Clinical Surgery

Obesity rather than neoadjuvant chemotherapy predicts steatohepatitis in patients with colorectal metastasis

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Abstract

INTRODUCTION: Neoadjuvant chemotherapy has been associated with an increased risk of surgery because of chemotherapy-associated steatohepatitis and sinusoidal obstruction. The aim of the current study was to assess for other predictors of steatohepatitis and sinusoidal obstruction and to determine the role of obesity as a risk factor in patients with colorectal liver metastasis (CLM).

METHODS: An institutional review board–approved prospectively maintained database of 1,605 patients who underwent hepatic procedures for CLM from 2001 to 2009 was reviewed.

RESULTS: In a review of 208 resected patients, body mass index was the only predictor of liver injury according to multivariate analysis ($P < .001$, odds ratio = 3.88). Diabetes, neoadjuvant chemotherapy, sleep apnea, alcohol use, tobacco use, age, and sex were not significant predictors. Among preoperative chemotherapy patients, BMI was a predictor of chemotherapy liver injury according to multivariate analysis ($P < .0001$). The rate of obesity (BMI $>$ 30) was 36%, and among obese patients (BMI $>$ 30) the rate of steatosis or steatohepatitis was 39%.

CONCLUSIONS: Obesity is the strongest predictor of steatosis and steatohepatitis in patients with CLM, and this risk is independent of the use of preoperative chemotherapy.

Hepatic resection offers potentially curative therapy for patients with colorectal metastasis confined to the liver. Modern reports of 5-year survival rates after complete resection are greater than 50%.\textsuperscript{1–4} Also, the use of multidrug chemotherapy regimens based on irinotecan or oxaliplatin with the potential addition of targeted biologic agents has shown improved responses and increased survival rates in patients with metastatic colorectal cancer.\textsuperscript{5–8} As a result, many institutions use multidrug chemotherapy in conjunction with resection for patients with colorectal liver metastasis.

Interest has arisen in administering chemotherapy before hepatic resection. Preoperative chemotherapy has been used with the goal of converting unresectable patients to resectability\textsuperscript{9–12} or as a neoadjuvant treatment for patients with resectable disease.\textsuperscript{13} The neoadjuvant approach has the possible advantages of the ability to monitor tumor response, early systemic treatment, and potential reduction in the extent of the required resection. However, preoperative chemotherapy has been associated with potentially harmful effects on non–tumor-involved liver parenchyma.

Chemotherapy-induced liver injury in the form of steatosis or steatohepatitis has been associated with
irinotecan-based regimens. Oxaliplatin has been specifically implicated in the development of sinusoidal obstructions syndrome, which is characterized by dilatation of the hepatic sinusoids and erythrocyte congestion.\(^{14,15}\)

Reports of the clinical impact of chemotherapy-associated liver injury have yielded conflicting results. Some have reported increased rates of perioperative morbidity and liver-related complications in patients treated with preoperative chemotherapy,\(^{13–15}\) whereas others have noted no difference in clinical outcome.\(^{16–19}\) Differences in both the duration of chemotherapy treatment and the time interval between the last treatment and surgery may account for the disparity in morbidity results between series. A shorter interval between chemotherapy and surgery has been associated with higher-grade lesions of sinusoidal obstruction syndrome.\(^{20,21}\) The number of preoperative chemotherapy cycles has been also been implicated in increased rates of hepatotoxicity.\(^{14,15}\)

Furthermore, histologic changes associated with preoperative chemotherapy can be difficult to distinguish from other causes of hepatic injury. In particular, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis are indistinguishable morphologically from chemotherapy-associated steatosis or steatohepatitis. Thus, obesity may be independently associated with liver injury, or obesity may be a potential risk factor for the development of chemotherapy-associated steatosis or steatohepatitis.\(^{22,23}\) A “second-hit” hypothesis has been proposed suggesting that obese patients with a baseline level of steatosis may develop worse liver injury in the form of steatohepatitis once they are submitted to hepatotoxic agents such as chemotherapy.\(^{23,24}\) An increased risk of steatohepatitis is noteworthy. Vauthey et al\(^{25}\) found that steatosis or sinusoidal injury did not adversely impact postoperative outcome, but the postoperative 90-day mortality of patients with steatohepatitis was significantly increased (15% vs 2%).

