Original Article
The clinical value of contrast-enhanced ultrasound and quantitative analysis parameters in the diagnosis and classification of portal vein tumor thrombus

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Abstract: Objective: To explore the application of contrast-enhanced ultrasound (CEUS) in the diagnosis and classification of portal vein tumor thrombus (PVTT) by means of contrasting with enhanced CT, and to analyze the clinical value of quantitative analysis parameters in PVTT. Methods: A total of 93 PVTT patients confirmed by clinic and pathology were recruited. The diagnostic and clinical classification accuracy rates were compared between CEUS and enhanced CT. And draw the ROC curve to calculate the accuracy, sensitivity, specificity rate and area under the curve (AUC) of the two methods. The arrival time (AT), time to peak (TTP), rise time (RT), peak intensity (PI), rising-slope rate (RSR), washout time (WT) and AUC of contrast agents in PVTT and surrounding liver tissue were analyzed by time-intensity curve. Results: There was no statistical difference in the PVTT pathological types among different HCC diameters. The CEUS performance of PVTT was "fast-in and fast-out". The accuracy, sensitivity and specificity rate of CEUS in the diagnosis of PVTT was 100%, 97.8% and 90.2%, respectively; and those of CECT were 97.7%, 96.7% and 86.4%. The AUC of the two methods were 0.939 and 0.933. The accuracy, sensitivity and specificity rate of CEUS in the classification of PVTT was 97.8%, 96.2% and 85.6%, respectively; and those of CECT were 96.7%, 95.6% and 81.9%. The AUC of the two methods were 0.889 and 0.828. There was no statistical difference in the PVTT diagnosis and classification of two methods. Compared to the surrounding liver tissue, the perfusion curve showed "fast-up and fast-down" in PVTT, and the differences of AT, TTP, RT, PI, RSR, WT and AUC between PVTT and the surrounding liver tissue were statistically significant (P<0.05). Conclusion: CEUS and enhanced CT have well consistency in the diagnosis and classification of PVTT. CEUS can visualize the morphological character of the time intensity curve in the perfusion area. As an important imaging method in the evaluation of PVTT before treatment, CEUS can provide accurate quantitative imaging information to clinicians.

Keywords: PVTT, CEUS, enhanced CT, classification

Introduction

Hepatocellular carcinoma (HCC) has insidious onset, most patients are already in the late period in their first diagnosis, and about 30%-40% of the patients are combined with visible PVTT. Over 90% of the patients have microvascular violations in autopsy [1, 2]. HCC combine with PVTT is the biological mark of the advanced HCC and it is a special clinical expression of HCC malignant behavior. Its formation involves many anatomy and biology mechanisms [3].

Early correct diagnosis and classification are very important in treatment planning, objective evaluation of the efficacy and prognosis determination. At present, enhanced CT is an important imaging method in evaluating PVTT. The value of contrast-enhanced ultrasound (CEUS) in hepatic lesions has been approved by clinicians, but the research about diagnosis and classification of PVTT are rare, and there is no research involves quantitative analysis of PVTT. In this study, we explored the application of CEUS in the diagnosis and classification of

Table 1. PVTT pathological type of different maximum diameters of HCC (n)

HCC maximum diameter	Cases	Type I	Type II	Type III	Type IV
<3 cm	12	2 (16.7%)	3 (25.0%)	5 (41.7%)	2 (16.7%)
3-5 cm	26	5 (19.2%)	8 (30.8%)	9 (34.6%)	4 (15.4%)
>5 cm	55	1 (18.2%)	17 (30.9%)	19 (34.5%)	9 (16.4%)
Total	93	17 (18.3%)	28 (30.1%)	33 (35.5%)	15 (16.1%)

Note. PVTT: portal vein tumor thrombus. HCC: hepatocellular carcinoma.

PVTT by means of contrasting with enhanced CT, and analyzed the clinical value of quantitative analysis parameters in PVTT.

