ORIGINAL ARTICLE

Patient Variability in Intraoperative Ultrasonographic Characteristics of Colorectal Liver Metastases

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Objective: To determine the distribution of echogenicity (hypoechoic, isoechoic, or hyperechoic) and predominant intraoperative ultrasonography (IOUS) echogenic appearance of colorectal liver metastasis. The interpatient and intrapatient variability of tumor IOUS echogenicity was assessed.

Design: Retrospective review of prospectively collected database.

Setting: Tertiary cancer center.

Patients: Between January 1998 and July 2001, 99 patients (194 tumors) underwent hepatic resection for colorectal metastases.

Main Outcome Measures: During surgery, IOUS of the liver was performed and the images were digitally recorded. Images were randomly coded, blindly reviewed, and scored for echogenicity and ultrasonographic appearance pattern.

Results: The ultrasonographic appearance of the colorectal liver metastasis was hypoechoic in 52.0%, isoechoic in 35.7%, and hyperechoic in 12.3% of cases. Most colorectal liver metastases appeared homogeneous (50.8%). Less commonly, identified lesions were characterized by a target or "bull's-eye" appearance (20%) or contained calcifications (19%). Clinicopathologic characteristics, including patient age and sex, as well as tumor size, number, and location and presence of hepatic steatosis, did not correlate with tumor echogenicity or ultrasonographic appearance pattern (all $P > .05$). Lesions within patients were more similar in echogenicity than lesions between patients ($P < .001$). Similarly, intrapatient variability in appearance pattern was significantly less than the variability between patients ($P = .002$).

Conclusions: The ultrasonographic characteristics of hepatic metastases within patients were more similar than between patients. Such information is important because it suggests that, in patients with more than 1 metastasis, the echogenic appearance of an index lesion may predict the echogenic appearance of additional occult disease.

Arch Surg. 2008;143(1):29-34

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INTRAOPERATIVE ULTRASONOGRAPHY (IOUS) is an important tool for accurately staging colorectal liver metastases at the time of resection.[1-5] Even after careful preoperative imaging, new intraoperative findings or findings different than those suggested on preoperative imaging studies are commonly found using IOUS.[3,6-10] Specifically, IOUS has been reported to identify at least 1 additional malignant lesion in 10% to 12% of cases.[10] Furthermore, in 20% of patients with colorectal metastases, IOUS offers new information that alters the operative plan.[10] Intraoperative ultrasonography has also been suggested to have an oncologic benefit. Several investigators have shown that IOUS beneficially influenced the surgical outcome of patients with colorectal liver metastases by guiding resection and identifying otherwise occult lesions.[8,11,12] As a result of these data, IOUS is now routinely used to evaluate the liver prior to resection of colorectal liver metastases.

See Invited Critique at end of article

The echogenicity of colorectal liver metastases on IOUS can vary considerably. Colorectal metastases can appear hypoechoic, isoechoic, or hyperechoic in comparison with the surrounding liver tissue.[13-15] The echogenicity of the metastasis can influence the surgeon's ability to detect lesions on IOUS because isoechoic

