The Effect of Steatosis on Echogenicity of Colorectal Liver Metastases on Intraoperative Ultrasonography

Mark G. van Vledder, MD; Michael S. Torbenson, MD; Timothy M. Pawlik, MD; Emad M. Boctor, PhD; Ulrike M. Hamper, MD; Kelly Olino, MD; Michael A. Choti, MD, MBA

Objective: To investigate the association of relative tumor echogenicity and hepatic steatosis in patients undergoing resection of colorectal liver metastases (CRLM).

Design: Prospective study.

Setting: The Johns Hopkins Hospital.

Patients: A total of 126 patients undergoing liver surgery for CRLM from January 1, 1998, through December 31, 2008, in whom 191 lesions had complete intraoperative ultrasonography images for review and adequate linked pathological data available.

Main Outcome Measures: The intraoperative ultrasonography images were reviewed and scored for echogenicity (hypoechoic, isoechoic, or hyperechoic). In addition, a histopathologic review of the nontumorous liver tissue was performed, and the extent of steatosis was scored and correlated with tumor echogenicity.

Results: Of the patients undergoing surgery, 49 (38.8%) were found to have mild to severe steatosis. Of the 191 total CRLM visualized by intraoperative ultrasonography, 91 (47.6%) were found to be hypoechoic, 65 (34.0%) were isoechoic, and 35 (18.3%) were hyperechoic. In patients with steatosis, lesions were significantly more likely to be hypoechoic when compared with patients without steatosis (odds ratio, 4.17; 95% confidence interval, 1.87-8.47; \( P = .001 \)). Echogenicity was independent of the cause of steatosis or response to chemotherapy.

Conclusions: The echogenicity of CRLM was significantly affected by the presence of liver steatosis, with decreased echogenicity and increased conspicuity of lesions despite overall poorer image quality. These findings might reinforce the usefulness of intraoperative ultrasonography in identifying additional CRLM in patients undergoing surgical therapy, even in those with fatty liver tissue.

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Hepatic steatosis is the most common liver disease in the United States and perhaps worldwide, affecting 17% to 33% of individuals in the US general population.\(^1,2\) Such fatty liver disease is commonly associated with obesity, type 2 diabetes mellitus, and other conditions that promote insulin resistance and free fatty acid accumulation in liver tissue. Importantly, the use of fluoropyrimidine-based chemotherapy for colorectal cancer is associated with pathological changes to the liver parenchyma, including hepatic steatosis.\(^3,4\)

Steatosis is associated with changes in the hepatic parenchymal appearance on ultrasonography.\(^5,6\) This feature can even be used as a noninvasive tool for diagnosing the condition using transcutaneous ultrasonography.\(^7,8\) However, the ultrasonographic appearance of fatty liver tissue is manifested as increased echogenicity and decreased image quality owing to signal attenuation, highlighting a potential concern for diminished ability of ultrasonography to detect metastases within fatty liver tissue. In particular, intraoperative ultrasonography (IOUS), an essential tool used for the detection of liver tumors, may be affected by steatosis. This point is particularly relevant in patients undergoing hepatic surgery for colorectal liver metastases (CRLM), in whom steatosis is more common and lesion detection is paramount for successful surgical therapy.\(^9,10\)

Therefore, the objective of the current study was to determine the effect of hepatic steatosis on the ultrasonographic appearance of CRLM. More specifically, we sought to evaluate the effect of fatty liver tissue on lesion echogenicity.

Methods

Data on the IOUS appearance of CRLM were collected prospectively on 196 patients who underwent resection at The Johns Hopkins Hosp...
Table 1. Clinical and Morphologic Features of the 126 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>60 (22-90)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>61 (48.5)</td>
</tr>
<tr>
<td>Male</td>
<td>65 (51.5)</td>
</tr>
<tr>
<td>No. of tumors</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>59 (46.7)</td>
</tr>
<tr>
<td>2-3</td>
<td>39 (31.0)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>28 (22.2)</td>
</tr>
<tr>
<td>Size of largest tumor, median (range), cm</td>
<td>4.0 (1.0-16.0)</td>
</tr>
<tr>
<td>Preoperative chemotherapy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>67 (53.2)</td>
</tr>
<tr>
<td>Fluoropyrimidine alone</td>
<td>15 (11.9)</td>
</tr>
<tr>
<td>Irinotecan based</td>
<td>20 (15.9)</td>
</tr>
<tr>
<td>Oxaliplatin based</td>
<td>24 (19.0)</td>
</tr>
<tr>
<td>Body mass indexb</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>90 (71.4)</td>
</tr>
<tr>
<td>≥30</td>
<td>30 (23.8)</td>
</tr>
<tr>
<td>Missing values</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (15.1)</td>
</tr>
<tr>
<td>No</td>
<td>107 (84.9)</td>
</tr>
<tr>
<td>Echogenicity</td>
<td></td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>55 (43.7)</td>
</tr>
<tr>
<td>Isoechoic</td>
<td>50 (39.6)</td>
</tr>
<tr>
<td>Hyperechoic</td>
<td>21 (16.7)</td>
</tr>
</tbody>
</table>