Materials and methods

Patients

This study was approved by the Institution Review Board of Guangxi Medical University and an informed consent was obtained from each patient. A total of 93 patients (167 lesions) with HCC combined PVTT confirmed by clinic and pathology in Affiliated Tumor Hospital of Guangxi Medical University between January 2014 and June 2015 were retrospectively analyzed. Among them, there were 58 male cases and 35 female cases, aged between 26 to 71 years old, average age was 43.8 years old. For the 167 lesions, the maximum diameters of HCC lesions were 1.2 to 9.8 cm, average (5.23±1.76) cm. We divided the PVTT patients into three groups according to the maximum diameter of HCC, 12 cases were <3 cm, 26 cases were 3 to 5 cm, 55 cases were >5 cm. The patients were suffered with abdominal discomfort, weight loss and long-term history of hepatitis B. All patients underwent CEUS and enhanced CT examination before surgery. Inclusion criteria: (1) PVTT and the surrounding liver tissue quantitative analysis area were fixed on the same section from the beginning of CEUS, and ultrasonic imaging should be at least 2 minutes continuous observation; (2) Breathing and heartbeat movement did not have a serious impact in CEUS observation and quantitative analysis; (3) The surrounding liver tissue of PVTT was enough to proceed quantitative analysis.

Instrument and methods

Instrument: GE E9 Color Doppler Ultrasonic Diagnosis Apparatus (Probe frequency 2~4 MHz) was applied in this study, it built with coded phase inversion mode (CPI) and Tru agent detection (TAD), mechanical index (MI)range were set between 0.08 and 0.2. Time-intensity curve (TIC) analysis software (wash-in/wash-out) and Sonovue contrast agent (Sonovue, Italian Bracco Corporation) were used.