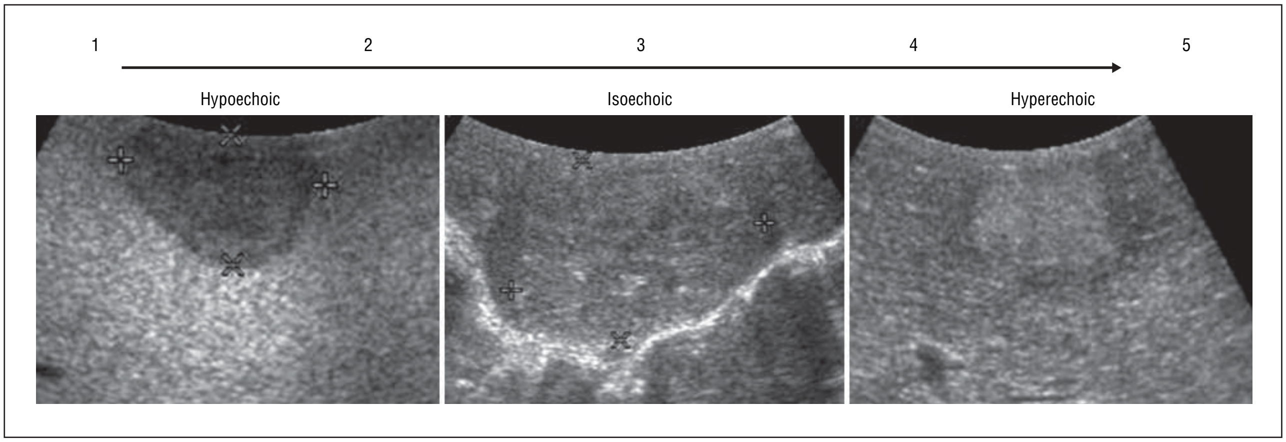

Figure 1. Ultrasonographic appearance. The E score was computed using a Likert (ordinal) scale for echogenicity, with 1 being the most hypoechoic, 3 being isoechoic, and 5 being the most hyperechoic.

lesions may be more difficult to discriminate from the adjacent liver parenchyma. Furthermore, in patients with multiple metastases, the ultrasonographic appearance of each distinct colorectal metastasis may not be the same, further complicating the surgeon's ability to use IOUS to detect occult lesions.

Currently, there are few data on the interpatient and intrapatient variability in echogenicity of colorectal metastases. Whether tumor echogenicity is associated with patient factors (eg, age, sex, history of chemotherapy) vs tumor-specific factors (eg, size, location) remains largely unknown. Correlation of radiologic and histologic findings with the varied types of echogenic lesions is also ill defined. Such information is important because it may predict the expected IOUS appearance of otherwise occult lesions. Moreover, in patients with more than 1 metastasis, the echogenic appearance of an index lesion may help predict the echogenic appearance of additional occult disease. Given this, the objective of the current study was to examine the sonographic features of colorectal liver metastases with respect to echogenicity. Specifically, we sought to determine the distribution of echogenicity (hypoechoic, isoechoic, or hyperechoic) and the predominant IOUS echogenic appearance of colorectal liver metastasis. The interpatient and intrapatient variability of tumor IOUS echogenicity was also assessed.

METHODS

Between January 1998 and July 2001, 99 patients with colorectal liver metastasis underwent resection by a single surgeon (M.A.C.) at the Johns Hopkins Hospital. Only lesions that were confirmed on histologic examination to be colorectal liver metastasis were included in the study. All patients were evaluated prior to surgery with a baseline history and physical examination; serum laboratory tests; computed tomographic scan or magnetic resonance imaging of the abdomen and pelvis; and a chest radiograph or computed tomographic scan. The following data were collected for each patient: demographics; history of preoperative chemotherapy; tumor size, number, and location; and operative details. The study was approved by the Johns Hopkins institutional review board.

At the time of surgery, IOUS of the liver was performed by 1 surgeon (M.A.C.) using a 4.0- to 8.0-MHz, commercially available curvilinear transducer (Philips ATL HDI-5000; Philips Medical Systems, Andover, Massachusetts). The IOUS was performed in a systematic manner to avoid missing any occult lesions.[9] When identified, lesions were imaged in both the longitudinal and transverse planes to define the relation of the lesion to surrounding structures, such as the portal or hepatic veins and biliary structures. Ultrasonography settings were kept consistent for image capture using standard presets, including the (1) depth of field, (2) location of focal zones, (3) scan orientation, and (d) image zoom settings. The gain was adjusted on a case-by-case basis to optimize visualization of the known hepatic lesions depending on the inherent echogenicity of the liver being examined. In each case, all evaluable IOUS images were digitally recorded as standing images in 2 views and randomly coded. In all cases, a sufficient sample of the surrounding nontumorous liver was captured on the recorded image to allow for comparison of the hepatic lesion with the surrounding nonmalignant hepatic parenchyma. Three independent reviewers (M.A.C., S.S., and S.N.) reviewed the IOUS and scored the images in a blinded fashion for echogenicity (E score) and ultrasonographic pattern (P score). The E score was computed using a Likert (ordinal) scale for echogenicity, with 1 being the most hypoechoic, 3 being isoechoic, and 5 being the most hyperechoic (**Figure 1**). The P score was based on 4 distinct (nominal) appearance patterns: (1) target/"bull's-eye," (2) scattered calcifications, (3) homogeneous, and (4) other (**Figure 2**). The average E score and the mode P score from the 3 reviewers were used for purposes of analysis. All lesions identified by IOUS were confirmed as metastatic adenocarcinoma on final pathologic examination.

