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Diagnosis of liver tumors by multimodal ultrasound imaging

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Abstract

To investigate the diagnostic value of multimodal ultrasound imaging composed of conventional ultrasonography (US), contrast-enhanced ultrasonography (CEUS), and shear wave elastography (SWE) for liver tumors.

Between October 2017 and October 2019, US, CEUS, and SWE examinations of a total of 158 liver tumors in 136 patients at The First Affiliated Hospital of Nanchang University were performed. The histopathological or imaging diagnostic results were used as controls to evaluate the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of US, CEUS, SWE, and multimodal ultrasound imaging, which combines these 3 modes, in the differential diagnosis of benign and malignant liver tumors.

Among the 158 tumors, there were 64 benign tumors, including 55 cases of hepatic hemangioma, 3 cases of focal nodular hyperplasia of the liver, 4 cases of hepatic cyst, and 2 cases of focal nonuniform distribution of fat in the liver. There were 94 malignant tumors, including 32 cases of hepatocellular carcinoma, 22 cases of intrahepatic cholangiocellular carcinoma, 29 cases of metastatic liver cancer, and 11 cases of dysplastic nodules in cirrhotic liver. In the diagnosis of benign and malignant liver tumors, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 82.56%, 68.06%, 75.96%, 75.53%, and 76.56% for US; 92.39%, 86.36%, 89.87%, 90.43%, and 89.06% for CEUS; 87.14%, 76.81%, 82.91%, 82.98%, and 82.81% for SWE; and 97.85%, 95.38%, 96.83%, 96.81%, and 96.88% for multimodal ultrasound imaging, respectively. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were all significantly higher for multimodal ultrasound imaging than those values for US, CEUS, and SWE (all $P < .05$). The areas under the receiver operating characteristic curve for US, CEUS, SWE, and multimodal ultrasound imaging in the diagnosis of benign and malignant liver tumors were 0.760, 0.897, 0.829, and 0.968, respectively.

US, CEUS, and SWE all have diagnostic value in the diagnosis of benign and malignant liver tumors. Multimodal ultrasound imaging could significantly increase the accuracy of the diagnosis of benign and malignant liver tumors and has higher value for clinical application.

Abbreviations: CEUS = contrast-enhanced ultrasonography, FNH = focal nodular hyperplasia, HCC = hepatocellular carcinoma, SWE = shear wave elastography, US = conventional ultrasonography.

Keywords: contrast-enhanced ultrasonography, conventional ultrasonography, liver tumor, multimodal ultrasound imaging, shear wave elastography

1. Introduction

Liver tumors are the most common diseases of the digestive system and can be divided into benign and malignant types depending on their characteristics.[1] Hepatic hemangioma is the most common benign liver tumor, and liver cancer is the common malignant liver tumor. At present, the incidence of liver cancer is the sixth in cancer worldwide, and the mortality rate is the third, second only to lung cancer and gastric cancer. However, the early clinical symptoms of

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JH, Z-YZ, and H-LR contributed equally to this work.

This study was approved by the ethical review committee of The First Affiliated Hospital of Nanchang University, and written informed consent was obtained from the patient.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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liver cancer are not obvious, disease progression is rapid, and most patients are identified and diagnosed in the middle and late stages; therefore, the morbidity is high. Globally, 45% of patients who die of hepatocellular carcinoma (HCC) are Chinese.[2,3] For liver tumor patients, determining the nature of the tumor as early as possible and effectively differentiating between benign and malignant tumors have great significance for formulating treatment plans and improving the survival rate. Such efforts are currently a focus and challenge in clinical work on hepatobiliary surgery.[4] As the preferred examination method for liver tumor screening, conventional ultrasonography (US) can reveal the location, size, morphology, internal echo, boundary, presence of acoustic halo at the edge, and condition of the blood flow of tumors.[5] Contrast-enhanced ultrasonography (CEUS) is a noninvasive imaging technology that can continuously and dynamically observe blood perfusion in tumors in real-time through injection of a contrast agent to enhance the blood flow reflux signal in the human body. Consequently, CEUS has a unique function in the imaging of capillaries and tissue perfusion in the human body.[6] Shear wave elastography (SWE) can determine the Young's modulus values of tissues and quantitatively evaluate tissue hardness to achieve ultrasound "palpation." In addition, SWE can reflect tissue hardness through color-coded graphs; redder color indicates a higher Young modulus and harder tissue, whereas bluer color indicates a lower Young modulus and softer tissue.[7] This study aimed to evaluate the value of multimodal ultrasound imaging combining US, CEUS, and SWE in the differential diagnosis of liver tumors and to compare the differential diagnosis performance of these 3 examination methods.

2. Methods and materials

2.1. Clinical data

A total of 136 patients (158 tumors) who had liver tumors identified at The First Affiliated Hospital of Nanchang University between October 2017 and October 2019 were enrolled. There were 75 men and 61 women. The age range was 31 to 83 years, and the average age was (43.96 ± 7.32) years. The tumors diameter ranged from 1.71 cm to 11.32 cm, and the average diameter was (4.72 ± 1.89) cm. Among all the patients, 76 patients had a medical history of hepatitis, 69 patients had clinical symptoms, and 38 patients had elevated alpha-fetoprotein. The clinical characteristics of all of the patients with liver tumors are shown in Table 1. All the tumors were examined by US, CEUS, SWE. The exclusion criteria were

(1) patients younger than 18 years age,
(2) patients who had a history of drug allergy,
(3) patients who had received systemic chemotherapy or local treatment,
(4) patients who had severe pulmonary emphysema, pulmonary embolism, or pulmonary arterial hypertension,
(5) patients who had respiratory failure,
(6) patients who had a lesion depth >80 mm,
(7) patients who were pregnant or lactating,
(8) patients with a tumor size <1 cm, and
(9) patients who had incomplete clinical data.

This study was reviewed and approved by the Hospital Ethics Committee. All patients signed informed consent before undergoing ultrasound imaging.

Table 1

Characteristics of patients.

Characteristics	Values
M/F ratio	75/61
Average age (yrs)	43.96 ± 7.32
Age range (yrs)	31–83
Average weight (kg)	61.41 ± 6.24
Weight range (kg)	43–92
Lesion size range (cm)	1.71–11.32
Average lesion size (cm)	4.72 ± 1.89
Asymptomatic, n (%)	67 (49.26%)
Symptomatic, n (%)	69 (50.73%)
History of hepatitis, n (%)	76 (55.88%)
Liver cirrhosis, n (%)	33 (24.26%)
AFP value is not in the normal range, n (%)	38 (27.94%)

AFP = alpha-fetoprotein.