CEUS: First, we scanned hepatic lobules, segment, portal vein trunk and branches with conventional ultrasound. Then we entered the CEUS model, 5 ml 0.9% NaCl was compatible with SonoVue into 5 mg/ml of sulfur hexafluoride microbubbles suspensions, and then bolus injected through elbow intravenous within 2 to 3 seconds, 2.4 ml each time, then 5 ml 0.9% NaCl solution was used for pipe washing. The real-time continuous observation was lasted for 5 min. After injection, arterial phase was 10 to 30 seconds, portal phase was 31 to 120 seconds, and delay phase was after 120 seconds.

Image diagnosis and quantitative analysis: The echo of PVTT, interior blood flow, its relation with the surrounding structures, and CEUS features were evaluated by experienced doctors. The definition of high/equal/low enhancement was the enhancement of PVTT was higher/ equal to/lower than the surrounding liver tissue. The classification of PVTT was according to the concept raised by Shanghai Eastern Hepatobiliary Hospital, Second Military Medical University: type I: tumor thrombosis involving the second-class or above portal branches; type II: tumor thrombosis involving the first-class portal branches; type III: thrombosis involving the portal trunks; type IV: thrombosis involving the superior mesenteric vein or inferior vena cava [4]. The CEUS imaging of DICOM form was exported for quantitative analysis, and then we started the TIC analysis software to analyze TIC. We lined out the PVTT region and liver tissue on the same level as regions of interests (ROI), and got the following contrast perfusion parameters through Gamma function fitted curve which reflected bolus tracer dilution principle: the arrival time (AT), time to peak (TTP), rise time (RT, RT=TTP-AT), peak intensity (PI), rising-slope rate (RSR, RSR=PI/RT), washout time (WT) and area under the curve (AUC).
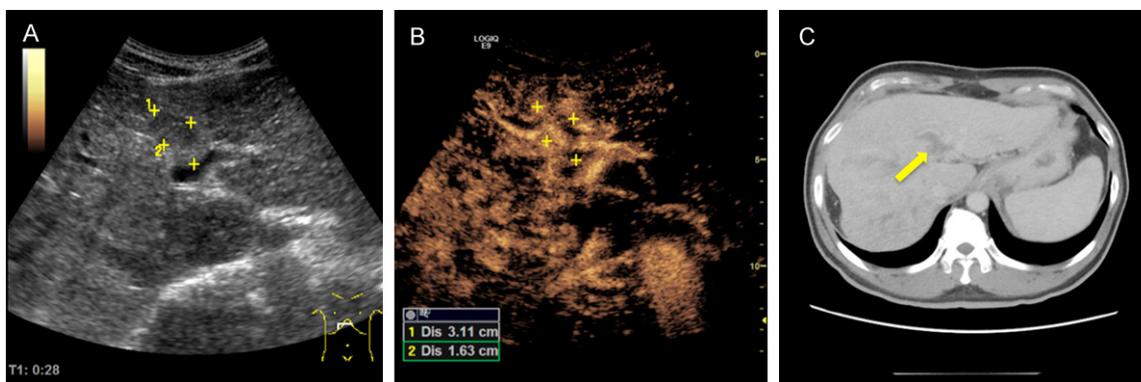
Figure 1. PVTT in sagittal section of portal vein. A: Conventional ultrasound imaging. B: CEUS imaging. C: Enhanced CT imaging.
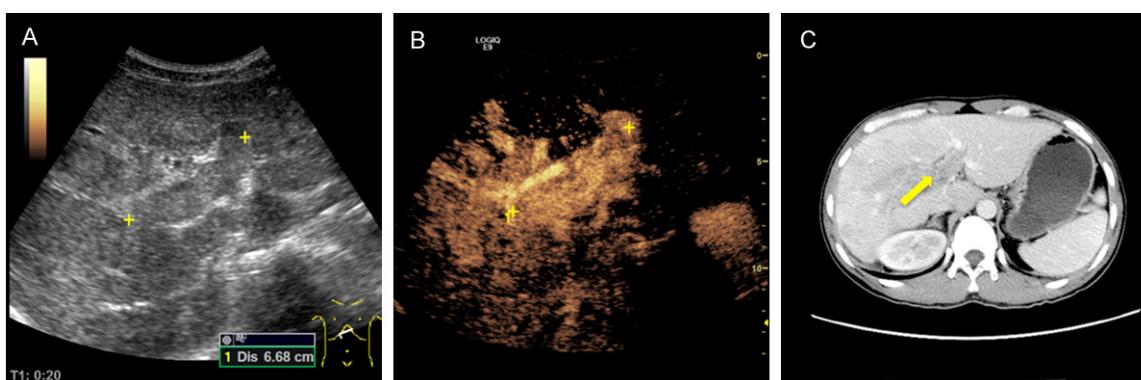