Statistical analyses were performed using the Kruskal-Wallis (ordinal) and permutation (ordinal and nominal) tests to assess the variability of the E and P scores both within patients (ie, intrapatient variation) and between patients (ie, interpatient variation). The Kruskal-Wallis test is a nonparametric (distribution-free) test used to compare 3 or more independent groups of sampled data. Unlike the parametric independent-group analysis of variance (1-way analysis of variance), this nonparametric test makes no assumptions about the distribution of the data (eg, normality).[16,17] For the permutation test, 1000 permutations were generated under the null hypothesis (ie, no intrapatient or interpatient variation in E or P scores). To do this, the E and P scores were randomly permuted, the tabular results were averaged, and then the χ^2 test statistic was calculated comparing the null result with the observed result. The *P* value was then interpreted to mean the probability of seeing the results under the null hypothesis (eg, that there was no correlation within lesions from the same patient).

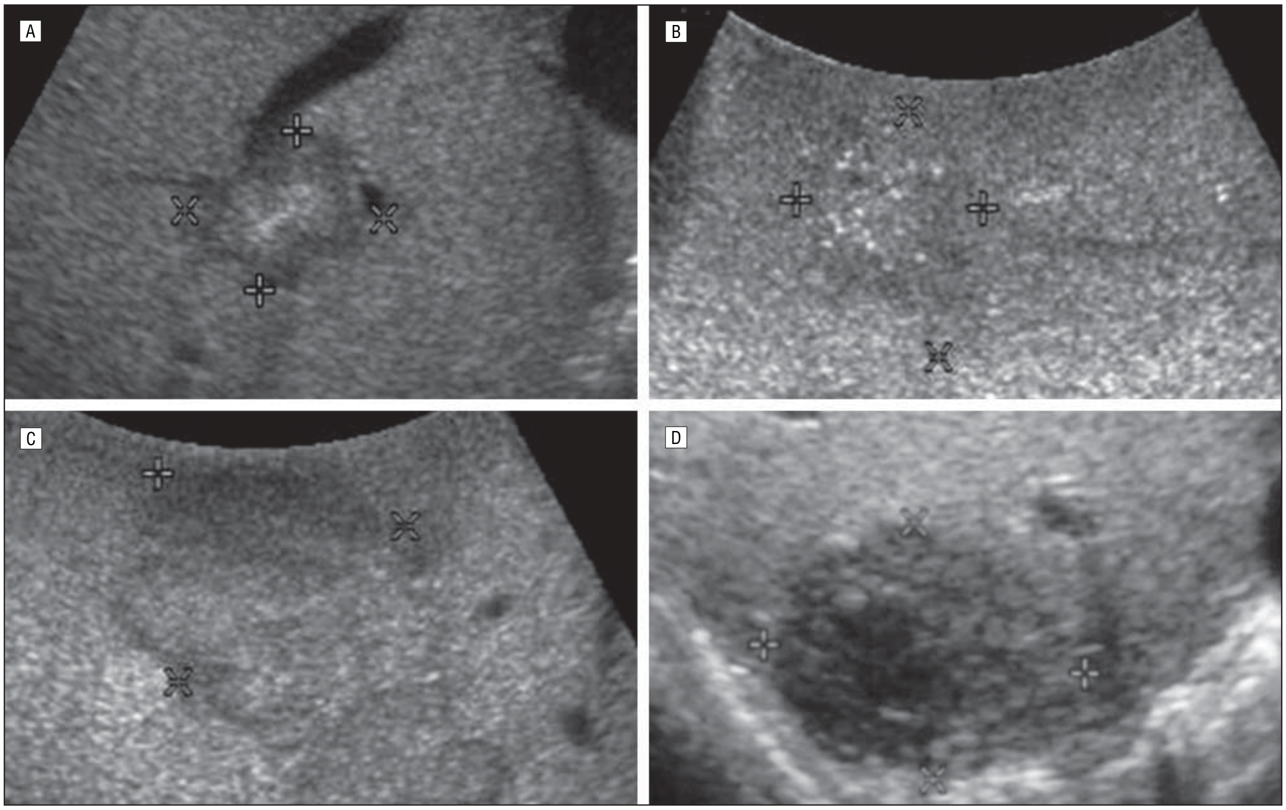

Figure 2. Ultrasonographic appearance. The P score was based on 4 distinct (nominal) appearance patterns. A, Target/"bull's-eye." B, Scattered calcifications. C, Homogeneous. D, Other.

Table 1. Clinical and Morphologic Features of 99 Patients

Variable	No. (%) of Patients
Age, y, median	62
Sex	
F	44 (44.4)
M	55 (55.6)
No. of tumors, median (range)	1.3 (1-7)
Tumor size, cm, median	2.9
Tumor location	
Unilobar	58 (58.6)
Bilobar	41 (41.4)
Preoperative chemotherapy	
No	37 (37.4)
Yes	62 (62.6)
Preoperative CEA level, ng/mL, median	9.4
<5	30 (30.3)
5-100	55 (55.5)
>100	10 (10.1)
Unavailable	4 (4.1)

Abbreviation: CEA, carcinoembryonic antigen.