The purpose of the current analysis was to assess the overall and relative role of obesity and preoperative chemotherapy in the histologic changes found in non–tumor-involved parenchyma of patients undergoing hepatic resection for colorectal liver metastasis. We also sought to assess whether liver injury related to preoperative chemotherapy or obesity was associated with increased morbidity or mortality after resection.

**Methods**

A review was performed of a prospectively maintained 1,656-patient hepatobiliary database. The study was approved by the institutional review board. Patients who underwent hepatic resections or combined resections and thermal ablations between 2001 and 2009 were included in the analysis. The study was limited to patients with available pathologic evaluation of a non–tumor-bearing liver. Patients who had preresection hepatic arterial–based therapies were excluded from the analysis. Patient demographic and perioperative outcomes were evaluated based on the use of preoperative chemotherapy and the presence of obesity. The types and duration of chemotherapy were nonstandardized and left to the discretion of the treating medical oncologist. Obesity was determined as body mass index (BMI) \(>30\) kg/m\(^2\) based on World Health Organization criteria.\(^{26}\) Postoperative complications were graded according to a previously defined 5-point severity scale,\(^{27}\) and postoperative mortality was defined as death within 90 days of surgery. The use, duration, and type of chemotherapy were decided on using a multidisciplinary approach based on established risk factors for recurrence after hepatectomy for Colorectal Metastasis (CRM), patient comorbidities, and patient recovery.

The presence of steatosis, steatohepatitis, or sinusoidal injury was determined by a surgical pathologist based on hematoxylin-eosin and Masson trichrome staining of regions of the non–tumor-involved liver. Slides of patients with liver injury findings based on original surgical pathology reports were then rereviewed and evaluated by 3 pathologists who were blinded to the patients’ clinical data. Steatohepatitis was graded according to the criteria of Kleiner et al.\(^{28}\) Patients with a Kleiner score \(\geq 4\) were categorized as having relevant steatohepatitis. Sinusoidal injury was graded according to a 4-point scale as described by Rubbia-Brandt et al,\(^{29}\) and patients with a sinusoidal injury score \(\geq 2\) were categorized as having sinusoidal injury. Steatosis was determined by an estimate of the percentage of involved hepatocytes and grouped according to absent (grade 0), \(\leq 30\%\) (grade 1), \(30\%\) to \(50\%\) (grade 2), and \(>50\%\) (grade 3). Only patients with steatosis \(\geq 30\%\) were selected as having liver injury related to steatosis.

Statistical analysis was performed with Predictive Analytics SoftWare (PASW) (version 16; SPSS Inc, Chicago, IL). Categoric variables were compared using the chi-square test, and continuous variables were compared using the Student \(t\) test. Multivariate analysis of possible predictors of liver injury was determined based on a binomial logistic regression model. \(P\) values <.05 were considered statistically significant.

**Results**

A total of 208 patients who underwent hepatic resections for colorectal liver metastasis were identified. Of these patients, 156 (75\%) were treated with preoperative chemotherapy. Seventy-five patients (36\%) were obese (BMI \(\geq 30\) kg/m\(^2\)), and the mean BMI for the entire patient population was 28.8 kg/m\(^2\). A variety of surgical procedures were performed including right hepatectomies (\(n = 53\)), extended right hepatectomies (\(n = 12\)), left hepatectomies (\(n = 17\)), extended left hepatectomies (\(n = 3\)), segmentectomies (\(n = 49\)), wedge resections (\(n = 43\)), and combined or atypical resections (\(n = 31\)). One hundred six patients (51\%) had hepatic resection combined with either microwave or radiofrequency ablation. No patients in this
cohort had preoperative portal vein embolization. The median follow-up for all patients was 32 months.