Figure 2. PVTT in left portal vein. A: Conventional ultrasound imaging. B: CEUS imaging. C: Enhanced CT imaging.

And we started the motion compensation function to avoid breathing effect.

Enhanced CT: GE OPTIMA CT660 64 ranks spiral CT was applied. Experienced CT doctors completed the examination.

Data analysis

Statistical analysis was performed with SPSS version 16.0 software (SPSS, Chicago, III). With post operation pathology as the gold standard, we draw the ROC curve to calculate the accuracy, sensitivity, specificity rate and AUC of CEUS and CECT in the diagnosis and classification. The AUC under the ROC curve were compared using Z-test. Measurement data was expressed by χ^2. ANOVA was applied in the comparison among each classification, and t test was adopted in the comparison among groups. P<0.05 was considered as significant statistical differences.

Results

PVTT pathological type of different maximum diameter of HCC

A total of 12 cases (12.9%) were <3 cm, 26 cases (28.0%) were 3 to 5 cm, 55 cases (59.1%) were >5 cm. The PVTT classification of different maximum diameter of HCC was of no significant statistical difference (χ^2=10.34, P>0.05). Detailed in **Table 1**.

Conventional ultrasound and CEUS results for PVTT

For conventional ultrasound results, among 93 cases of PVTT, there were 62 cases showed low level echo (66.7%), 29 cases of equal echo (31.2%) and 2 cases of high echo (2.1%). Among these cases, there were 57 cases (61.3%) showed sparse blood flow signals inside the PVTT, and the signals were confirmed to be
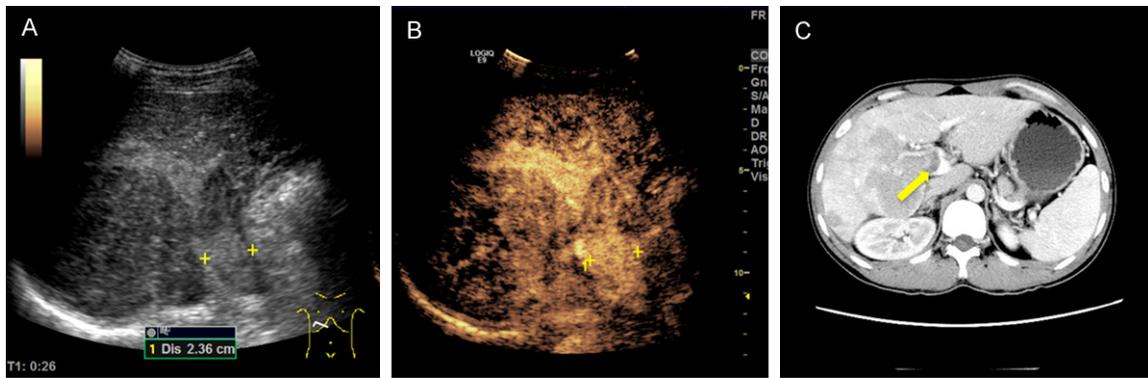
Figure 3. PVTT in portal vein trunk. A: Conventional ultrasound imaging. B: CEUS imaging. C: Enhanced CT imaging.
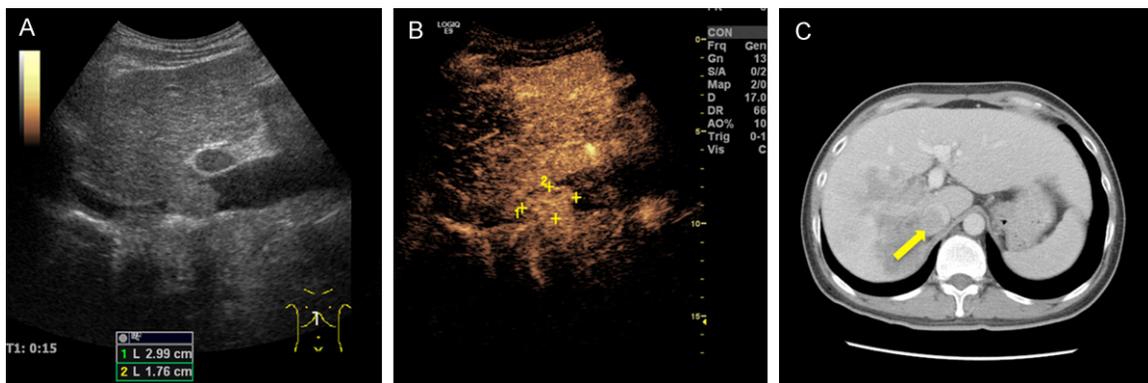

Figure 4. PVTT in the inferior vena cava. A: Conventional ultrasound imaging. B: CEUS imaging. C: Enhanced CT imaging.

mainly artery by spectrum. For CEUS, PVTT showed "fast-in and fast-out": 94.6% (88/93) of PVTT showed high enhancement in arterial phase; 80.6% (75/93) showed low enhancement in portal phase; and all PVTT (93/93) showed low enhancement in delayed phase.

Results of CEUS and enhanced CT in the diagnosis and classification for PVTT

The diagnostic accuracy rate of PVTT for CEUS was 100%, while enhanced CT was 97.7% (92/93), enhanced CT misdiagnosed 1 case of type I PVTT as thrombus; the differences between the two examination was of no statistical significance (P>0.05). The classification accuracy rate of CEUS was 97.8% (91/93), and that of enhanced CT was 96.7% (90/93), 2 cases of type III PVTT were misdiagnosed as type II by CEUS and enhanced CT; the differences between the two examination was of no statistical significance (x^2=2.79, P>0.05). Detailed in **Figures 1**-**4**. With post operation

pathology as the gold standard, ROC curves were obtained (**Figure 5**). The accuracy, sensitivity and specificity rate of CEUS in the diagnosis of PVTT was 100%, 97.8% and 90.2%, respectively; and those of CECT were 97.7%, 96.7% and 86.4%. The AUC of the two methods were 0.939 and 0.933. The accuracy, sensitivity and specificity rate of CEUS in the classification of PVTT was 97.8%, 96.2% and 85.6%, respectively; and those of CECT were 96.7%, 95.6% and 81.9%. The AUC of the two methods were 0.889 and 0.828. There was no statistical difference in the PVTT diagnosis and classification of two methods (P>0.05).

Results of the perfusion curve shape in the quantitative analysis zone and CEUS quantitative parameters of PVTT and the surrounding liver tissue

