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Accuracy of Gray-Scale and Color Doppler Sonography in Diagnosis of Hepatic Hemangioma, Hepatocellular Carcinoma and Liver Metastasis.

Background/Objective: Distinguishing cavernous hemangioma from malignant neoplasms represents a diagnostic challenge. Knowledge of the entire spectrum of gray-scale ultrasonography (US) and color Doppler appearances of these tumors is important. The objective of this study was to determine the diagnostic accuracy of gray-scale US and color Doppler appearances of liver tumors.

Patients and Methods: 88 patients with 93 focal hepatic lesions were prospectively studied with gray-scale and color Doppler US. The final diagnoses of the liver lesions as confirmed by pathology or ^{99m}Tc-red blood cell scintigraphy were 41 hemangiomas, 15 hepatocellular carcinomas (HCCs) and 37 metastases.

Results: 87.8% of hemangiomas and 66.7% of HCCs were hyperechoic, while 54.1% of metastases were hypoechoic. In lesions $<$ 3 cm in diameter, the sensitivity and specificity of the hyperechoic pattern for differentiation of hemangioma from metastasis and HCC were 94.1% and 80.0%, respectively. They were higher than the lesions with a diameter $\geq$3 cm (83.3% and 45.9%, respectively, both P=0.001). Posterior acoustic enhancement was seen in 78% of hemangiomas ($P<0.001$), as compared to 24.4% in metastases and 13.3% in HCCs. 10 hemangiomas had an echogenic rim. The peripheral hypoechoic rim, named as the target sign, was seen in 37.8% of metastases, 26.7% of HCCs and 2.4% of hemangiomas ($P<0.001$). Most hemangiomas (85.4%) showed no lesional blood flow, while most HCCs (80%) had both intra- and peri-lesional vascularity ($P<0.001$). There was intratumoral blood flow in 86.7% of HCCs. Lesional flow, whether intratumoral or peritumoral or both, was seen in all 14 patients with HCC while absence of the lesional flow was not noted in any of the HCCs.

Conclusion: Most hemangiomas had no detectable blood flow in color Doppler US. Almost all HCCs had intra- and/or peri-tumoral vascularity in color Doppler sonography, so the probability of hepatocellular carcinoma is low in a hepatic mass without intra- or peri-lesional vascular blood flow. So these findings together with morphological criteria may help narrow down the differential diagnosis in certain clinical conditions.

Keywords: Liver, Doppler Ultrasound, Hemangioma, Hepatocellular Carcinoma, Metastasis

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Introduction

Focal hepatic lesions are a common diagnostic problem referred to radiologists for evaluation. Distinguishing cavernous hemangioma—the most common benign hepatic lesion—from malignant neoplasms represents a diagnostic challenge.[1,2] Because the vast majority of hepatic hemangiomas are asymptomatic and require no treatment, they must be differentiated from hepatic malignancies.[2] Of the various modalities available, gary-scale sonography is a screening technique for patients suspected of having liver tumors.[3] As sonography plays a key role in the initial evaluation of hepatic hemangiomas, knowledge of the entire spectrum of sonographic appearances of liver tumors is important.[2]

However, a specific liver tumor diagnosis can rarely be established based

on the gray-scale sonographic characteristics.[4]

Duplex sonography and color Doppler imaging of liver lesions have shown characteristic vascular patterns. Some authors claim that these patterns reflect the vascular anatomy of specific types of hepatic lesions, suggesting that these techniques can establish a tentative diagnosis of malignancy, although this has been controversial.[3-7] However, when properly performed, Doppler ultrasonography provides rapid, comprehensive, and accurate evaluation of the entire hepatic vasculature.[5,8]

Traditionally, needle biopsy is the gold standard method for the diagnosis of solid tumors of the liver, after ruling out hemangioma by ^{99m}Tc-red blood cell (RBC) isotope scan. Occasionally biopsy is contraindicated as in patients with coagulopathy or it may be inconclusive pathologically.

At present, the study of tumoral vascularization is one of the most interesting aspects of Doppler technology and is often described in the literature.[1-10]. Regarding focal hepatic lesions, Mito et al., were the first to diagnose hepatocellular carcinoma (HCC) by Doppler signals.[9] Since then, there have been many attempts to assess the usefulness of Doppler in the study of liver tumors. However, conventional color Doppler imaging has some drawbacks,[11] specifically it cannot detect low-flow velocity or fine blood flow.[10] Fobbe et al., considered the overlap in vascularization patterns between benign and malignant lesions.[12]

The objective of this study was to further elucidate characteristic patterns of gray-scale and color Doppler ultrasonography, especially to determine the accuracy of color Doppler ultrasonography in diagnosis of focal liver lesions, including cavernous hemangioma, HCC and liver metastasis.