2.2. Methods

US: The instrument was a Philips IU Elite color Doppler ultrasound diagnostic instrument (C5-2 convex broadband probe, the Netherlands) with a variable frequency of 3.0 to 5.0 MHZ and real-time CEUS matching imaging technology. Patients in the supine or lateral position underwent conventional 2-dimensional grayscale US examination to observe and record the number, location, morphology, boundary, size, internal echo, and presence of an acoustic halo at the edge of the tumors. Next, the color Doppler blood flow imaging technology was used to observe the blood supply in the tumors and to measure the blood flow resistance index of the tumors. US diagnostic standards: Tumor morphology, the tumor boundary, internal echo, and blood flow within the tumor were comprehensively analyzed. Characteristic presentations on 2D and color Doppler US were used as the standards for differential diagnosis of tumor properties.

CEUS: The best section for observation of the tumors in 2-dimensional US was selected, and the instrument was switched to contrast imaging mode. The range of the mechanic index was 0.07 to 0.20. The ultrasound contrast agent was the 3rd-generation ultrasound contrast agent SonoVue (Bracco, Italy). Each bottle contained 59 mg of sulfur hexafluoride gas and 25 mg of white lyophilized powder. Five milliliters of normal saline was aspirated and added to prepare the suspension solution. After vortexing for 5 seconds, 2.4 mL of solution was aspirated and injected through the cubital vein, followed by a rapid flush with 5 mL of 0.9% sodium chloride solution. At the injection of the contrast agent, the timer and built-in video recorder were turned on to continuously observe the tumors in real time for 6 minutes. The whole ultrasound imaging process was recorded and stored. The Guidelines and Good Clinical Practice Recommendations for CEUS in the Liver (2012 edition) developed by the European Federation of Societies for Ultrasound in Medicine and Biology and the World Federation for Ultrasound in Medicine and Biology[31] classified CEUS into 3 phases: the arterial phase (start time 10–20 seconds and end time 30–45 seconds), the portal venous phase (start time 30–45 seconds and end time 120 seconds), and the late phase (start time >120 seconds and end time when microbubbles in the contrast agent have completely disappeared, which occurs at approximately 360 seconds). The stored dynamic CEUS images were analyzed to observe and assess the following characteristics:

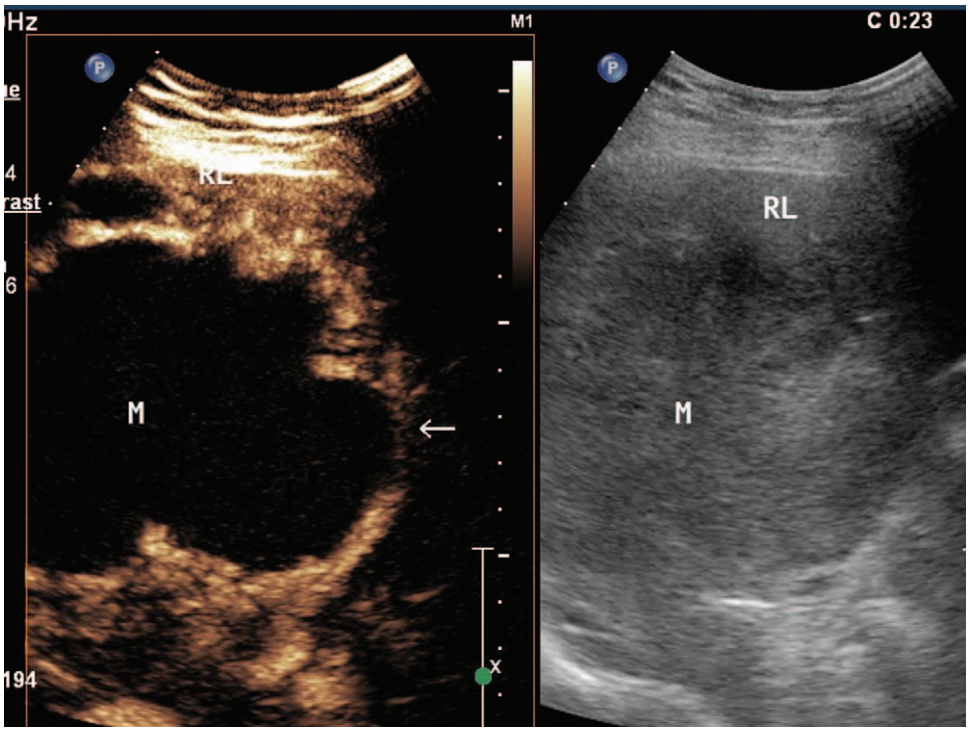

Figure 1. The CEUS examination revealed that the contrast agent in the tumor was filled from the edge of the tumor to the center of the tumor in the arterial phase. CEUS = contrast-enhanced ultrasonography.

(1) enhancement degree: the degrees of enhancement of the contrast agent in disease lesions were classified into hyperenhancement (higher than the enhancement level in adjacent normal liver tissues), isoenhancement (equivalent to the enhancement level in adjacent normal liver tissues), hypoenhancement (lower than the enhancement level in adjacent normal liver tissues), and non-enhancement (no contrast agent in the tumor);
(2) enhancement pattern: even enhancement, uneven enhancement, peripheral nodular enhancement, or peripheral ring enhancement; and
(3) enhancement type: sustained enhancement (hyperenhancement in the arterial phase and sustained enhancement or isoenhancement in the portal venous phase and the late phase), enhanced clearance (hyperenhancement in the arterial phase and hypoenhancement in the portal venous and/or late phases), hypoenhancement (hypoenhancement in all 3 phases), non-enhancement (no enhancement in all 3 phases), or centripetal progression (peripheral nodular enhancement in the arterial phase, centripetal filling of the contrast agent in the portal venous and late phases, and partial or overall enhancement of disease lesions in the late phase).

CEUS diagnostic standards: In this study, the diagnostic criteria in The Guidelines and Good Clinical Practice Recommendations for CEUS in the Liver (2012 edition)[31] were used for tumor diagnosis. Tumors with hyperenhancement or isoenhancement in the arterial phase and sustained hyperenhancement or isoenhancement in the portal venous and late phases were diagnosed as benign (Figs. 1 and 2). Tumors with hyperenhancement in the arterial phase and hypoenhancement in the portal venous or late phases were diagnosed as malignant (Figs. 3 and 4).

SWE: A Supersonic AixPlorer, a real-time SWE US diagnostic instrument (SuperSonic Imagine, France) with a SC6-1 convex probe, was used. The patients assumed the supine or lateral position, elevated their right arms and placed them on their heads, and held their breath (nonforced breath holding) to clearly display the tumors and adjacent liver parenchyma on the 2-dimensional acoustic image. The SWE was turned on, and when the sampling frame of elastography was mostly filled with colors, and the image was stable at 5 to 6 frames, the image was captured and stored. The Q-box was turned on, and regions of interest were placed in locations with harder disease lesions (with 3 regions of interests placed). Areas with calcification and liquefaction were avoided. The maximum value of the Young's modulus in the disease lesion (Emax) was stored and recorded. The above process was repeated 3 times, and the average value was obtained. SWE diagnostic standards[32]: Emax = 39.60 kPa was used as the cut-off value; Emax ≥ 39.60 kPa was regarded as indicative of a malignant liver tumor (Fig. 5), and Emax < 39.60 kPa was regarded as indicative of a benign tumor (Fig. 6).