a Data are presented as number (percentage) of patients unless otherwise indicated. Percentages may not equal 100 because of rounding.
b Calculated as weight in kilograms divided by height in meters squared.

Two hundred seventy-nine lesions were resected in 126 patients. Of these, 191 lesions had complete IOUS images for review and adequate linked pathological data available and were included in the final analysis. Table 1 gives the clinico-pathologic features of the patient cohort. There were 65 men (51.5%) with a median age of 60 years (range, 22-90 years). Diabetes mellitus was present in 19 patients (15.1%), and 30 patients (23.8%) had a body mass index less than 30. The median number of hepatic metastases per patient was 2 (range, 1-14), with 46.7% being solitary tumors, 31.0% tumors with 2 to 3 metastases, and 22.2% tumors with 4 or more lesions resected. The median size of the largest tumor was 4.0 cm (range, 1.1-16.0 cm). Fifty-nine patients (46.8%) were treated with chemotherapy for their metastatic disease before surgery. In these 59 patients, a partial or complete radiologic response was observed in 31 patients (52.5%). Thirteen patients (22.0%) had a complete radiologic response in at least 1 lesion, of which 9 metastases were available for analysis.

The distribution of clinical features among echogenicity groups is summarized in Table 2. Overall, 55 patients (43.7%) were found to have hypoechoic metastases, 50 patients (39.6%) had isoechoic lesions, and 21 patients (16.7%) had hyperechoic lesions. No difference in echogenicity was observed in patients with increased number or size of the largest metastases. Tumor echogenicity was not significantly different between those with or without diabetes mellitus, and no difference was seen in those with obesity. Tumor echogenicity was not significantly different among those receiving preoperative chemotherapy, and it did not differ by chemotherapy type or radiologic response.

HISTOLOGIC FEATURES

Microscopic assessment of the nontumorous liver tissue revealed the presence of steatosis (>5%) in 49 pa-
Intraoperative ultrasound (IOUS) was performed on 201 tumors to assess for microcalcifications, sinusoidal dilatation, and steatosis. Microcalcifications were identified in 45 tumors (23.6%), including mild steatosis in 33 patients (26.2%) and moderate-to-severe steatosis in 16 patients (12.6%) (Table 3). Only 2 patients (1.6%) were found to have steatohepatitis. Thirty-six patients (28.6%) had evidence of sinusoidal dilatation, with moderate-to-severe sinusoidal dilatation seen only in 5 patients (3.9%).

Of the 191 individual lesions evaluated, 45 tumors (23.6%) had evidence of microcalcifications on histologic analysis. This finding was more common in patients who received preoperative chemotherapy when compared with those who received no chemotherapy (8.7% vs 39.4%, \(P < .001\)).

TUMOR ECHOGENICITY AND STEATOSIS

The influence of histologic abnormalities of the surrounding liver tissue on the tumor echogenicity is summarized in Table 4. Specifically, patients with steatosis were more frequently found to have hypoechoic lesions (67.9%) compared with isoechoic lesions (22.2%) or hyperechoic lesions (9.9%). In contrast, patients without steatosis were found to have hypoechoic metastases in only 32.7% of cases, with 42.8% appearing as isoechoic and 24.5% as hyperechoic (\(P < .001\)). These hypoechoic tumors were frequently more conspicuous despite the diminished image quality and definition seen...
Evidence of sinusoidal dilatation was not associated with differences in tumor echogenicity. The extent of steatosis significantly affected the relative echogenicity of CRLM (Figure 2). The probability of finding hypoechoic tumors with mild (relative risk ratio, 2.91; 95% confidence interval, 1.33-6.37; \( P = .007 \)) and moderate-to-severe (2.16; 4.74-98.0; \( P < .001 \)) vs no steatosis.