Results of the perfusion curve shape in the quantitative analysis zone: The perfusion curve showed "fast-up and fast-down" in PVTT com-
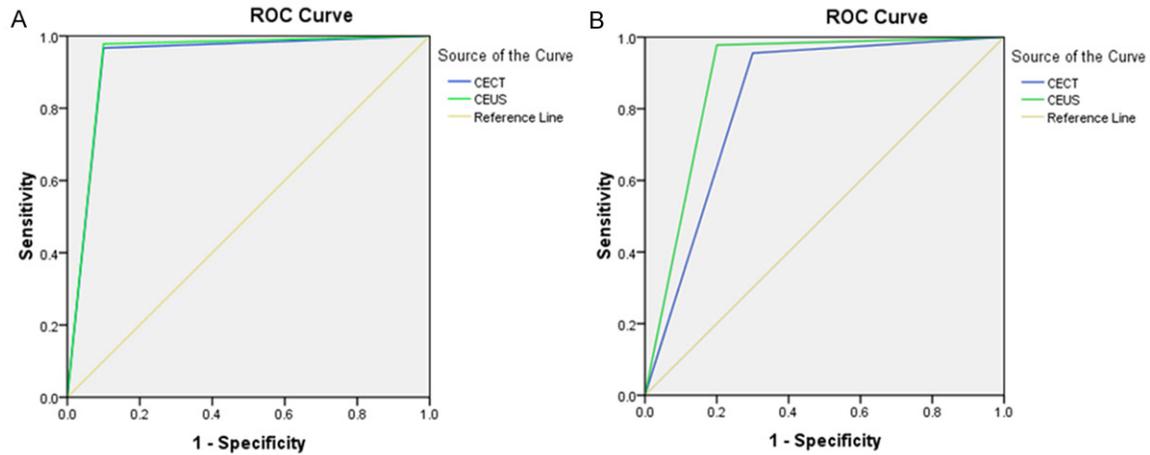
Figure 5. ROC curve for CEUS and CECT in the diagnosis and classification of PVTT. A: ROC curve of PVTT diagnosis. B: ROC curve of PVTT classification.
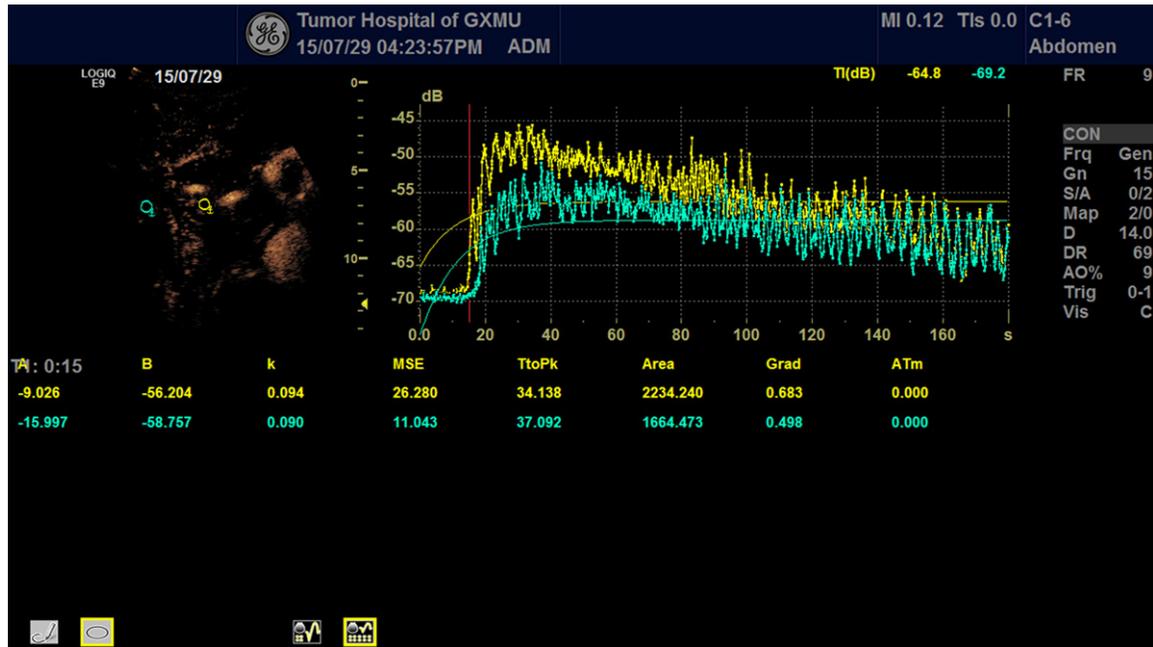

Figure 6. The Time-intensity curve of PVTT and the surrounding liver tissues.

pared to the surrounding liver tissue (the AT, TTP and RT were earlier in PVTT than the surrounding liver tissue, PT and RSR were higher in PVTT, and WT was lower in PVTT). Detailed in **Figure 6**. The differences of AT, TTP, RT, PI, RSR, WT and AUC among each PVTT type were not statistically significant (P>0.05). The differences of AT, TTP, RT, PI, RSR, WT and AUC between PVTT and the surrounding liver tissues were statistically significant (P<0.0001). Detailed in **Tables 2**, **3** and **Figure 7**.