All medical examinations were independently completed by the same doctor. One doctor in the ultrasound diagnosis department with more than 10 years of working experience completed data analysis and diagnosis in a double-blind manner.

2.3. Statistical methods

SPSS 23.0 statistical software was used to analyze the study data. Measurement data are expressed as the mean ± standard deviation ($\overline{\chi} \pm S$), and count data were examined using the χ^2 test. The diagnostic results from US, CEUS, SWE, and multimodal ultrasound were compared with the results of pathology or imaging-based diagnoses. The sensitivity, specificity, positive

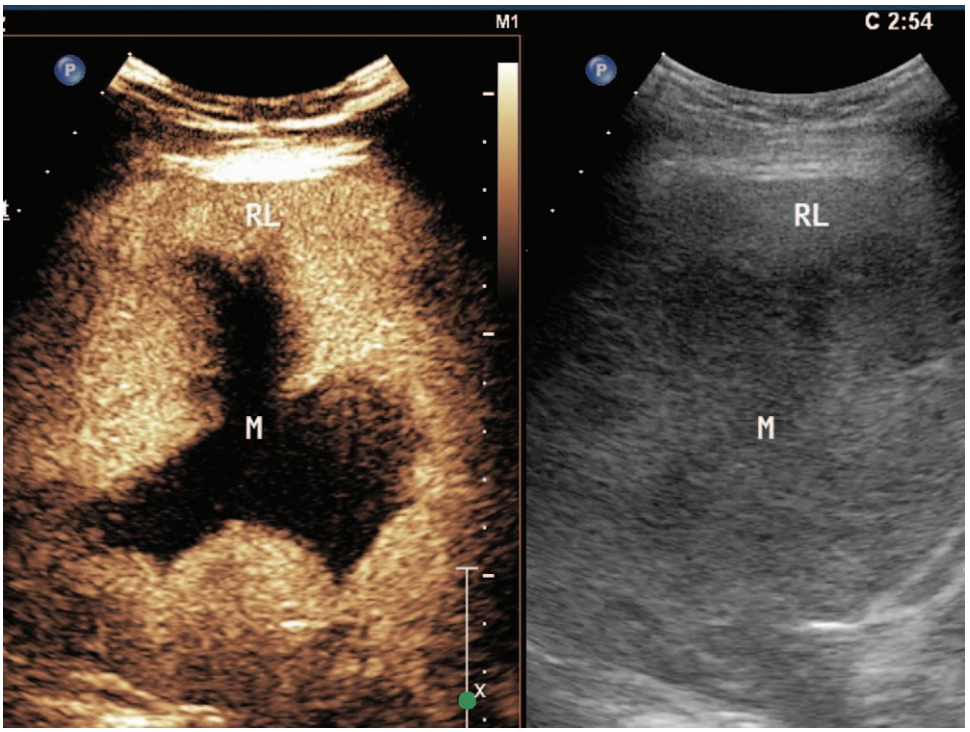

Figure 2. Sustained hyperenhancement in the portal venous and late phases.

predictive value, negative predictive value, and accuracy of US, CEUS, SWE, and multimodal ultrasound diagnosis were calculated separately. The receiver operating characteristic curve was plotted, and the area under the curve (AUC) was calculated separately for different examination methods. Based on the AUCs, the diagnostic values of US, CEUS, SWE, and multimodal ultrasound were compared. $P < .05$ was regarded as indicative of a statistically significant difference.

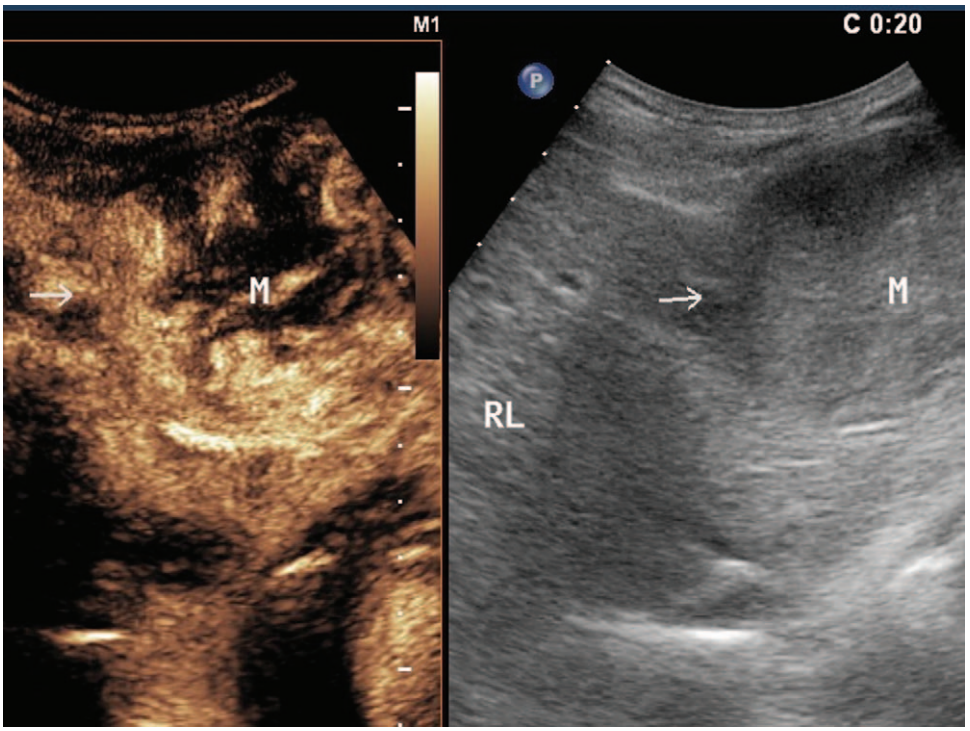

Figure 3. The CEUS examination revealed that the contrast agent in the tumor was rapidly filled during the arterial phase. CEUS = contrast-enhanced ultrasonography.