The chemotherapy regimens used were diverse (Table 1). The median duration of treatment was 4 months (range 2 to 10 months). The most common regimen was fluorouracil, oxaliplatin, 5FU and Oxaliplatin (FOLFOX), and bevacizumab. Overall, 92 patients (44%) received oxaliplatin, and 19 patients (9%) received irinotecan. The patients who received preoperative chemotherapy were younger (mean 58.7 vs 63.5 years, \( P = .003 \)). However, preoperative and nonpreoperative chemotherapy groups showed similar rates of steatosis, steatohepatitis, or sinusoidal injury (Table 2). Preoperative chemotherapy also did not adversely impact the morbidity rate (21.2% vs 18.6%, \( P = .412 \)) or the mortality rate (1.3% vs 1.9%) of patients undergoing hepatic resection. Complications related to the liver (bile leak or hepatic insufficiency) were not elevated in the chemotherapy group.

In contrast, obesity was associated with increased rates of steatosis and steatohepatitis (Table 3). Among patients with BMI \( \geq 30 \), the combined rate of steatosis or steatohepatitis was 39% compared with 12.8% in nonobese patients (\( P < .001 \)). Furthermore, the addition of chemotherapy did not appear to adversely impact liver injury in obese patients because the rate of histologic liver injury was 40% in obese patients receiving chemotherapy and 37% in obese patients not receiving chemotherapy (\( P = .790 \)). Obese patients were also more likely to have received preoperative chemotherapy (85.1% vs 69.4%, \( P = .012 \)). Also, despite increased rates of steatosis and steatohepatitis, obese patients did not show increased rates of perioperative complications or mortality.

Univariate analysis of possible risk factors for histologic findings of liver injury (ie, steatosis, steatohepatitis, or sinusoidal injury) revealed that diabetes, obstructive sleep apnea, and BMI \( \geq 30 \) were associated with liver injury. The use of preoperative chemotherapy or the chemotherapy regimen type was not associated with an increased risk of liver injury. Neither oxaliplatin nor irinotecan were associated with sinusoidal injury compared with no chemotherapy (3.2% vs 1.9%, \( P = .93 \); 10.5% vs 1.9%, \( P = .111 \), respectively). In addition, neither oxaliplatin nor irinotecan were associated with steatosis or steatohepatitis compared with no chemotherapy (8.5% vs 5.8%, \( P = .548 \); 5.3% vs 5.8%, \( P = .935 \), respectively). BMI \( \geq 30 \) was the only independent predictor of liver injury on multivariate analysis (Table 4).

A subset analysis of patients who did or did not receive preoperative chemotherapy revealed that based on univariate analysis BMI \( \geq 30 \) was associated with liver injury in both groups (\( P < .001 \)). Among preoperative chemotherapy patients, only BMI was a predictor of liver injury on multivariate analysis (\( P < .0001 \)). However, diabetes was the only significant predictor of liver injury on multivariate analysis in the nonchemotherapy group (\( P = .024 \)). Histopathologic liver injury was not associated with increased rates of major morbidity (18.5% vs 21.7%, \( P = .625 \)).

**Comments**

The present study indicates that regardless of the use of preoperative chemotherapy, obesity is a major contributor to findings of liver injury in patients undergoing hepatectomy for colorectal liver metastasis. However, these data clearly identify that obese patients regardless of the duration of chemotherapy will have a risk of hepatic insufficiency, but in combination with greater than 3 months duration of chemotherapy, concerns for hepatic failure should be mitigated. The relevance of obesity in the management of patients with colorectal metastasis will continue to grow because the problem of obesity has reached epidemic levels in the United States. The Centers for Disease Control currently estimates that 33% of US adults are overweight (BMI 25.0 to 29.9), and 34% are obese (BMI \( \geq 30 \)) including nearly 6% who are extremely obese (BMI \( \geq 40.0 \)).