Discussion

HCC is one of the most common malignant tumors in China, and Guangxi province is one of HCC high incidence areas in China, the mortality rate of HCC is the highest among malignant tumors in Guangxi province [5]. The most common transfer and relapse way of HCC is spread inside the liver by portal system. PVTT is a severe complication and important transfer way for HCC and it is an important factor to

Table 2. CEUS quantitative parameters of PVTT and the surrounding liver tissue ($\bar{x}\pm S$)

Type	No.	AT (s)	TTP (s)	RT (s)	PI (dB)	RSR (db/s)	WT (s)	AUC
PVTT	93	10.12±4.37	31.31±5.49	21.39±4.11	36.15±5.99	1.24±0.22	97.38±5.61	2225±228
Liver	93	14.02±4.82	38.96±6.94	24.86±5.21	29.94±7.41	0.89±0.14	108.18±4.52	1664±187
T value		8.99	7.67	6.37	5.84	9.11	4.65	7.14
P value		*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001

Note. CEUS: contrast-enhanced ultrasound. PVTT: portal vein tumor thrombus. AT: arrival time. TTP: time to peak. RT: rise time. PI: peak intensity. RSR: rising-slope rate. WT: washout time. AUC: area under the curve.

Table 3. CEUS quantitative parameters of PVTT ($\bar{x}\pm S$)

Type	No.	AT (s)	TTP (s)	RT (s)	PI (dB)	RSR (db/s)	WT (s)	AUC
I	17	9.53±3.39	30.35±5.93	21.25±3.96	36.28±6.22	1.25±0.15	98.36±4.89	2234±237
II	30	9.62±2.98	30.79±5.51	21.01±4.39	35.84±5.75	1.29±0.17	99.31±5.97	2199±206
III	31	10.23±3.92	31.91±4.89	20.92±4.56	34.95±6.29	1.18±0.23	96.16±5.41	2168±199
IV	15	9.97±4.25	31.79±5.68	21.35±4.34	36.23±5.59	1.34±0.29	97.33±4.90	2245±233
F		3.91	2.88	2.77	5.32	2.17	4.19	3.64
P value		P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05

Note. CEUS: contrast-enhanced ultrasound. PVTT: portal vein tumor thrombus. AT: arrival time. TTP: time to peak. RT: rise time. PI: peak intensity. RSR: rising-slope rate. WT: washout time. AUC: area under the curve.
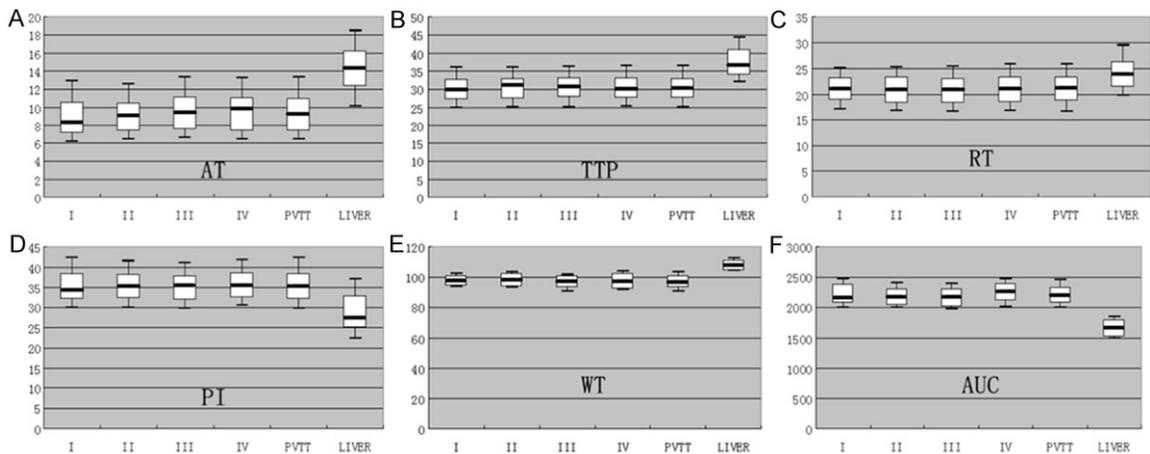