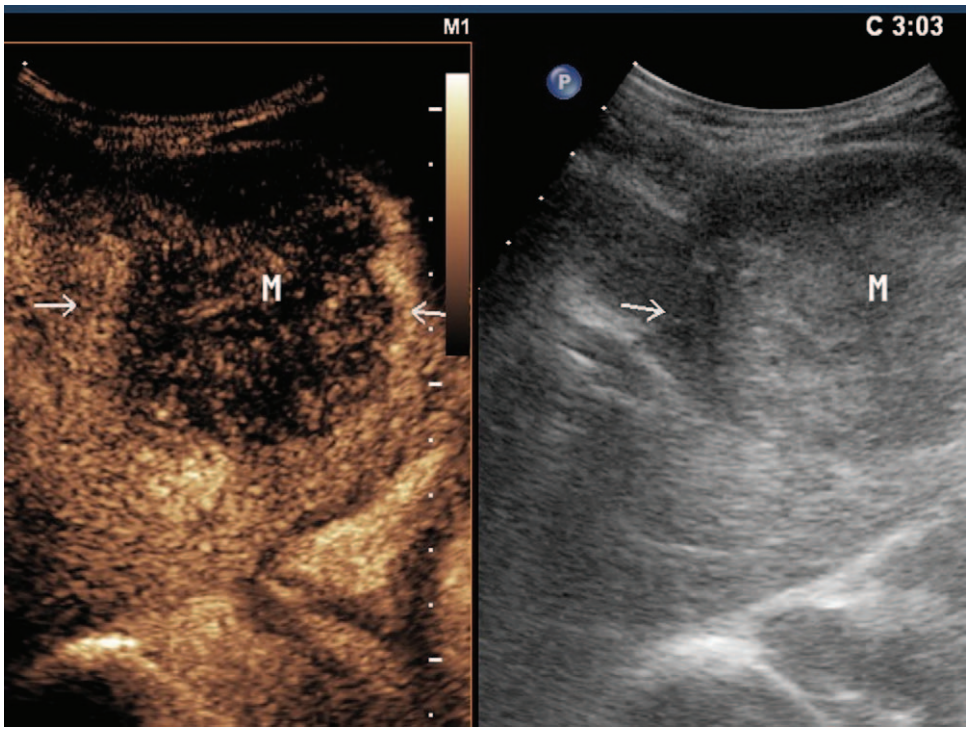

Figure 4. Contrast agent in tumor decreases during the delay period, showing hypoenhancement.

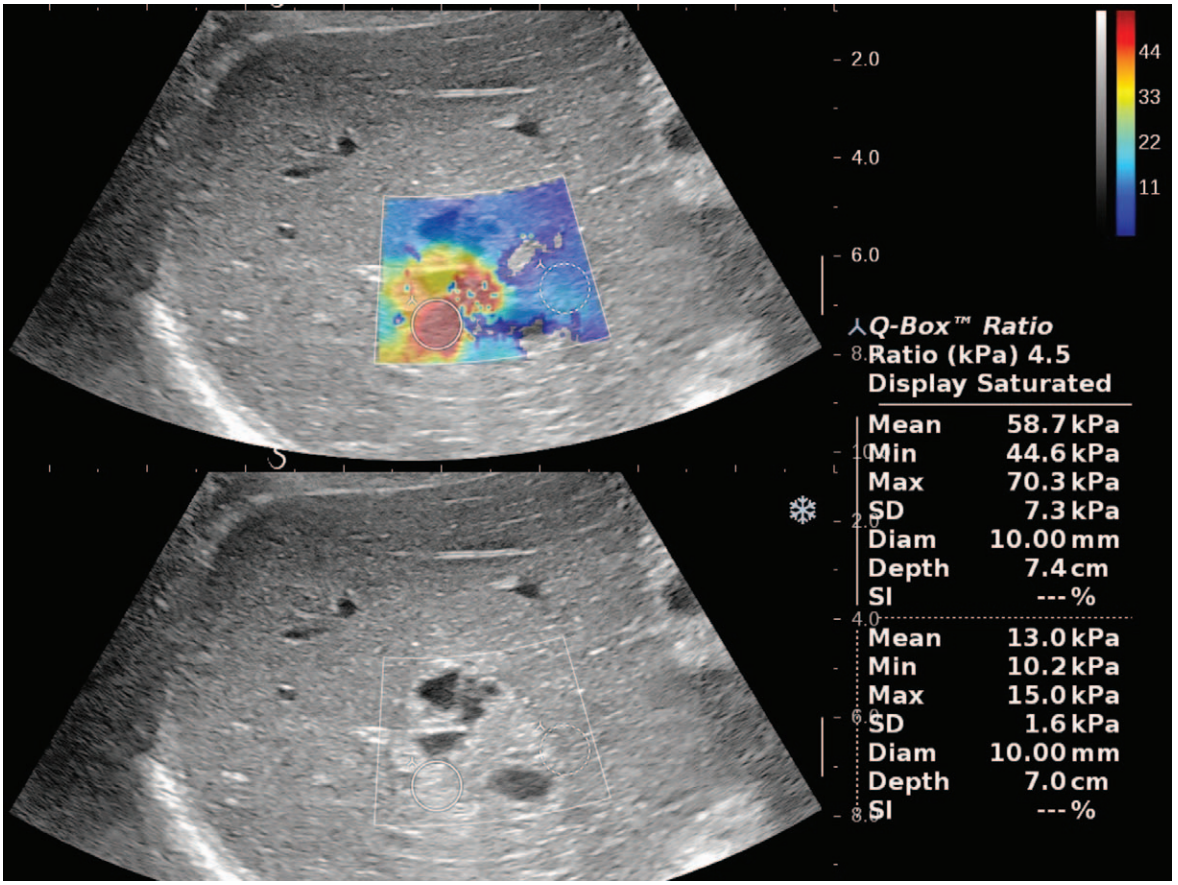

Figure 5. The maximum value of Young modulus of tumor measured by SWE, Emax = 70.30 kPa. SWE = shear wave elastography.