SI conversion factor: To convert CEA to micrograms per liter, multiply by 1.

Table 2. Number of Colorectal Tumor Metastases per Patient

No. of Lesions	No. (%) of Patients
1	59 (59.6)
2	16 (16.2)
3	10 (10.1)
4	4 (4.0)
5	4 (4.0)
6	5 (5.1)
7	1 (1.0)

RESULTS

PATIENT AND IOUS LESION CHARACTERISTICS

The clinical features of the 99 patients in the study are presented in **Table 1**. There were 55 men and 44 women, for a male-female ratio of 1.25:1. Most patients (62.6%) received preoperative chemotherapy; a minority of patients (18.3%) treated with preoperative chemotherapy had evidence of hepatic steatosis greater than 30% on final pathologic examination. At the time of surgery, sonographic evaluation of the entire liver was possible in all cases. A total of 194 lesions were identified and evaluated. The median number of lesions was 1.3 (range, 1-7), with the majority of patients having 3 or fewer lesions (**Table 2**). The median tumor size was 2.9 cm (range, 0.4-10.9 cm).

The ultrasonographic appearance of the colorectal liver metastasis compared with the surrounding liver tissue was hypoechoic in 52.0% (E score=1, 18.3% and E score=2, 33.7%), isoechoic in 35.7% (E score=3), and hyperechoic in 12.3% (E score=4, 10.8% and E score=5, 1.5%) of cases. Clinicopathologic characteristics, including patient age and sex, as well as tumor size, number,

Table 3. Patient and Tumor Characteristics Stratified by Ultrasonographic Appearance

Variable	Patients, % Hypoechoic	Isoechoic	Hyperechoic	*P* Value
Age >65 y	36.5	38.9	41.6	.52
Male	57.7	55.5	50.0	.79
Preoperative chemotherapy	71.2	61.1	58.3	.69
CEA >100 ng/mL	7.7	11.1	8.3	.54
Multiple tumors	61.5	44.4	50.0	.27
Tumor size >5 cm	17.3	16.7	25.0	.49
Bilobar location	34.6	22.2	25.0	.31

Abbreviation: See Table 1.
SI conversion factor: See Table 1.