The effect of various histopathologic characteristics, including steatosis and microcalcifications, on tumor echogenicity was evaluated using univariate and multivariate clustered multinominal regression models. On univariate analysis, the presence of steatosis was the only parameter found to be independently associated with finding hypoechoic vs isoechoic tumors (RRR, 3.98; \( P = .001 \)) (Table 5). No other features, including microcalcifications, mucin, tumor size or location, preoperative chemotherapy use, or chemotherapy response, were associated with a hypoechoic tumor appearance. In contrast, the finding of hyperechoic lesions compared with isoechoic ones was only associated with the presence of tumor microcalcifications (RRR, 4.76; 95% CI, 1.89-12.5; \( P = .003 \)). Tumor size, number, and location; use of or response to preoperative chemotherapy; mucin; sinusoidal dilatation; and steatosis were not associated with hyperechogenicity. When adjusting for all other factors, steatosis (RRR, 4.24; \( P = .001 \)) and calcifications (RRR, 4.33; \( P = .003 \)) remained the only independent factors associated with echogenicity in the multivariate analysis.

We also sought to determine whether the association between steatosis and tumor echogenicity was owing to the effect of preoperative chemotherapy on the tumor itself rather than only the presence of steatosis. Specifically, when the percentage of hypoechoic lesions was compared between patients with steatosis who received preoperative chemotherapy and those who did not, no difference was seen (61.7% vs 76.5%; \( P = .16 \)). Similarly, tumor echogenicity was comparable, regardless of the attributed cause of the steatosis.

Finally, we investigated the influence of preoperative chemotherapy on the echogenicity of CRLM and the ability of IOUS to detect CRLM. Nine liver tissue metastases showed a complete radiologic response on preoperative imaging studies and were only detected by IOUS. These were hypoechoic in 8 of 9 instances (88.8%), with only 1 lesion being isoechoic. Moreover, 6 (66.7%) of these metastases were found in steatotic liver tissue, 4 of which were found in liver tissue with moderate-to-severe steatosis.

**COMMENT**

Intraoperative ultrasonography is well known as an important tool for accurately staging liver tumors, and it frequently affects intraoperative decision making.\(^{13-20}\) However, tumor echogenicity and image quality can have a significant bearing on the sensitivity and usefulness of

![Figure 1](image1.png)

*Figure 1.* Intraoperative ultrasonographic images of hepatic colorectal metastases. Circles indicate outer boundaries of lesions. A, A small hypoechoic lesion imaged in liver tissue with mild steatosis; B, An isoechoic lesion identified in liver tissue without histologic evidence of steatosis.

![Figure 2](image2.png)

*Figure 2.* Correlation between tumor echogenicity and the extent of hepatic steatosis (none [<5%], mild [5%-30%], and moderate to severe [>30%]). Increased probability of finding hypoechoic tumors with mild (relative risk ratio, 2.91; 95% confidence interval, 1.33-6.37; \( P = .007 \)) and moderate-to-severe (2.16; 4.74-98.0; \( P < .001 \)) vs no steatosis.
Hyperechoic vs Isoechoic

The liver parenchyma appears brighter than the surrounding liver tissue in the presence of fatty liver disease. Yet, few data exist regarding the IOUS image characteristics in such patients. Such data have important implications regarding the ability to visualize and detect metastases during planned liver resection.

In our study, we found a strong correlation between hepatic steatosis and the relative tumor echogenicity of CRLM. Specifically, isoechoic tumors (which are often difficult to distinguish from the surrounding liver tissue) were found in only 22.0% of patients with steatosis, half the percentage of those without steatosis. These findings are likely explained by the ultrasonographic characteristics of fatty liver tissue. When hepatic fat content increases, the parenchyma becomes brighter (hyperechoic) because of an increased sonographic attenuation. Because one might expect the ultrasonographic characteristics of the tumors themselves (ie, absolute echogenicity) not to change with hepatic steatosis, metastases, then, become relatively more hypechoic when compared with the surrounding liver tissue in the presence of steatosis.