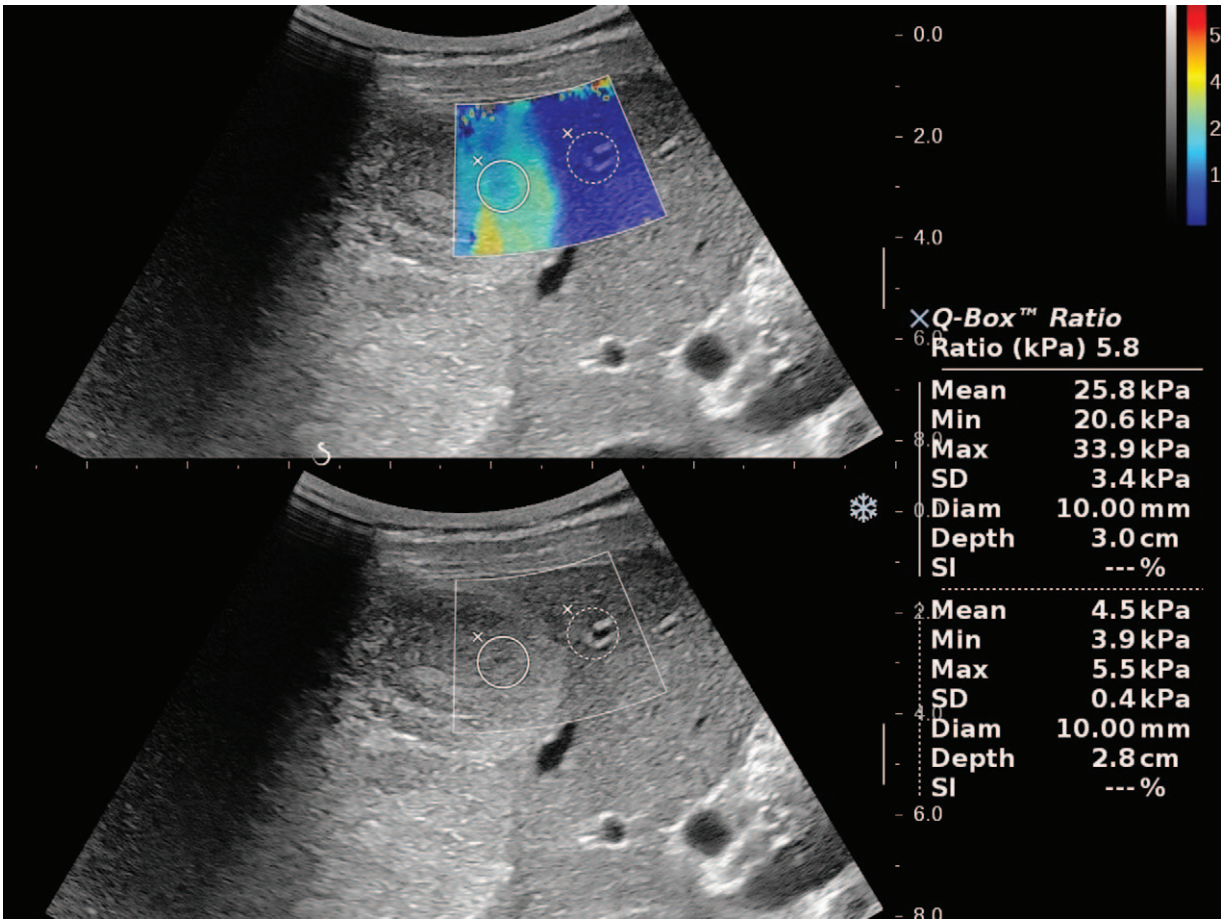

Figure 6. SWE examination showed that the texture of the tumor was stiffer than the adjacent liver parenchyma, but overall it was soft, Emax = 33.9 kPa. SWE = shear wave elastography.

3. Results

3.1. US results

There were 158 evaluated tumors, including 39 tumors in the left liver and 119 tumors in the right liver. On 2D US, 38 disease lesions had irregular morphology, and 120 lesions had regular morphology; 46 lesions had an unclear boundary, and 112 lesions had a clear boundary. With respect to internal echo in the disease lesions, there were 60, 12, 57, and 19 lesions that were hypoechoic, isoechoic, hyperechoic, and mixed echoic, respectively. An acoustic halo at the lesion edge was observed for 27 lesions. Color Doppler Flow Imaging showed blood flow signals for 99 lesions but no obvious blood flow signals for the remaining 59 lesions. Among the 158 examined tumors, 72 and 86 tumors were categorized as benign and malignant, respectively, based on US findings. A comparison of US-based diagnoses with pathology- or imaging-based diagnostic results revealed that 23 malignant tumors were misdiagnosed as benign and 15 benign tumors were misdiagnosed as malignant. The details were presented in Table 2.

3.2. CEUS results

The enhancement degrees of lesions were analyzed. The results showed that 92 lesions had even enhancement and 61 lesions had uneven enhancement. There were 27 lesions with peripheral ring

Table 2

UE, CEUS, SWE, multi-model ultrasound identification benign and malignant liver tumors and surgical pathology or imaging diagnosis results.

Pathological or imaging diagnosis	Number (n)	US		CEUS		SWE		Multi-model ultrasound imaging	
		Malignant (n)	Benign (n)	Malignant (n)	Benign (n)	Malignant (n)	Benign (n)	Malignant (n)	Benign (n)
Malignant	94	71	23	85	9	78	16	91	3
Benign	64	15	49	7	57	11	53	2	62

CEUS = contrast-enhanced ultrasonography, SWE = shear wave elastography, US = conventional ultrasonography.