Table 4. Comparison of E Scores From Multiple Tumors Within the Same Patient[a]

E Score	No. (%) Observed Agreement	Expected Agreement Under Null Hypothesis
Same E score	78 (40.2)	49 (25.3)
Different by		
1 Point	85 (43.8)	80 (41.2)
2 Points	29 (14.9)	45 (23.2)
3 Points	2 (1.1)	17 (8.8)
4 Points	0	3 (1.5)

[a] There was less variability in lesion tumor echogenicity within the same patient than would be expected by chance alone ($P<.001$).

and location and presence of hepatic steatosis, did not correlate with tumor echogenicity on IOUS (all $P>.05$) (**Table 3**). However, in patients who otherwise had occult and/or small (<1.0 cm) metastases detected by IOUS, the index lesion was more likely to be hypoechoic or hyperechoic ($P<.05$). No relationship between preoperative chemotherapy, hepatic steatosis, and echogenicity was observed. Patients receiving preoperative chemotherapy were as likely to have a hypoechoic (31.6%), isoechoic (35.8%), or hyperechoic (32.6%) lesion as patients who did not receive preoperative chemotherapy (hypoechoic [26.5%], isoechoic [37.9%], and hyperechoic [35.6%]) ($P=.13$).

With regard to the pattern appearance on IOUS, most colorectal liver metastases appeared homogeneous (50.8%). Less commonly, identified lesions were characterized by a target/bull's-eye appearance (20.0%), calcifications (19.0%), or other distinct features (10.2%). Tumors receiving preoperative chemotherapy were more likely to have an IOUS target appearance (P score=A: preoperative chemotherapy, 11.5% vs no preoperative chemotherapy, 5.3%) or scattered calcifications (P score=B: preoperative chemotherapy, 19.7% vs no preoperative chemotherapy, 1.3%) than patients who did not receive chemotherapy (both $P<.05$). Other clinicopathologic factors, such as age, sex, and tumor size and location within the liver, were not associated with tumor IOUS appearance (all $P>.05$).

IOUS ECHOGENICITY AND APPEARANCE: VARIABILITY ANALYSIS

To determine how the echogenicity and IOUS appearance of tumors correlated within the same patient and between different patients, an analysis of all possible lesion pairs in patients with more than 1 lesion was performed. Forty patients had multiple lesions, for a total of 135 tumors and 206 lesion pairs. If a patient had 3 lesions, for example, 3 lesion pairs were available for analysis (lesion 1 compared with lesion 2; lesion 1 compared with lesion 3; lesion 2 compared with lesion 3). Using the permutation test, the expected agreements under the null hypothesis (ie, lesions within patients are no more associated than lesions between patients) were determined. To do this, the E scores and P scores of the 135 lesions were randomly permuted to estimate the expected agreement between lesion pairs if there were no association between tumors from within the same patient. The observed percentage of agreement within tumors from the same patient and the expected agreement under the null hypothesis were then compared using χ^2 tests.

For patients with multiple tumor metastases, the majority (84%) of lesions within the same patient had either the same E score (40%) or an E score that differed by 1 grade (44%). In patients with multiple metastases, only 16% of lesions differed in the E score by 2 or more grades. The high degree of E-score correlation between tumors within the same patient was more than would have been expected by chance alone (**Table 4**) ($P<.001$), suggesting that the echogenicity of lesions within the same patient was more similar than the echogenicity of lesions between different patients. A similar analysis of P scores revealed a 50% agreement in the P score of lesions from within the same patient compared with an expected 35% agreement under the null hypothesis ($P=.002$). In aggregate, these data indicate that lesions within patients were more similar with regard to both echogenicity and appearance pattern than lesions found between different patients.

COMMENT

Despite advances in preoperative imaging technology, IOUS remains the gold standard for accurately staging patients with hepatic tumors.[10] Several studies have shown that IOUS often reveals important new information not seen on preoperative imaging and that these findings can change the operative plan in up to 50% of patients.[1,4,6,18,19] The accuracy of IOUS to detect colorectal metastases depends, however, on an exact analysis and knowledge of the tumor's sonographic characteristics. The present study is, to our knowledge, the largest report that has specifically evaluated and characterized the sonographic features of colorectal liver metastases with regard to both intrapatient and interpatient variability. The use of prospectively collected standardized digital image recording and blinded review of the IOUS images allowed us not only to evaluate the sonographic features of colorectal liver metastasis but also to assess more directly the variability in tumor IOUS appearance.