The presence of nonalcoholic fatty liver disease was common in our study population of patients undergoing surgery for CRLM (39.0%). These demographics reflect the general population within the United States, with a prevalence of steatosis in Western countries ranging from 3.0% to 23.0%. Moreover, increasing rates of obesity and diabetes will likely increase the rates of nonalcoholic fatty liver disease in surgical patients in the future. Numerous authors have also reported on the correlation between preoperative chemotherapy and the development of steatosis in various degrees of severity. In one study, 18.3% of patients undergoing surgery for CRLM and treated with preoperative chemotherapy had moderate-to-severe steatosis compared with 3.4% of patients who received no chemotherapy. In another report, 26 steatosis was observed in 24% of patients treated with preoperative irinotecan hydrochloride and oxaliplatin. Our results are important for several reasons. First, when grossly steatotic-appearing liver tissue is found during surgery, one should anticipate hypoechoic lesions on IOUS when screening for additional tumors. Previously, we have shown that echogenicity is consistent among tumors within the same patient. This finding is supported by the correlation found here between echogenicity and steatosis, affecting all tumors within the same patient similarly. Second, we have shown that the fraction of tumors with decreased echogenicity diminishes with the extent of steatosis, likely reflecting increased ultrasonographic signal attenuation with increasing attenuation owing to fatty changes in the liver.

The association between tumor appearance and steatosis was found to occur regardless of the cause of the type of liver injury. Patients with chemotherapy-induced steatosis were found to have a comparable proportion of hypoechoic tumors when compared with those with steatosis owing to other causes. Although echogenicity was not found to be influenced overall by preoperative chemotherapy use or tumor response to chemotherapy, it is likely the presence of the steatosis that influences the tumor appearance. These findings have important implications regarding the sensitivity of IOUS in these patients. Although the use of preoperative chemotherapy has significant potential advantages in patients undergoing liver resection, some have raised concern that the associated steatosis may negatively affect the ability to visualize metastases on IOUS. This study suggests that steatosis results in fewer isoechoic lesions and likely increased tumor conspicuity. Smaller, otherwise occult lesions may, paradoxically, become more visible and easier to detect in fatty liver tissue. Indeed, we found that metastases that had a complete radiologic response from preoperative chemotherapy and were detected during surgery with IOUS were almost always hypoechoic and most frequently detected in steatotic liver tissue.

In summary, we found that the echogenicity of CRLM was significantly affected by the presence of fatty liver disease, resulting in a decreased echogenicity and increased conspicuity of lesions despite overall poorer image quality. These findings reinforce the usefulness of IOUS in visualizing hepatic metastases in patients undergoing surgical therapy for advanced colorectal cancer, even in those with steatosis.

Table 5. Univariate Analysis of Histologic Factors Influencing the Echogenicity of Colorectal Liver Metastases on Intraoperative Ultrasonography

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypoechoic vs Isoechoic</th>
<th>P Value</th>
<th>Hyperchoic vs Isoechoic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis &gt;5%</td>
<td>3.98 (1.87-8.47)</td>
<td>.001</td>
<td>0.77 (0.27-2.22)</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>0.52 (0.22-1.25)</td>
<td>.14</td>
<td>4.76 (1.89-12.5)</td>
</tr>
<tr>
<td>Extracellular mucin</td>
<td>0.46 (0.19-1.08)</td>
<td>.07</td>
<td>2.33 (0.57-9.50)</td>
</tr>
<tr>
<td>Sinusoidal dilatation</td>
<td>0.68 (0.28-1.69)</td>
<td>.42</td>
<td>0.96 (0.34-2.67)</td>
</tr>
<tr>
<td>Preoperative chemotherapy</td>
<td>1.09 (0.53-2.27)</td>
<td>.81</td>
<td>2.22 (0.89-5.56)</td>
</tr>
<tr>
<td>Largest tumor size</td>
<td>0.47 (0.15-1.46)</td>
<td>.19</td>
<td>0.87 (0.21-3.54)</td>
</tr>
<tr>
<td>Pathological tumor response, major</td>
<td>1.06 (0.36-3.09)</td>
<td>.91</td>
<td>1.37 (0.35-5.37)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; RRR, relative risk ratio.

*The RRR is 4.24 (95% CI, 1.82-9.90; P = .001) after adjusting for all other variables.

b The RRR is 4.33 (95% CI, 1.62-11.6; P = .003) after adjusting for all other variables.
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Correspondence: Michael A. Choti, MD, MBA, Department of Surgery, The Johns Hopkins Hospital, The Johns Hopkins University School of Medicine, 600 N Wolfe St, Blalock 665, Baltimore, MD 21287 (mchoi@jhmi.edu).