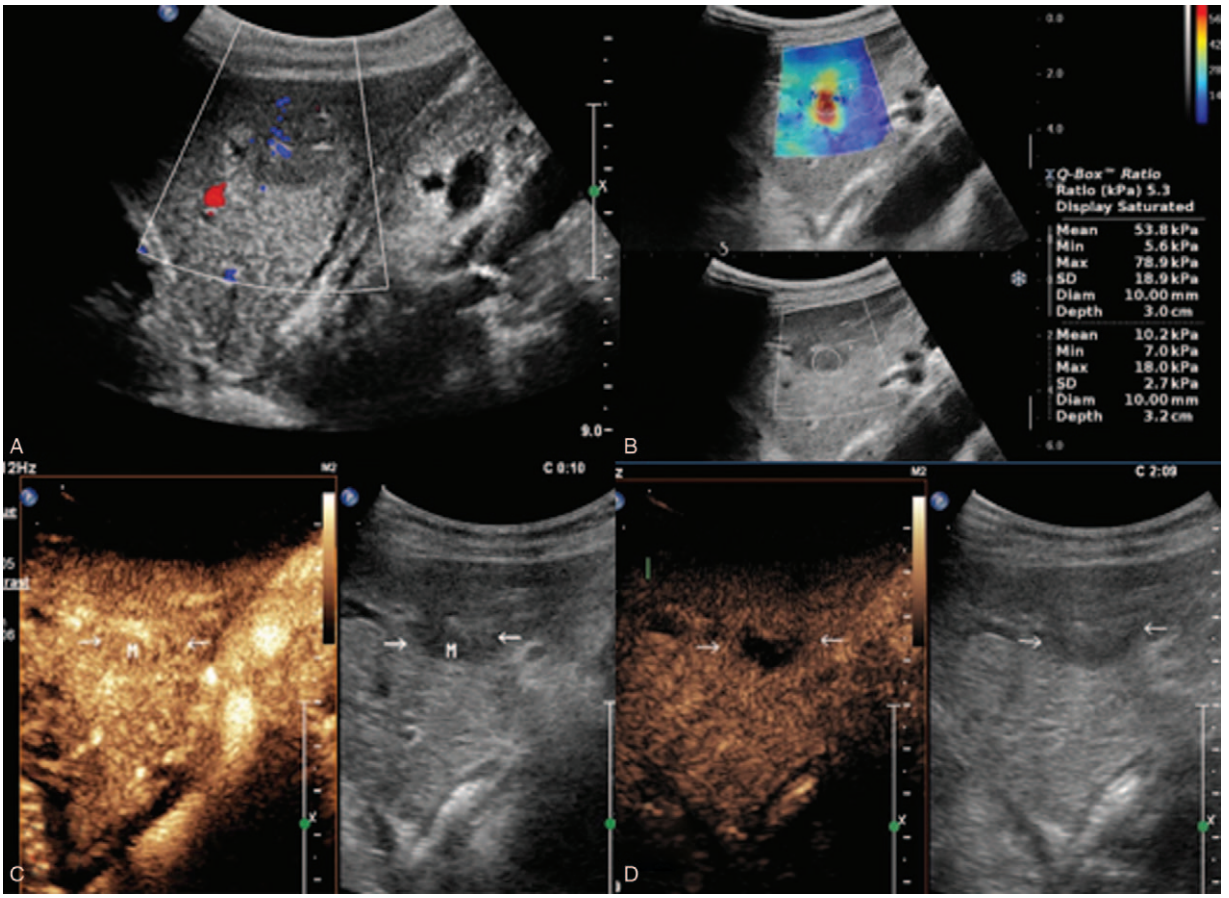

Figure 7. The US examination revealed that there was a hypoechoic irregular tumor, and the boundary with the bile duct was not clear, no obvious blood flow signal (A). The SWE examination found that the hardness value of the tumor was significantly larger than the hardness of the surrounding liver tissue (B). The CEUS examination revealed that the contrast agent in the tumor was rapidly filled during the arterial phase and cleared during the delay period (C, D). Pathological diagnosis is intrahepatic cholangiocellular carcinoma and infiltration around. CEUS = contrast-enhanced ultrasonography, SWE = shear wave elastography, US = conventional ultrasonography.

enhancement and 31 lesions with peripheral nodular enhancement. Analysis of the enhancement types of the examined lesions showed that 89, 29, 4, 3, and 33 lesions were of the enhanced clearance type, sustained enhancement type, non-enhancement type, hypoenhancement type, and centripetal progression type, respectively. Among the 158 examined lesions, 92 and 66 lesions were categorized as malignant and benign, respectively, based on CEUS findings. A comparison of CEUS-based diagnoses with pathology- or imaging-based diagnostic results revealed that 9 malignant tumors were misdiagnosed as benign and 7 benign tumors were misdiagnosed as malignant. The details were presented in Table 2.

3.3. SWE results

Among the 158 tumors, 89 tumors had a critical value ≥39.60 kPa, and 69 tumors had a critical value <39.60 kPa. A comparison of SWE-based diagnoses with pathology- or imaging-based diagnostic results revealed that 16 malignant tumors with an Emax value lower than the cut-off value were misdiagnosed as benign and that 11 benign tumors with an Emax value higher than the cut-off value were misdiagnosed as malignant. The details were presented in Table 2.

3.4. Multimodal ultrasound imaging diagnostic results

Tumors' sonographic presentations in US, CEUS, and SWE were comprehensively analyzed. Among the 158 tumors diagnosed using multimodal ultrasound imaging, 93 tumors were diagnosed as malignant (Fig. 7), and 65 tumors were diagnosed as benign (Fig. 8). In addition, 3 malignant tumors were misdiagnosed as benign, and 2 benign tumors were misdiagnosed as malignant. The details were presented in Table 2.

3.5. Pathological or imaging diagnostic results

A total of 158 tumors in 136 patients were included in this study; 33, 101, and 24 tumors were diagnosed via puncture biopsy, surgical pathology, and CECT or CEMR imaging, respectively. Typical presentation on CECT or CEMR imaging and more than 6 months of follow-up could be used as the diagnostic standards, for cases that cannot obtain histopathological results, use the diagnostic results of imaging as a reference standard. Among the 159 tumors, there were 64 benign tumors (55 cases of hepatic hemangioma, 3 cases of focal nodular hyperplasia (FNH), 4 cases of hepatic cyst, and 2 cases of focal nonuniform distribution of fat in the liver) and 94 cases of malignant tumors (32 cases of HCC, 22 cases of intrahepatic cholangiocellular carcinoma, 29 cases of

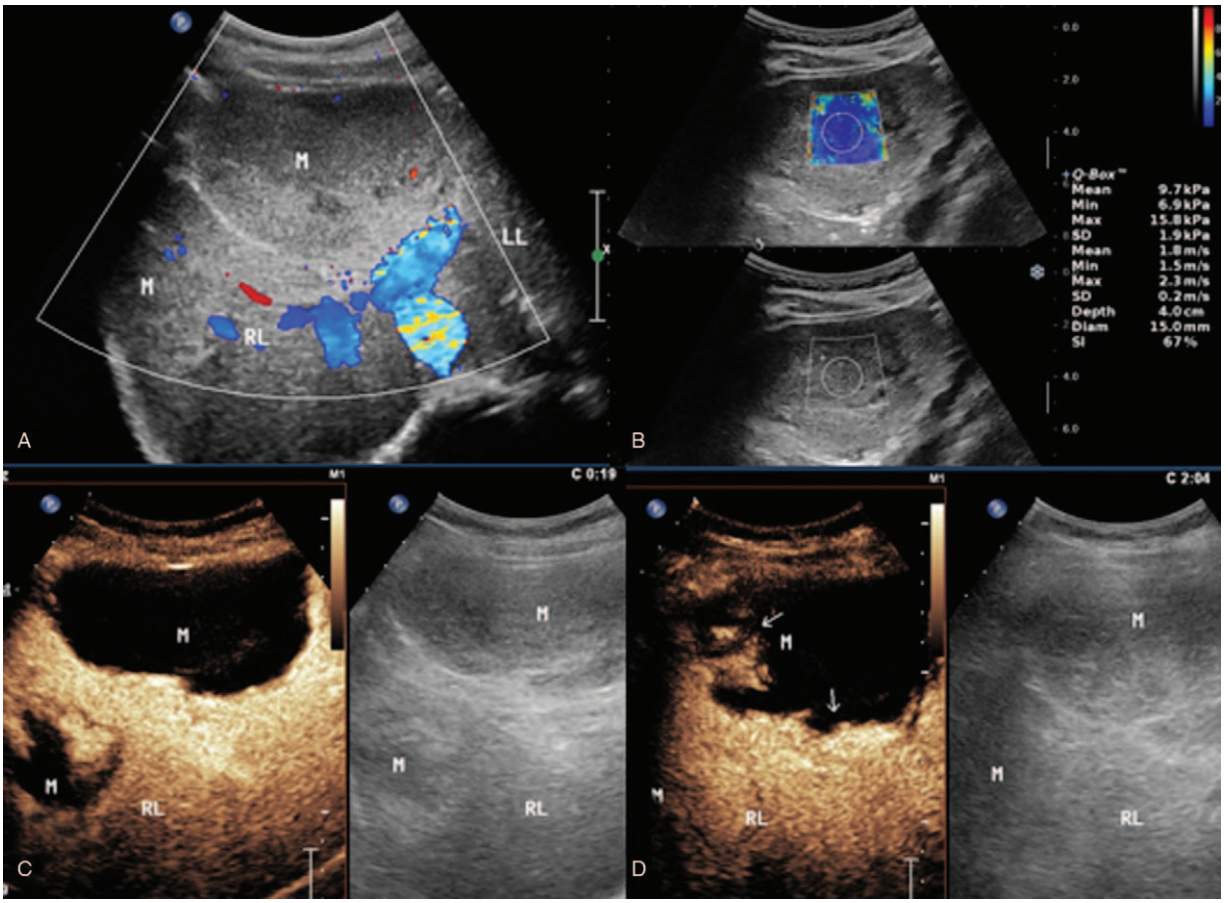

Figure 8. US examination revealed large tumor in the right lobe of the liver, and color Doppler examination did not detect significant blood flow signals (A). The SWE examination detected that the color of the tumor is uniform blue (B). The CEUS examination revealed that peripheral nodular enhancement in the arterial phase, centripetal filling of the contrast agent in the late phases (C, D). Pathological diagnosis is hemangioma. CEUS = contrast-enhanced ultrasonography, SWE = shear wave elastography, US = conventional ultrasonography.

metastatic liver cancer, and 11 cases of dysplastic nodules in cirrhotic liver). The details were presented in Table 3.