Previous reports have concluded that obesity is a risk factor for histopathologic injury associated with preoperative chemotherapy. Brouquet et al examined 146 patients given preoperative chemotherapy. With multivariate analysis, the authors found that among the risk factors studied only BMI \( > 27 \) was a significant predictor of chemotherapy-associated liver injury. Fernandez et al. examined a series of 37 patients undergoing resection for liver metastasis, found that BMI was associated with steatosis, and the authors also concluded that obese individuals were more likely to develop steatohepatitis in the setting of preoperative chemotherapy. The results of this study indicate that obesity can contribute to findings of liver injury independent of preoperative chemotherapy.

The observed decreased relative impact of preoperative chemotherapy compared with obesity in the development of hepatoxicity may be related to several factors. First, the observed rate of sinusoidal injury (3%) was significantly lower than the rate (10% to 59%) that has been reported in other series. One of the possible reasons for this is the lower median duration of chemotherapy (ie, 4 months) in relation to the other studies that reported a greater incidence of sinusoidal injury. Sinusoidal injury is specifically related to preoperative oxaliplatin-based chemotherapy regimens. However, this decreased rate of sinusoidal injury was observed despite the fact that oxaliplatin-based regimens were the most common form

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Chemotherapeutic regimens used in the 208 patients who underwent hepatic resection for colorectal liver metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy regimen</td>
<td>N (%</td>
</tr>
<tr>
<td>Oxaliplatin/fluorouracil</td>
<td>41 (26.3)</td>
</tr>
<tr>
<td>Oxaliplatin/fluorouracil/bevacizumab</td>
<td>51 (32.7)</td>
</tr>
<tr>
<td>Irinotecan/fluorouracil</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Irinotecan/fluorouracil/bevacizumab</td>
<td>14 (9.0)</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>19 (12.2)</td>
</tr>
<tr>
<td>Other</td>
<td>26 (16.7)</td>
</tr>
</tbody>
</table>
of chemotherapy used (45%). The differences in the reported rate of sinusoidal injury were most likely caused by variations in chemotherapy regimens, operative technique, and pathologic interpretation. The average timing of chemotherapy and surgery may have been a factor. Rubbia-Brandt et al.29 noted that in patients who underwent repeat resections or biopsies, the degree of sinusoidal liver injury decreased with time. Soubrane et al.20 also noted that the degree of sinusoidal injury decreased with an increasing interval between chemotherapy and surgery. Data were not available regarding the time delay between the final chemotherapy administration and surgery, but our standard practice is to delay surgery by at least 4 weeks.

The high rate of obesity and specifically the high rate of markedly elevated BMI may have contributed to the increased rate of obesity-associated liver injury in this series population. The mean BMI was 28.8 kg/m² (median 27.5 kg/m²), and 36% of patients were obese. The degree and frequency of steatosis or steatohepatitis have been associated with the level of BMI.33 Thus, one would expect higher rates of liver injury particular in this North American population. However, based on current obesity trends, these results will become more widely applicable.

In regards to the postoperative course, morbidity and mortality rates were similar in chemotherapy and preoperative chemotherapy patients. Again, this trend may be the result of low rates of histopathologic injury directly related to preoperative chemotherapy. Similarly, in a study by Vauthey et al.25 that reviewed 406 patients, 248 of which had received prehepatectomy chemotherapy, sinusoidal injury associated with oxaliplatin did not influence operative morbidity or mortality. Aloia et al.14 also investigated 303 patients who underwent liver resection and found that those receiving an oxaliplatin-based chemotherapy regimen had higher rates of vascular lesions of the liver. Patients with vascular lesions were more likely to require a blood transfusion but did not have an increase in morbidity or mortality rates.14

In contrast, Vauthey et al.25 noted that irinotecan was associated with increased rates of steatohepatitis, which, in turn, led to increased mortality. The association between irinotecan and steatohepatitis was observed in patients with BMI <25 kg/m² and ≥25 kg/m². Irinotecan-associated steatohepatitis may reflect a more severe form of liver injury compared with steatohepatitis associated with obesity in our series.