Author Contributions: Drs van Vledder and Pawlik had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: van Vledder, Pawlik, Hamper, and Choti. Acquisition of data: van Vledder, Torbenson, Boncoro, Olinlo, and Choti. Analysis and interpretation of data: van Vledder, Torbenson, Olinlo, and Choti. Drafting of the manuscript: van Vledder, Torbenson, Boncoro, Hamper, and Choti. Critical revision of the manuscript for important intellectual content: Torbenson, Pawlik, Hamper, Olinlo, and Choti. Statistical analysis: van Vledder. Obtained funding: Doctor and Choti. Administrative, technical, and material support: Pawlik and Hamper. Study supervision: Torbenson, Pawlik, and Choti.

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REFERENCES


Vijay Maker, MD, Chicago, Illinois: Dr van Vledder and members of Dr Choti’s group have systematically approached a problem that is only growing in recognition and scope—that of resection of colorectal liver metastases in the metastatic liver. I commend them on this compilation of data that spans a decade of liver resection. Their research supports the notion that when searching for a metastatic lesion in a heavily pretreated or fatty liver, one is more likely to find a relatively hypochoic mass on intraoperative ultrasound and that this lesion may, in fact, be more visible owing to its appearance against a highly echogenic background. This piece of information is helpful, especially in pre-treated chemotherapy patients where the lesions have regressed in size but may still contain viable tumor cells. They have elegantly demonstrated to us the better visibility of dark hypochoic lesions against a bright fatty liver. However, because of the overall poor resolution caused by the fat content, do we miss more isoechic lesions and maybe even some hyperechic lesions? How often did computed tomographic scan demonstrate metastases that were not found on intraoperative ultrasound at all?

Second, in your series there were 2 pathologically identified cases of steatohepatitis. I am curious as to whether you ob-
served any ultrasound characteristics to differentiate reversible steatosis from the more serious steatohepatitis in this study or in your previous investigations of these damaged livers?

Third, your group and others have stated that hypoechogenic colorectal metastases may have a worse prognosis. Much like a World War II sonar would transmit clearly through water, do these liver lesions contain greater water content, perhaps owing to a higher mitotic rate and greater cell turnover? If they do contain more water, I wonder if you have seen any differences between hyperechogenic and hypoechogenic lesions when treated with radiofrequency ablation?

Dr Choti: You have asked 1 of the key questions as to whether this observed association between the presence of steatosis and increased probability of finding hypoechogenic metastases translates into an improved detection rate of intraoperative ultrasound in the fatty liver. We do not know the full answer to that, although we are currently looking at this question. I can tell you that it does appear that patients whose known tumors are hypoechogenic are less likely to have missed lesions on IOUS. Thus, the presence of steatosis may contribute, paradoxically, to increased sensitivity of ultrasound. However, as you point out, we do not know if tumors that might remain isoechoic or hyperechoic in fact become more difficult to detect in the steatotic liver. In other words, it may be that the presence of steatosis increases the relative conspicuity of some tumors yet may reduce the ability to identify tumors that still remain isoechoic, given the overall decreased image quality seen in the fatty liver.

Regarding the correlation of preoperative computed tomographic scan with operative lesion detection, we did not address this by comparing them lesion by lesion, specifically whether some tumors seen on computed tomographic scan failed to be detected intraoperatively on IOUS in the patient with steatosis. Because of the diminished overall quality of ultrasonography with steatosis, it is very possible that some tumors seen on computed tomography were not visualized by IOUS, particularly if they were isoechoic.

Your question regarding the IOUS appearance of steatohepatitis is an interesting one. As you point out, we found steatohepatitis in very few patients in this study, less than 2%, even in those receiving preoperative chemotherapy. Given these low numbers, it is difficult to draw any conclusions regarding echogenicity and steatohepatitis.

Finally, you commented on our previous study, which found that hypoechogenic metastases were associated with poorer prognosis. As I have suggested here, it appears that the decrease in relative tumor echogenicity seen is largely a function of the surrounding parenchyma and not a feature of the metastases. Why then would our prior studies have found prognostic implications of tumor echogenicity? It may be that patients with steatosis are more heavily pretreated with chemotherapy, perhaps worse biology, thus explaining the finding. Clearly, the reasons are likely multifactorial as to why hypoechogenic tumors have a poorer prognosis. Our current study suggests that it is the parenchyma of the liver that significantly contributes the relative tumor echogenicity rather than the features of the tumor itself.

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