3.6. Comparison of the performance among US, CEUS, SWE, and multimodal ultrasound imaging in the diagnosis of benign and malignant liver tumors

The diagnostic performance of CEUS was better than those of US and SWE, and the diagnostic performance of SWE was better than that of US. The diagnostic sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of multimodal ultrasound imaging were all higher than those of US, CEUS, and SWE. The details were presented in Table 4. According to the receiver operating characteristic curves plotted based on the regression equation, the AUCs were 0.760, 0.897, 0.829, and 0.968 for US, CEUS, SWE, and multimodal imaging, respectively (Fig. 9).

4. Discussion

US is the most commonly used liver tumor screening method, including 2-dimensional grayscale ultrasonography and color Doppler ultrasonography. Two-dimensional grayscale ultrasonography can observe the morphological presentations of tumors, and color Doppler ultrasonography can supplement 2-dimensional US to increase the diagnostic sensitivity.[8,9] Among the 158 tumors in this study, there were 64 benign foci and 94 malignant foci. Using tumor morphology, boundary, internal echo, and blood flow signal as the observation indicators in conventional US to compare benign and malignant liver tumors, the majority of benign and malignant liver tumors had regular morphology and clear boundary. Some studies[10,11] have indicated that the difference in the internal echo between benign and malignant tumors is caused by different pathological tissue

Table 3

Pathological or CECT or CEMRI imaging diagnosis classification.

Disease classification	Number (n)	Puncture biopsy	Surgical pathology	CECT or CEMRI
Hepatocellular carcinoma	32	0	32	0
Intrahepatic cholangiocarcinoma	22	0	22	0
Metastasis liver cancer	29	16	13	0
Dysplastic nodule	11	7	4	0
Hepatic hemangioma	55	7	28	20
Focal nodular hyperplasia	3	1	2	0
Hepatic cyst	4	0	0	4
Uneven liver fat distribution	2	2	0	0

Table 4

Diagnostic performance of US, CEUS, SWE, multi-model ultrasound in 158 Lesions in 136 patients.

Methods	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
US	82.56	68.06	75.95	75.53	76.56
CEUS	92.39	86.36	89.87	90.43	89.06
SWE	87.64	76.81	82.91	82.98	82.81
Multimodal ultrasound imaging	97.85	95.38	96.83	96.81	96.88

CEUS = contrast-enhanced ultrasonography, SWE = shear wave elastography, US = conventional ultrasonography.

components in tumors. Benign tumors are mostly of the hyperechoic type, and malignant tumors are mainly of the hypoechoic type, which is consistent with the results in this study. In this study, the presence of blood flow signals in tumors was the most sensitive indicator for the differential diagnosis of benign and malignant tumors in conventional US. The majority of benign tumors did not have obvious blood flow signals, whereas a small portion of benign tumors, such as FNH, had blood flow signals. Malignant tumors generally have a rich blood supply or vasa vasorum; therefore, blood flow signals can be detected. However, among the 94 malignant cases in this study, blood flow signals were not detected in 30 cases. It is possible that the blood flow rate in the tumors was lower and the sound velocity angle of blood flow or tumor location was deeper, thus causing errors in examinations. The results of this study showed that the diagnostic performance of using only conventional US in the differentiation between benign and malignant liver tumors was lower and could not meet the clinical requirement.

As an emerging noninvasive ultrasound imaging technology, CEUS can dynamically and sensitively display the morphology and flow of small blood vessels in real time to reflect the blood supply in tumors. CEUS is extensively applied in clinical practice and is the most well-developed method for liver imaging.[12] The Guidelines and Good Clinical Practice Recommendations for CEUS in the Liver (2012 edition) developed by the European Federation of Societies for Ultrasound in Medicine and Biology and World Federation for Ultrasound in Medicine and Biology[13] point out that the arterial phases of liver benign tumors mainly exhibit hyperenhancement, whereas the portal venous phases and delayed phases exhibit persistent hyperenhancement or iso-enhancement. The typical presentations of malignant tumors are rapid hyperenhancement in the arterial phases and hypoenhancement in the portal venous or delayed phases. However, there is an overlap of enhancement between the benign and malignant tumor foci, and the time nodes of classification of these 3 phases do not have very uniform standards. The observation of the enhancement and washout of diseased tissues relies on observation by the naked eye, and there is a lack of objective and unified quantitative diagnostic criteria, which reduces the diagnostic rate of CEUS to a certain extent. The TIC curve in CEUS can quantitatively evaluate blood supply and blood flow perfusion conditions in tumors and has high sensitivity and specificity.[14,15] SWE quantitatively evaluates information on tissue hardness using the Young's modulus value of tissues obtained from real-time SWE based on 2-dimensional images. A higher Young's modulus value and redder color indicate harder tissue, whereas a lower Young's modulus value and bluer color indicate softer tissue. SWE is extensively applied in the diagnosis of tumors of the thyroid gland and mammary gland.[16] SWE can differentiate between benign and malignant tumors because the hardness of biological tissues reflects their nature to a certain extent.[17] Pathological tissues differ between benign and malignant liver tumors. The interior of hepatic hemangioma is composed of blood vessel lumens with different diameters and different amounts of fibrous tissues. Blood vessel lumens show cystic expansion and form blood sinuses. The blood content in blood sinuses is high; therefore, the property is soft, but the hardness is higher than that of normal liver tissues.[18] The Emean value of hepatic hemangioma positively correlates with its diameter. When the diameter of hepatic hemangioma is larger, the content of fibrous blood vessels, the hardness, and Young modulus are higher.[19] Liver cancer is mainly composed of dense cancer nest tissues and can invade surrounding tissues to induce hyperplasia and the adhesion of surrounding tissues, thereby increasing hardness. Therefore, Young modulus of liver cancer is higher than those of hepatic hemangioma and normal liver tissues.[20] The results of this study indicated that SWE technology can quantitatively analyze the hardness values of liver tumors and has higher accuracy in differentiating between benign and malignant liver tumors, which is consistent with results reported by Guo et al,[21] and, the moderate improvement of the diagnostic performance of CEUS by SWE.