Patients and Methods

Patient Selection

From October 2004 to September 2005, 93 solid liver lesions were prospectively studied in 88 consecutive patients (56 women, 32 men) aged from 20 to 93 (mean: 55.1) years. Inclusion criteria were patients with a) liver masses referred to our radiology department for more evaluation; and b) any liver mass incidentally detected by sonography in routine studies of patients referred to our department. Patients who did not return for more evaluation to determine the final diagnosis were excluded from the study.

The study was approved by our institutional review board and was done according to the declarations of Helsinki code of ethics. Written informed consent was obtained from all patients. All patients were evaluated by gray-scale sonography and color Doppler sonography by an experienced radiologist without knowledge of the final diagnosis of the liver lesion. Interpretation was performed without information about clinical data or other imaging findings (observer blinding). No Doppler study was performed after biopsy.

A specific and final tumor diagnosis was established based on histologic findings using sonographically guided needle biopsy or nuclear medicine—^{99m}Tc-RBC single photon emission computerized tomography (SPECT). The final diagnoses of the 93 focal liver lesions were 37 (39.8%) metastases, 41 (44.1%) hemangiomas, and 15 (16.1%) HCCs.

Equipments and Imaging Protocols

Real-time gray-scale sonography and color Doppler sonography were performed by the same examiner using the same ultrasound unit (Hitachi, EUB-525 system) with a 2.5–3.5 MHz convex probe. Gray-scale and color gain were adjusted dynamically during scanning. The color Doppler parameters were optimized for each patient using the lowest pulse repetition frequency and filter settings and the highest gain that would not produce background noise.

At first, the morphological characteristics of the lesions including echogenicity, posterior enhancement, echogenic rim and target appearance were evaluated by B mode sonography. Then, the presence or absence of intra- or peri-lesional vascularity and type of vascular flow (continuous or pulsatile) were assessed. In all cases, the lesions with the greatest diameter and closer to the transducer were evaluated to optimize the Doppler signal.

Statistical Analysis

Statistical analysis was performed using chi square or Fisher's exact tests when appropriate. Referring to the final diagnoses, sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios

were calculated for different findings in these two diagnostic modalities. The level of significance was set to a P<0.05 in all statistical tests. Data management and statistical analyses were performed using SPSS® 11.5 for Windows® (SPSS corporation, Chicago, Illinois).

Results

Ninety-three solid liver lesions of 88 consecutive patients were prospectively studied. There was significant difference in the frequency of liver hemangioma in men and women (P<0.001) (Table 1).

In gray-scale sonographic examination, 88% (36 of 41) of hemangiomas and 67% (10 of 15) of HCCs were hyperechoic, while 54% (20 of 37) of metastases were hypoechoic (Table 2). The sensitivity and specificity of hyperechoic appearance in the differentiation of hemangioma from metastasis and HCC were 87.8% and 55.8% respectively. PPV, NPV, positive and negative likelihood ratio were 61%, 85.3%, 1.98 and 0.22, respectively.

The data were also analyzed for the effect of the lesion size on the appearance of sonographic echogenicity. Different cut-off points for lesion size were selected and analyzed for the evaluation of how lesion size affects study findings. After statistical analysis, we noticed that differences between different imaging findings were statistically significant when lesions were classified based on a 3-cm cut-off value. Thus, patients were classified into two groups based on the size of the lesion. In hepatic lesions <3 cm in diameter, 94% (16 of 17) of the hemangiomas were hyperechoic, while 50% (2 of 4) of the HCCs and 55% (6 of 11) of the metastases were hypoechoic (Table 3). In lesions sized ≥3 cm, 83% (20 of 24) of the hemangiomas and 82% (9 of 11) of the HCCs were hyperechoic. In lesions <3 cm in diameter, the sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios of the hyperechoic pattern for differentiation of hemangioma from metastasis and HCC were 94.1%, 80.0%, 84.2%, 92%, 4.7 and 0.07, respectively. The above-mentioned diagnostic indices for lesions≥3 cm in diameter were 83.3%, 45.9%, 50%, 81%, 1.53 and 0.36, respectively (P=0.001).

Most hemangiomas (32 of 41, 78%) had posterior acoustic enhancement, as compared to the metastases (9 of 37, 24%) and HCCs (2 of 15, 13%) (P<0.001). This appearance had the sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios of 78%, 78.9%, 74%, 82%, 3.69 and 0.28, respectively, in the differentiation of hemangioma from the two other lesions.

