IHR		EHR	
		HR (95%CI)	p	HR (95%CI)	p
Microsteatosis			0.828		0.058
	Steatosis = 1	0.96 (0.67-1.37)		0.66 (0.43-1.01)	
	Steatosis = 0	1.00		1.00	
Severe HPD			0.008		0.015
	NAS = 3	1.93 (1.19-3.12)		0.17 (0.04-0.71)	
	NAS < 3	1.00		1.00	
Steatohepatitis			0.245		0.240
	NAS = 4	1.61 (0.72-3.57)		0.43 (0.10-1.75)	
	NAS < 4	1.00		1.00	
Sinusoidal Injury			0.744		0.542
	Yes	0.90 (0.49-1.66)		1.20 (0.66-2.18)	
	No	1.00		1.00	
BMI			0.718		0.844
	< 25	1.00		1.00	
	≥ 25	0.93 (0.65-1.35)		0.96 (0.64-1.45)	
Diabetes			0.573		0.437
	Yes	1.16 (0.69-1.96)		0.77 (0.40-1.49)	
	No	1.00		1.00	
Preoperative Chemotherapy			0.019		0.710
	Yes	1.58 (1.07-2.32)		0.92 (0.60-1.36)	
	No	1.00		1.00	
HAI-FUDR Chemotherapy			0.808		0.056
	Yes	0.96 (0.67-1.36)		1.46 (0.99-2.14)	
	No	1.00		1.00	
Clinical Risk Score			0.299		0.046
	Low (0-2)	1.00		1.00	
	High (3-5)	1.24 (0.82-1.88)		1.59 (1.01-2.49)	
Primary Node Status			0.157		0.262
	N−	1.00		1.00	
	N+	1.29 (0.91-1.85)		1.25 (0.84-1.86)	
Preoperative CEA			0.240		0.214
	< 200 mg/dL	1.00		1.00	
	≥ 200 mg/dL	1.64 (0.72-3.74)		1.69 (0.74-3.88)	
Disease-Free Interval			0.006		0.139
	< 1 year	0.60 (0.41-0.86)		1.34 (0.91-1.97)	
	≥ 1 year	1.00		1.00	
Number of CRLM			0.049		0.695

Univariate Analysis					
		IHR		EHR	
		HR (95%CI)	p	HR (95%CI)	p
Largest CRLM Size	Solitary	1.00		1.00	
	Multifocal	1.44 (1.00-2.07)		0.93 (0.63-1.36)	
			0.616		0.009
	< 5cm	1.00		1.00	
	5cm	1.12 (0.71-1.76)		1.82 (1.16-2.85)	
Multivariable Analysis					
		IHR		EHR	
		HR (95%CI)	p	HR (95%CI)	p
Severe HPD			0.027		0.019
	NAS 3	1.76 (1.07-2.90)		0.18 (0.04-0.75)	
	NAS < 3	1.00		1.00	
Preoperative Chemotherapy			0.042		0.740
	Yes	1.50 (1.02-2.22)		0.93 (0.62-1.41)	
	No	1.00		1.00	
Clinical Risk Score			0.400		0.024
	Low (0-2)	1.00		1.00	
	High (3-5)	1.19 (0.79-1.77)		1.70 (1.07-2.70)	

Abbreviations: IHR=Any intrahepatic recurrence, EHR=Extrahepatic recurrence only, HPD=Hepatic parenchymal disease, BMI=Body-mass index, HAI-FUDR=Hepatic artery infusion of floxuridine prior to liver resection or beginning after pump insertion at the time of liver resection, N-=Node-negative, N+=Node-positive, CEA=Carcinoembryonic antigen, CRLM=Colorectal liver metastasis. **Bolded p-values** represent those meeting the statistical threshold for significance < 0.05.