Figure 7. The comparison box plot of different types PVTT and the surrounding liver tissues. A: Arrival time (AT). B: Time to peak (TTP). C: Rise time (RT). D: Peak intensity (PI). E: Washout time (WT). F: Area under the curve (AUC).

affect resection rate and prognosis. Studies have pointed out that PVTT is the strongest independent factor in the prognosis of the HCC patients [6]. In this study, PVTT occupied 59.1% in patients with HCC maximum diameter >5 cm, which was significantly higher than <3 cm and 3-5 cm. This may be the reason that larger HCC has a longer growth time, and the violated area of the surrounding portal veins is larger, and at the same time, it may press hepatic veins to exacerbate countercurrent of the venous blood. These lead to PVTT appearance.

While in this study, the PVTT classification of different maximum diameter of HCC was of no significant statistical, which prompt that the PVTT pathological type was not related to HCC maximum diameters.

At present, the diagnosis and classification of PVTT mainly depend on imaging technology. Conventional ultrasound and enhanced CT are the most common noninvasive imaging techniques [7]. Conventional ultrasound can provide continuous observation to the total portal

system inside/outside the liver and its relation with the surrounding structures, and it is the first choice to diagnose PVTT [8]. Conventional ultrasound can judge PVTT mainly through the features of abnormal substantive echo, blood-filling defect, expansion of the blocked lumen, and cavernous transformation appears in the portal vein lumen. Blood supply inside embolus is the most direct evidence to distinguish PVTT and thrombus, and it is also the main standard for imaging technology in judging PVTT. Color Doppler ultrasound can reflect the arterial blood supply of tumor thrombus by detecting the artery spectrum. But the arteries are very small and the flows are slow inside tumor thrombus, and some tumor thrombus has a deep location, which will limit the detection rate of Color Doppler ultrasound for tumor thrombus. In this study, most PVTT (91 cases, 97.8%) had infiltrative growth, low or equal level echo and had no obvious comparison with the surrounding liver tissue, therefore conventional ultrasound could not make correct detection of the PVTT boundary. Only 57 cases (61.3%) of PVTT showed detectable blood flow signal with low speed, and 36 cases (38.7%) showed no obvious blood flow signal inside and peripheral the PVTT. These made Color Doppler ultrasound provided low sensitivity assessment of the blood flow inside PVTT. And conventional ultrasound could not evaluate the actual invasion range of PVTT, which brought bad accuracy in PVTT classification. Clinical doctors often have the aid of enhanced CT to clear-up diagnosis [9]. The enhanced CT diagnoses of PVTT mainly based on feeding artery intensify in arterial phase. Although enhanced CT has good space resolution, its time resolution is poor. In this study, there was 1 misdiagnosis case of type I PVTT, we find that the PVTT range was small and contrast flowed fast (Iohexol contrast had completely faded at the beginning of arterial phase scanning), it was misdiagnosed as thrombus. Therefore, PVTT shows fast enhancement and fast fade away in the early artery phase is easily to be misdiagnosed as thrombus, which will lead to false-negative diagnosis and low diagnosis sensitivity.

CEUS is a specificity technology that use contrast agent to enhance the back scattering echo, so as to enhance ultrasound resolution and diagnosis sensibility. CEUS can overcome the limitations of conventional ultrasound. The average diameter of contrast microbubbles is only 2.5 um, which is much less than the diameter of nutrient arteries inside the tumor thrombus. It can contribute to the evaluation of low velocity blood flow inside small blood vessels. Meanwhile, with the combination of ultrasound contrast imaging technology, CEUS can provide both anatomical and functional information in the radiography area [10-12]. CEUS has become an important imaging technology in noninvasive method to evaluate tissue micro-circulation and tumor neovascularization, its diagnosis sensitivity and accuracy are higher than conventional ultrasound [8, 13]. Ultrasound contrast agents are blood pool imaging agents. CEUS can increase the display and classification accuracy rate of PVTT by dynamically reflecting its perfusion characteristics and increasing acoustic impedance contrast of PVTT and the surrounding liver tissue. The pathophysiological and hemodynamic basis of CEUS is that PVTT and normal liver parenchyma are both double blood supplies, while hepatic arteries mainly supply PVTT while normal liver parenchyma is portal veins. The increase of newborn capillary makes an obvious increase of blood flow in PVTT. During CEUS, the agent enters the PVTT capillary network quickly in the artery phase, which can clearly show the distribution of capillary network inside PVTT. But PVTT intakes the contrast agent less after artery phase, while the surrounding liver tissue have an intake peak of the agent in the portal phase. Therefore, PVTT mainly shows low enhancement in the late portal stage and delay stage, and the surrounding liver tissue shows high enhancement. This increases the contrast of the both, and makes the boundary of PVTT clear. In this study, 88 cases (94.6%, 88/93) of PVTT showed high enhancement in the artery phase, 75 cases (80.6%, 75/93) showed low enhancement in portal phase, all cases showed low enhancement in the delay phase, the performance of CEUS was "fast-in, fast-out".