Ten (24%) of the hemangioma lesions had an echogenic rim (Fig. 1), while none of the metastases and HCCs had this appearance (P<0.001).

Peripheral hypoechoic rim or the target sign, was seen in 38% (14 of 37) of the metastases, 27% (4 of 15) of the HCCs and 2% (1 of 41) of the hemangiomas (P<0.001) with a sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios of 37.8%, 73.3%, 73.7%, 68.9%, 1.41 and 0.85, respectively, for the diagnosis of metastasis.

As shown in Table 4, color Doppler sonography revealed no detectable blood flow in most hemangiomas (35 of 41, 85%), while most HCCs (12 of 15, 80%) had both intra- and peri-lesional vascularity. There was intra-tumoral blood flow in 10% (4 of 41) of the hemangiomas, 43% (16 of 37) of the metastases and 87% (13 of 15) of the HCCs. Sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios of absent detectable vascularity were 85.4%, 73.1%, 71.4%, 86.4%, 3.17 and 0.57, respectively, in the diagnosis of hemangioma. Presence of both intra- and peri-lesional vascularity had the sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios of 80.0%, 80.8%, 44.4%, 95.5%, 4.17 and 0.25, respectively, in the differentiation of HCC from the two

Table 1. Frequency of Different Solid Liver Lesions Stratified by Gender

Lesion	Male	Female	P value
Hemangioma	6/38 (15.8%)	32/38 (84.2%)	<0.001
Metastasis	19/36 (52.8%)	17/36 (47.2%)	0.739
Hepatocellular Carcinoma	7/14 (50%)	7/14 (50%)	1.00

Table 2. Appearance of Solid Liver Lesions in Gray-Scale Sonography

Lesion Type (n)	Echogenicity		
	Hyperechoic	hypoechoic	Isoechoic
Hemangioma (41)	36 (87.8%)	3 (7.3%)	2 (4.9%)
Metastasis (37)	13 (35.1%)	20 (54.1%)	4 (10.8%)
Hepatocellular carcinoma (15)	10 (66.7%)	3 (20%)	2 (13.3%)
Total	59 (63.5%)	26 (27.9%)	8 (8.6%)

Table 3. Appearance of Solid Liver Lesions in Gray-Scale Sonography Stratified by the Lesion Size

Lesion Size	Lesion Type(n)	Echogenecity		
		hyperechoic	hypoechoic	isoechoic
<3 cm	Hemangioma(17)	16 (94.1%)	0 (0%)	1 (5.9%)
	Metastasis(11)	2 (18.2%)	6 (54.5%)	3 (27.3%)
	HCC(4)	1 (25.0%)	2 (50.0%)	1 (25.0%)
≥3 cm	Hemangioma(24)	20 (83.3%)	3 (12.5%)	1 (4.2%)
	Metastasis(26)	11 (42.3%)	14 (53.8%)	1 (3.8%)
	HCC(11)	9 (81.8%)	1 (9.1%)	1 (9.1%)

Table 4. Color Doppler Blood Flow of Focal Liver Lesions

Lesion Type (n)	Vascularity				P value
	No vascularity	peritumoral	Peri and intratumoral	intratumoral	
Hemangioma (41)	35 (85.4%)	2 (4.9%)	1 (2.4%)	3 (7.3%)	<0.001
Metastasis (37)	14 (37.8%)	7 (18.9%)	14 (37.8%)	2 (5.5%)	0.011
Hepatocellular Carcinoma (15)	0 (0%)	2 (13.3%)	12 (80%)	1 (6.7%)	0.001

other lesions.

In lesions with peri-lesional blood flow (38 of 93), a continuous pattern was seen in 67% (2 of 3) of hemangiomas, 62% (13 of 21) of metastases (Fig. 2) and 57% (8 of 14) of HCCs (P=0.81; Fisher's exact test).

In lesions with intra-lesional blood flow (n=33), a continuous pattern was seen in 100% (4 of 4) of hemangiomas, 56% (9 of 16) of metastases and 54% (7 of 13) of HCCs (P value=0.30; Fisher's exact test).