Obesity did not negatively influence the operative outcome even though obesity was associated with histopathologic changes. Also, evidence of liver injury itself was not associated with increased morbidity or mortality. The

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BMI &lt;30 (n = 133)</th>
<th>BMI ≥30 (n = 75)</th>
<th>All patients (N = 208)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>61.4 y</td>
<td>57.0 y</td>
<td>59.9 y</td>
<td>.003</td>
</tr>
<tr>
<td>Sex (male, n [%])</td>
<td>72 (54)</td>
<td>46 (61)</td>
<td>116 (56)</td>
<td>.333</td>
</tr>
<tr>
<td>Chemotherapy (%)</td>
<td>93 (69.4)</td>
<td>63 (85.1)</td>
<td>156 (75.0)</td>
<td>.012</td>
</tr>
<tr>
<td>Liver injury (%)</td>
<td>17 (12.7)</td>
<td>29 (39.2)</td>
<td>52 (25.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Steatosis (%)</td>
<td>12 (9.0)</td>
<td>15 (20.3)</td>
<td>27 (13)</td>
<td>.019</td>
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<tr>
<td>Steatohepatitis (%)</td>
<td>5 (3.7)</td>
<td>14 (18.9)</td>
<td>19 (9.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sinusoidal injury (%)</td>
<td>5 (3.7)</td>
<td>1 (1.4)</td>
<td>6 (2.9)</td>
<td>.305</td>
</tr>
<tr>
<td>Morbidity (%)</td>
<td>29 (21.2)</td>
<td>11 (18.6)</td>
<td>40 (19.2)</td>
<td>.273</td>
</tr>
<tr>
<td>Liver-related complications (%)</td>
<td>8 (6.0)</td>
<td>3 (4.0)</td>
<td>11 (5.3)</td>
<td>.412</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>1 (0.7)</td>
<td>2 (2.7)</td>
<td>3 (1.4)</td>
<td>.289</td>
</tr>
</tbody>
</table>

BMI = body mass index.
subject of obesity and perioperative outcomes has been of increasing research interest because of the current obesity epidemic. In the setting of hepatectomy, steatosis has been found to be an independent risk factor for complications after surgery.\textsuperscript{34} However, some studies have even shown improved outcomes in obese patients. In a series of 2,258 patients undergoing major intra-abdominal cancer surgeries, including 554 hepatectomies, Mullen et al\textsuperscript{35} found that obesity was not a risk factor for death or major perioperative complications. Mathur et al\textsuperscript{36} reviewed 279 patients with hepatic resections for malignancy and reported that obese patients had higher rates of perioperative complications but improved recurrence-free and overall survival. Pathak et al\textsuperscript{33} found in a study of 102 patients who had undergone resection for colorectal liver metastasis that the severity of steatosis correlated with increasing BMI levels. However, the same study found that neither hepatic steatosis nor BMI values influenced long-term survival. The cause of improved survival outcomes in obese patients is multifactorial and likely partly reflects the detrimental impact of malnourished and underweight patients. In this study, obese patients were more likely to be younger and to undergo preoperative chemotherapy. Thus, obese patients who enrolled in treatment may actually represent a healthier subset of the overall obese population.

Although the histologic changes associated with obesity do not necessarily correlate with a worse overall outcome, they do merit increased caution in dealing with morbidly obese patients in terms of hepatic resection. Careful attention should be given to preoperative planning and assessment of the extent of tolerable resection. For high-risk patients, consideration may be given to incorporating portal vein embolization to increase hepatic reserve or using a 2-stage procedure. Percutaneous biopsy and diagnostic laparoscopy may be considered to determine the degree of liver injury. Current research is being conducted on the use of supplements in order to prevent chemotherapy- and obesity-related liver injury. Antioxidants, glutamine, insulin-sensitizing drugs, and antithrombotic agents have shown potential in preventing liver injury.\textsuperscript{22}

### References