The classification of PVTT is mainly based on the violation of PVTT in different branches; CEUS can increase the ability of PVTT classification by showing the location and infiltration range of PVTT clearly. In this study, there was good consistency within CEUS and CECT in accuracy, sensitivity and specificity of the diagnosis and classification of PVTT. With further analysis of CEUS results, and we found that

there were 2 cases of type III PVTT were misdiagnosed as type II. We found that the PVTTs were located in the confluence of the left and right portal vein branches; the PVTTs were small and did not fill the lumen; the blood supply in the PVTTs was few; and the partial volume effect led to unclearance of the boundary. These reasons made wrong classification of the PVTT. And it also prompted us that conventional ultrasound should be combined when we classify the PVTT type, and dynamic scanning should be applied with multi-sections. The PVTT boundary and the violation of the portal vein must be clear to make accurate classification, which will benefit the clinical doctors in making reasonable treatment plan.

Although CEUS can show blood flow features dynamically, it can only show the enhancement and fade away of contrast agent, which is called "the change of the gray-scale". The judgments of CEUS results mainly rely on ultrasound doctors' subjective observation, which is lack of objective quantification standard. Based on CEUS, CEUS quantitative analysis can objectively reflect the perfusion features of PVTT area and the surrounding liver tissue through TIC curve and Gamma curve drawn by wash-in/wash-out software [14-19]. The forms and parameters of TIC curve are related to the structure and blood supply features of the organization. By comparing the time strength parameters, AT, TTP, RT, PI, RSR, WT and AUC of PVTT and the surrounding liver tissue were all different, while the differences among each type of PVTT were not significant. This means the difference between TIC parameter of PVTT and the surrounding liver tissue was significant, but the TIC parameters of different PVTT types are consistent. AT and TTP express the time when contrast agent enters into tissue microcirculation and the time when the agent reaches the peak. PI reflects the equilibrium state of the inflow and outflow of the contrast agents, which has a close relationship with the accumulation of the microbubbles. It can quantitative reflect the blood pouring state inside ROI by the peak intensity of the contract agent. PI and AUC reflect the total contrast agents entering or accumulating inside the tissue microcirculation in a unit time. RT, RSR and WT indirect reflect the rate of the contrast agents entering into tissue microcirculation. RT has a close relationship with the blood supply richness in artery phase, the smaller the RT, the bigger the RSR,

the smaller the WT, the faster the microbubbles enter and exit the tissue microcirculation [3, 14-19]. In this study, AT, TTP and WT of PVTT were less than the surrounding liver tissue, while PI, AUC and RSR are greater. In comparison with the surrounding liver tissue, PVTT showed "fast up and fast down" form, which is the same as "fast-in and fast-out" in CEUS. Through quantitative analysis of CEUS, we can use specific quantitative index to reflect the features of PVTT, so as to reduce the dependency of ultrasound doctors' subjective judgment. It can offer accuracy quantitative data of PVTT to clinical doctors, which is benefit in faster and better treatment planning for clinical doctors.

Conclusion

In conclusion, CEUS and enhanced CT have well consistency in the diagnosis and classification in PVTT. CEUS not only can dynamically display the blood flow features of PVTT, but also can show the actual infiltration range through enhancing the acoustic impedance contrast of PVTT and the surrounding liver tissue. CEUS can directly analyze TIC and show its morphological characteristics through wash-in/wash-out software to provide accurate quantization imaging information to clinical doctors. CEUS is an important imaging method to evaluate PVTT before treatment; it can offer help to clinical doctors in choosing treatment programs.

Disclosure of conflict of interest

None.

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