Discussion

Although ultrasound is commonly used to detect liver lesions, ultrasonographic characterization of liver lesions based on gray-scale morphological features rarely leads to specific tumor diagnosis.[1-10] It is often reasonable to follow an incidentally detected liver lesion, unless suspicious imaging features are present. Conversely, percutaneous biopsy is often considered if imaging findings or the clinical settings suggest that malignancy is likely. Most hemangiomas and most common benign tumors of the liver have a distinctive ultrasonographic appearance[13-15], but some known as "atypical hemangiomas," show various ultrasonographic patterns.[16-19] Our study showed that most hemangiomas (88%) and HCCs (67%) were hyperechoic, while 54% of the metastases were hypoechoic with a low specificity (44.2%) of the hyperechogenicity for the diagnosis of liver hemangioma. As seen in Table 3, hyperechoic appearance is more frequent in hemangiomas <3 cm in diameter and it may be more helpful for the diagnosis of hemangioma in lesions <3

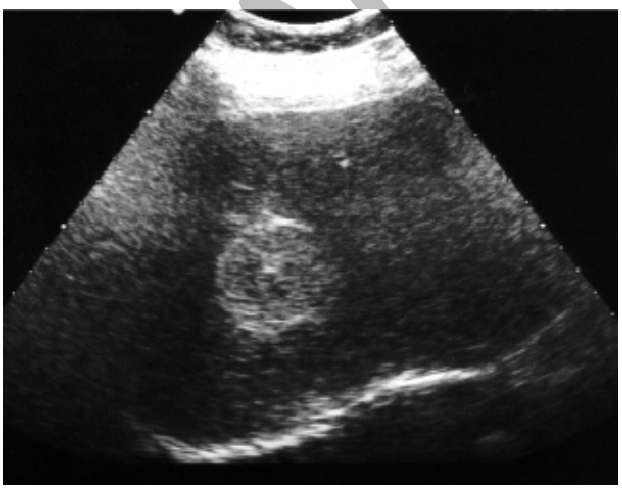

Fig. 1. A 37-year-old woman with a hepatic hemangioma. Gray-scale sonogram shows an echogenic rim.

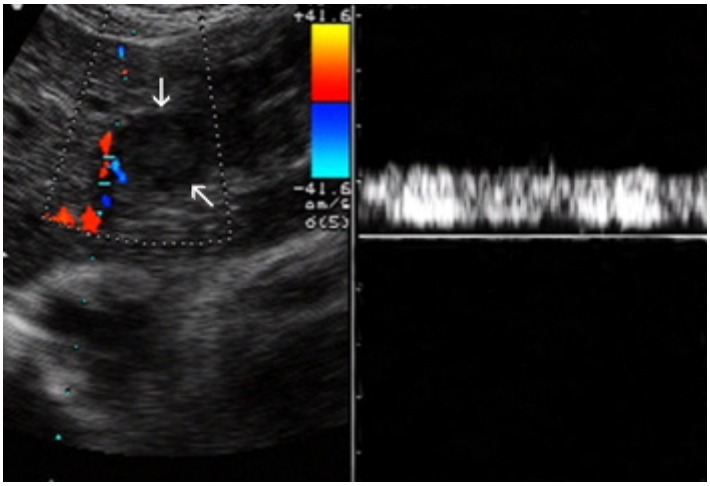

Fig. 2. A 41-year-old man with a metastasis from gastric carcinoma: color Doppler sonography shows continuous peritumoral flow.

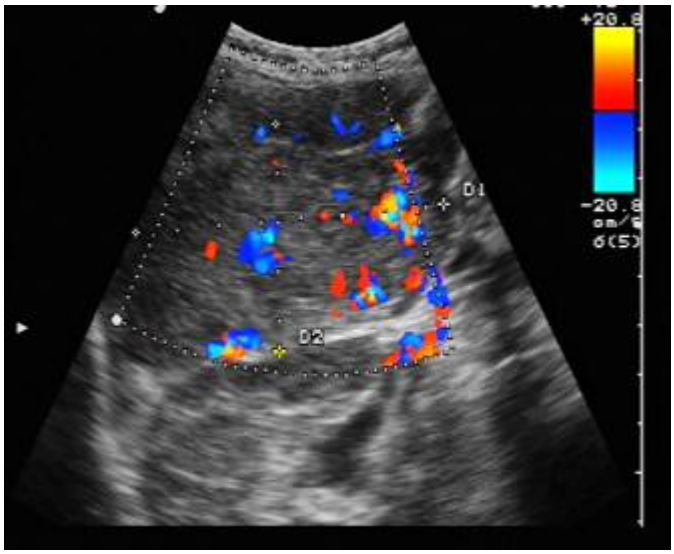

Fig. 3. A 50-year-old woman with hepatocellular carcinoma. Color Doppler shows remarkable intratumoral vascular flow.