Currently, there are few data on the IOUS characteristics of colorectal liver metastases. The few previous studies[13-15] that have examined the echogenicity of colorectal liver metastasis reported that the majority (54%-65%) of colorectal liver metastases were hyperechoic in nature. In contrast, in the current study, most colorectal liver metastases were found to be hypoechoic (52.0%). A number of factors may account for this discrepancy. Previous studies did not involve dedicated rereview of IOUS images but relied instead on retrospective review of operative notes.[13,15] Such retrospective reviews may be subject to selection biases, whereby only the most prominent lesions (ie, the hyperechoic metastasis) are recorded. A major strength of the current study was that a dedicated blinded rereview of the IOUS images was performed. Such a review is more likely to provide an accurate account of the echogenicity of colorectal liver metastases.

In addition, previous studies classified tumors as either hypoechoic or hyperechoic, while omitting any reference to an "isoechoic" classification.[13,15] Since the IOUS appearances of liver metastases may occur over a broad continuum, a Likert or ordinal scale, which includes a category for isoechoic lesions, is a more appropriate tool for assessing echogenicity. Given that isoechoic lesions have an appearance most similar to the echotexture of the surrounding liver and are therefore the most likely metastases to be missed, it is critical to account for this category of metastases in any investigation of liver metastases and IOUS echogenicity. In fact, we found that a significant minority of tumors had an isoechoic appearance (35.7%). In aggregate, these data serve to emphasize that the echogenicity of colorectal liver metastasis can vary considerably. In addition to hyperechoic lesions that are often easier to identify on routine IOUS, surgeons need to be attentive for isoechoic and hypoechoic lesions, which can be found in more than 40% of patients.

One interesting finding in the current study was that the index lesion of patients who otherwise had occult and/or small (<1.0 cm) metastases detected by IOUS was more likely to be hypoechoic or hyperechoic. Size itself, however, was not significantly associated with echogenicity or overall IOUS appearance (both $P > .05$). Similarly, other factors such as age, sex, tumor number and location, preoperative chemotherapy, and presence of hepatic steatosis were all not associated with echogenicity. The lack of an association between these factors and echogenicity needs to be interpreted cautiously, however, as only 99 patients (194 lesions) were analyzed and the current study therefore may have been underpowered. Nonetheless, these data do suggest that issues related to IOUS test sensitivity, rather than biology, may have accounted for the preponderance of hypoechoic or hyperechoic lesions noted in the otherwise occult small lesion category. Rather than small occult lesions being inherently hypoechoic or hyperechoic, a more plausible explanation would be that IOUS was not as sensitive for small otherwise occult isoechoic lesions. That is, small hypoechoic or hyperechoic lesions were probably easier to identify whereas small isoechoic lesions, which were similar to the echo texture of the surrounding liver, were more prone to go unnoticed. Data suggesting that IOUS is helpful in identifying an additional 10% to 20% of lesions have not discussed whether the additional lesions are more likely to be hypoechoic or hyperechoic.[3,6,7,9,10] Our data strongly suggest that although the sensitivity of IOUS may be good for small lesions with different echo textures, IOUS may not be as sensitive in identifying small otherwise occult isoechoic lesions.