A total of 32 tumors in this study were HCC, of which 28 showed hyperenhancement in the arterial phases and hypo-enhancement in the portal venous and delayed phases. The Emax value were higher than that in benign tumors. However, in 4 cases, the delayed phases still exhibited iso-enhancement, and the surface was in "fast wash-in and equal wash-out" enhancement

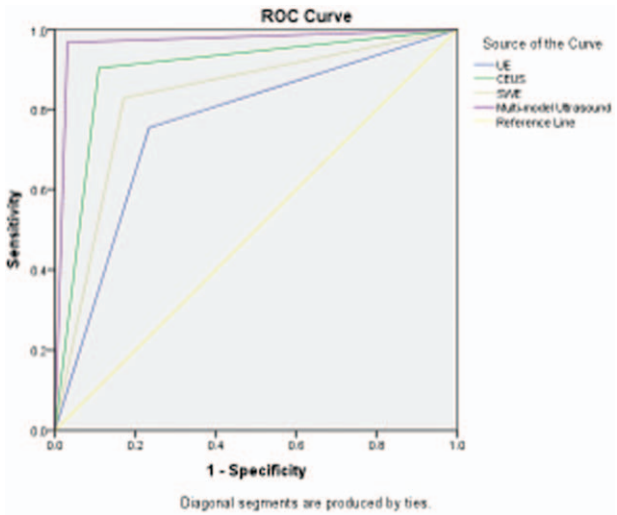

Figure 9. ROC curves of US, CEUS, SWE in evaluating benign and malignant Liver tumor. CEUS = contrast-enhanced ultrasonography, ROC = receiver operating characteristic, SWE = shear wave elastography, US = conventional ultrasonography.

mode; these tumors could easily be misdiagnosed as liver benign tumors. However, SWE showed that the Young's modulus value was higher, and pathological diagnosis showed highly differentiated HCC. It has been reported that a small proportion of well-differentiated HCC might exhibit iso-enhancement or slight hyperenhancement in the portal venous or delayed phases, whereas some highly differentiated or poorly differentiated HCC may exhibit hypoenhancement in all 3 phases.[22] Some study data also indicate that the Young's modulus value of liver tumors is associated with pathological differentiation types. As the differentiation level decreases, Young modulus increases because the cancer cell density of poorly differentiated liver cancer is high, and there are fewer sinusoidal lumen spaces than in highly differentiated liver cancer.[23] In this study, there were 29 cases of metastatic liver cancer. The CEUS arterial phases showed homogenous or heterogeneous hyperenhancement, and a small proportion exhibited peripheral annular hyperenhancement. The differences in enhancement in these methods may reflect the relative richness of the blood supply of the primary focus of the tumors. Studies have shown that the arterial phases of metastatic liver cancer with a rich blood supply mainly exhibit homogenous or heterogeneous hyperenhancement, whereas the arterial phases of metastatic liver cancer with a poor blood supply mainly exhibit peripheral annular hyperenhancement.[24] However, the majority of metastatic liver cancers begin to clear in the early portal venous or late arterial phases. The delayed phases exhibit significant hypoenhancement. For very small metastatic liver cancers, the delayed phases also show the "black hole" sign observed under the homogenous enhancement background in normal liver. Therefore, when metastatic liver cancer is suspected, a whole liver scan should be performed in the delayed phase to identify small metastatic foci that are difficult to find by conventional US. However, some metastatic liver cancers with larger tumor bodies are prone to liquefaction and necrosis, in which case no enhancement will be observed in the necrotic region in all 3 phases; therefore, SWE examination should avoid the necrotic region as much as possible. In this study, the enhancement morphology in the arterial phases of the 22 cases of ICC was mainly peripheral annular hyperenhancement, with washout starting in the early portal venous phases and clearance in the delayed phases. CEUS of some cholangiocarcinomas is similar to metastatic liver cancer. The levels of hardness of metastatic liver cancer and ICC are both higher than those of HCC.[25] In this study, the benign liver tumors were mainly hepatic hemangioma. The imaging presentations of the majority of the hepatic hemangiomas were peripheral nodular enhancement in the arterial phases followed by slow partial or full centripetal filling. Sites of thrombosis and fibrous tissue in hemangioma typically do not show enhancement and are easily mistaken as clearance. The Emax value of fibrotic hemangioma are also higher and can be easily mistaken as metastatic liver cancer. Some of the hepatic hemangioma in this study showed "fast wash-in and fast wash-out." After analyzing the potential reasons, we concluded that the most likely reason was the presence of an arteriovenous fistula in hepatic hemangioma. One case of FNH in this study was misdiagnosed as hepatic hemangioma, the enhancement pattern was homogenous hyperenhancement in the arterial phases, mild hyperenhancement in the portal venous phases, and iso-enhancement in the delayed phases, and the "fast wash-in and slow wash-out" perfusion mode was observed. Because the imaging presentation was not typical, this case was misdiagnosed as hepatic hemangioma. FNH contains a large number of fibrous septa, and the presentation is slightly harder nodules. The typical imaging presentations are rapid centrifugal enhancement from the center in the arterial phases and central stellate scars with hypoenhancement or no enhancement in the portal venous or delayed phases.[10] In our clinical manipulation, the method could be switched to color Doppler to use the remaining microbubbles to enhance the Doppler signals in order to increase the display of spoke-wheel blood vessels. However, it is difficult to distinguish between FNH and liver malignant tumors via SWE. The focal nonuniform distribution of fat in liver can be divided into 2 conditions. The first condition is focal fatty infiltration. The usual presentation is local patchy hyperechoic presentation. US has higher diagnostic performance. The second condition is focal fatty sparing, which has a hypoechoic presentation and can be difficult to identify using US. However, CEUS allows a clear diagnosis. The imaging presentations in the 3 phases are all iso-enhancement, which is consistent with the enhancement pattern and level of surrounding liver parenchyma.[26] Dysplastic nodules in cirrhotic liver are precancerous tumors of HCC. These tumors can also be enhanced together with the surrounding liver parenchyma.[27] In this study, the early presentation of arterial phases in 3 cases was hypoenhancement, and the portal venous phases and delayed phases had iso-enhancement. It is possible that, during the transformation of hyperplastic nodules into dysplastic nodules, arterial blood flow in the nodules decreases while new arterial blood vessels have not yet been generated; thus, blood is mainly supplied by the portal vein.[28] Some studies[29] have noted fast wash-in and slow wash-out when hyperplastic nodules develop into atypical hyperplastic nodules and precancerous tumors. To differentiate between small liver cancers and dysplastic nodules in cirrhotic liver, SWE had low sensitivity and low specificity in this study, while CEUS was superior to computed tomography and magnetic resonance imaging.[30]

5. Conclusion

In summary, multimodal ultrasound imaging has complementary advantages, particularly for liver tumors with atypical ultrasound presentation and unclear diagnosis or that are difficult to define via a single examination method. For these tumors, multimodal ultrasound imaging can supplement the diagnosis results to provide a reliable theoretical basis for the differential diagnosis of liver tumors; therefore, multimodal ultrasound imaging has favorable prospects for clinical application.

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