cm than in lesions ≥3 cm. There was clearly less frequent hyperechoic HCCs or metastases in lesions ≥3 cm in diameter than smaller lesions. The posterior acoustic enhancement also had a relatively low specificity (66.7%) in the differentiation of hemangioma from the two other lesions. The echogenic rim, which was only seen in hemangioma, is not sensitive (32.2%), but has a high specificity for the characterization of hemangioma (Fig. 1). We suggest that the echogenic rim is an invaluable finding in gray-scale sonography for the diagnosis of hemangioma. Some authors describe this sign as the most suggestive sonographic feature of atypical hemangioma.[2,15] It is suggested that the most common and generally accepted typical ultrasonographic features of hepatic hemangioma are their small size, uniform hyperechogenicity, well-defined margin and posterior echo enhancement. The target sign (hypoechoic rim) was more prevalent in metastases (38%) and HCCs (27%) than hemangiomas (2%). Consequently, the target sign is a useful sign for the differentiation of metastasis from hemangioma, but it cannot discriminate between metastasis and HCC.

Since the introduction of Doppler sonography, there has been considerable interest in the potential utility of flow characteristics to improve the specificity of sonographic diagnosis of focal lesions. The likelihood of demonstrating flow in a given case depends not only on the lesion's vascularity, but also on the flow sensitivity of the equipment, the operator's skill, the depth of the lesion and the patient's ability to maintain a breath hold.

In the present study, color Doppler sonography revealed no detectable blood flow in most hemangiomas (85%), while most HCCs (80%) had both intra- and peri-lesional vascularity. Lesional flow, whether intra-tumoral (Fig. 3) or peri-tumoral or both, was seen in all 14 HCC patients while absence of lesional flow was not noted in any of HCCs. HCCs are usually very vascular lesions, showing the presence of tumor blush and tumoral neovascularity on angiography. Nino-Murcia et al., found an intra-tumoral flow in 76% of HCCs, 23% of metastases and 25% of benign lesions.[20] Thirteen (87%) of 15 HCCs in our study showed the presence of intra-lesional flow; it was absent in only two HCCs. Consistent with our findings, Srivastava et al., reported intra-tumoral blood flow in 15 patients with HCC, while it was absent in one patient with HCC.[21]

In the present study, 62% (23 of 37) of metastases showed lesional vascularity whether they had intra- or peri-tumoral blood flow, while no vascularity was detected in 38% of the metastases. Nino-Murcia et al., and Srivastava et al., found lesional blood flow in 33% and 56% of the metastases, respectively.[20,21]

Peri-tumoral flow, whether due to displaced vessels or due to vessels in the hypoechoic halo around the lesions, was seen in 38% (14 of 37) of the metastatic lesions.

Hemangiomas are benign lesions with large cavernous spaces containing slow-flowing blood. In the present study, only four (10%) of 41 hemangiomas showed intratumoral flow, while three (7%) of 41 had peri-tumoral flow. Srivastava et al., reported lesional flow in only two hemangiomas, while the remaining did not show any flow.[21] Also consistent with our findings, Perkins et al., reported that Doppler imaging showed no internal blood flow in 23 of the 25 hemangiomas. Of these 23 lesions, 11 showed a peripheral flow pattern, believed to represent flow in the displaced blood vessels.[1]

Possible flow patterns seen in metastases are as follows: no vascularity, both intra- and peri-lesional blood flow, and only peri-lesional or intra-lesional vascularity. Regarding no significant difference in the continuous or pulsatile pattern of the lesional blood flow between hemangiomas, metastases and HCCs, these patterns are not useful for differentiation.

Lin et al., evaluated 72 patients with HCCs (80 lesions), 30 with metastases (82 lesions), and 39 with hemangiomas (54 lesions) and concluded that color Doppler sonography can help in the differentiation of HCC from hemangioma, but it may be unreliable in the differentiation of HCC from hypervascular metastases.[22] Weimann et al., concluded that the yield of color Doppler sonography is not high for the differential diagnosis and prediction of the tumor dignity.[23]

For all patients in our study, the final diagnosis was not confirmed by histology using guided needle biopsy. Furthermore, we used ^{99m}Tc-RBC SPECT as a specific procedure for the diagnosis of liver hemangioma in patients who did not have histologic confirmation. On the other hand, sonographically guided needle biopsy was performed for only available lesions in patients with multiple liver space occupying lesions.

Almost all HCCs had intra- and/or peri-tumoral vascularity in color Doppler sonography, so the probability of HCC is low in a hepatic mass without intra- or peri-lesional vascular blood flow. Lesional flow, whether intra- or peri-tumoral or both, was seen in all 14 patients who had HCC, while absence of the lesional flow was not noted in any of the HCCs. Most hemangiomas had no detectable blood flow in color Doppler sonography. Therefore, these findings together with the morphological criteria may help narrow down the differential diagnosis in particular clinical situations.

We declare that we have no conflict of interests regarding this study.

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