Another important finding was that lesions within patients were significantly more likely to be similar in echogenicity and appearance than lesions between patients. Thus, although the echogenicity of colorectal metastases in general was quite variable, metastases within a given patient were ultrasonographically similar. In other words, if a patient was found to have 1 colorectal metastasis that was hyperechoic, any subsequent metastases were more likely to also be hyperechoic (Table 3) ($P < .001$). Hence, for any given patient, the ultrasonographic characteristics of 1 metastatic colorectal lesion may help predict the appearance of subsequent lesions. Such information has important diagnostic and therapeutic implications. First, from a diagnostic perspective, knowledge that subsequent lesions are more likely to have a similar echogenicity and appearance as the index colorectal metastasis can alert the surgeon to be more deliberate in searching for lesions of the same echogenic pattern. For example, if the index lesion is hypoechoic, then a second or third previously undiagnosed lesion is much more likely to be hypoechoic. In addition, if the index lesion is isoechoic, one might anticipate that otherwise occult lesions will also be isoechoic and likely more difficult to detect. Prospective use of such knowledge may help to increase IOUS sensitivity in detecting small occult lesions. Occasionally, IOUS can reveal a lesion of indeterminate significance for which the surgeon has a low clinical suspicion (eg, hyperechoic lesion possibly representing a hemangioma). Based on our data, the surgeon's suspicion of occult malignant disease should be heightened considerably if the "indeterminate" lesion has the same echogenicity as the index lesion.

A potential weakness of the current study was our reliance on a visual grading scheme. Visual grading of liver echogenicity has been criticized as being inaccurate because it is subjective and observer dependent.[20] As such, some investigators have advocated the use of densitometry to more accurately assess the density/echogenicity of liver lesions.[20] Vehmas et al[21] reported, however, that visual grading correlated better with indirect determinants of liver pathologic features than computerized quantitative measurements. In the study by Vehmas et al,[21] the mean grade of the reviewing radiologists correlated the best with early liver pathologic features (R^2=0.55 for mean radiologists' visual scoring vs R^2=0.31 for ultrasonographic measurement of liver-kidney ratio).[21] Vehmas et al noted that local echo artifacts often impeded and confounded automated echogenicity measurements. In the current study, we used 3 independent reviewers to assess the IOUS images and score echogenicity. As with the Vehmas et al study,[21] we used the mean grades of the reviewers for the purposes of analyses. Currently, an experienced IOUS user—one who pays attention to vascular architecture, intraparenchymal artifacts, and the general echogenicity of the liver—remains the preferred method for evaluating the appearance and echogenicity of liver metastasis.[21]

In summary, our findings demonstrate that the echogenicity and appearance of colorectal metastases on IOUS vary considerably. Although most lesions are either hypoechoic or hyperechoic, a significant minority are isoechoic and may be underappreciated on IOUS. Isoechoic lesions were particularly underrepresented as small otherwise occult lesions, suggesting that the sensitivity of IOUS to detect these lesions may be less than that for hypoechoic or hyperechoic lesions. Although clinicopathologic characteristics failed to predict colorectal metastasis appearance on IOUS, we report that lesions within patients were more similar in echogenicity and IOUS appearance than lesions between patients. These findings have diagnostic and clinical implications because the IOUS echogenicity of 1 lesion may be useful in tailoring the operating surgeon's expectations for the detection of additional metastases using IOUS. The association of pathologic findings (eg, tumor necrosis, tumor grade, steatosis of the nontumorous liver), as well as response to preoperative chemotherapy, with IOUS characteristics are important clinical questions that require further investigation.

Accepted for Publication: July 10, 2006.
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Author Contributions: Drs Choti and Pawlik had full access to all of 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:* Choti, Kaloma, and de Oliveira. *Acquisition of data:* Choti, Nour, and Pawlik. *Analysis and interpretation of data:* Choti, Garrett-Mayer, Sheth, and Pawlik. *Drafting of the manuscript:* Choti, Kaloma, Nour, Garrett-Mayer, and Pawlik. *Critical revision of the manuscript for important intellectual content:* Choti, de Oliveira, Sheth, and Pawlik. *Statistical analysis:* Garrett-Mayer. *Administrative, technical, and material support:* Kaloma, de Oliveira, Nour, Sheth, and Pawlik. *Study supervision:* Choti.
Financial Disclosure: None reported.
Additional Contributions: M. Robert De Jong, RDMS, RVT, ultrasound technical manager, and Sharon Balzarini, RDMS, RVT, senior sonographer, provided technical assistance.

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