Imaging performance and clinical value of contrast-enhanced ultrasonography and computed tomography in the diagnosis of liver cancer

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Abstract. The imaging performance and clinical value of contrast-enhanced ultrasonography (CEUS) combined with CT in diagnosis of liver cancer were investigated. A total of 426 liver cancer patients treated in Yuhuangding Hospital (Yantai, China) from February 2011 to May 2016 were selected. Among them, 222 patients underwent CEUS examination, 204 patients underwent CT examination, and 102 patients underwent CEUS combined with CT examination. Sensitivity and specificity of the three methods were examined. CT showed a low density in 92.6% of patients (189 patients) and a high-low hybrid density in 6.4% (13 patients), with calcification seen in 2.5% of patients (5 patients) and bleeding in 3.4% (7 patients). Lesions: 76.5% (156 cases) of patients with multiple type, 23.5% (48 cases) with single type. CEUS showed overall enhancement in 53.2% patients (118 cases), heterogenous enhancement in 16.7% (37 cases), peripheral enhancement in 18.9% of patients (42 cases), necrosis of liquefaction in 11.3% (25 cases). In 65.3% (145 cases) of patients, the portal venous phase and the delayed phase showed a low enhancement, while 34.7% (77 cases) showed no enhancement. The sensitivity and specificity rates of CEUS combined with CT detection of liver cancer were 87.8, 88.2 and 94.1%, respectively. The ROC curve analysis showed that the sensitivity and specificity of CEUS in the diagnosis of liver cancer were 76.8 and 78.9%, respectively. The sensitivity and specificity of CT were 81.2 and 85.5%, respectively. The sensitivity and specificity of CEUS combined with CT were 90.4 and 92.7%, respectively. CEUS combined with CT detection can make-up for the deficiencies of each other and effectively improve the coincidence rate of liver cancer diagnosis, which can be used as an effective examination method for the diagnosis of liver cancer.

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Introduction

Liver cancer is one of the most common malignant tumors in the digestive system. The mortality rate is relatively high, and the early stage of liver cancer can be asymptomatic. Once the symptoms appear, most of the patients have advanced into the late stage, which seriously affects the treatment and prognosis of the patients (1,2). Therefore, early diagnosis and treatment of liver cancer is a crucial step. China is a country with high hepatitis B incidence, therefore, many liver cancers are derived from the development of hepatitis B cirrhosis, and hepatitis C patients are gradually increasing, leading directly to the huge number of liver cancer patients in recent years, therefore, the diagnosis and treatment of liver cancer is very important to our medical system (3). Recently, the imaging diagnosis of liver cancer in many hospitals is still mainly based on the characteristics of blood supply, and contrast-enhanced ultrasonography (CEUS) which is a widely-used technology developed in recent years providing real-time monitoring of the dynamic distribution of blood vessels of liver cancer patients revealing the hemodynamic characteristics of liver cancer patients (4). However, CEUS has low repeatability and limitations of detection time, and it can only observe one lesion at one time. As a noninvasive imaging technique, CT also has a good diagnostic value in patients with liver cancer (5). However, CT cannot accurately detect early lesions with small or limited density changes and early lesions in cellular levels, and it is extremely easy to produce artifacts due to movement or metal. Therefore, we considered that combining CEUS and CT in the diagnosis of liver cancer can make up for the deficiencies of each other, and through the CEUS and CT imaging results of 426 cases of liver cancer patients, the imaging performance and the value of diagnosis of liver cancer were analyzed.

Patients and methods

General information. A total of 426 patients with liver cancer confirmed by pathology and admitted to Yuhuangding Hospital (Yantai, China) from February 2011 to May 2016 were selected. There were 336 males and 90 females, with an average age of 56.3±10.5 years. Among them 195 cases

Table I. Basic information of 426 patients (n, %).

Parameters	CEUS group (n=222)	CT group (n=204)	CEUS+CT group (n=102)	F-value	P-value
Age (years)				2.350	0.293
<59	124 (55.9)	119 (58.3)	61 (59.8)		
≥59	98 (44.1)	85 (41.7)	41 (40.2)		
Sex				3.280	0.448
Male	184 (82.9)	167 (81.9)	87 (85.3)		
Female	38 (17.1)	37 (18.1)	15 (14.7)		
Ethnicity				3.185	0.485
Han	214 (96.6)	199 (97.5)	99 (97.1)		
Others	8 (3.6)	5 (2.5)	3 (2.9)		
Marital status				2.212	0.410
Married	207 (93.2)	184 (92.2)	89 (87.3)		
Unmarried	11 (5.0)	18 (8.8)	10 (9.8)		
Widowed	4 (1.8)	2 (1.0)	3 (2.9)		
Living area				3.038	0.455
Countryside	134 (60.4)	119 (58.3)	64 (62.7)		
City	88 (39.6)	85 (41.7)	38 (37.3)		
Smoking index				3.074	0.332
<400	61 (27.5)	59 (28.9)	24 (23.5)		
≥400 - <800	77 (34.7)	69 (33.8)	37 (36.3)		
≥800	84 (37.8)	76 (37.3)	41 (40.2)		
Drinking				2.584	0.310
No drinking or occasionally	74 (33.3)	51 (25.0)	22 (21.6)		
Often	148 (66.7)	153 (75.0)	80 (78.4)		

CEUS, contrast-enhanced ultrasonography; CT, computed tomography.

were benign and 231 cases were malignant. Two hundred and twenty-two patients underwent CEUS examination, 204 patients underwent CT examination and 102 patients underwent CEUS combined with CT examination. Inclusion criteria: Forty-five years of age and above, liver cancer patients confirmed by histology or cytology, no previous diagnosis of liver cancer, patients with no family history of genetic disease. Exclusion criteria: Critically ill patients, patients with incomplete limbs, patients not cooperating with the relevant examination, patients suffering from cancer other than liver cancer. All the patients included in this study or their families signed informed consent. The relevant study was carried out under the approval of the Ethics Committee of Yuhuangding Hospital, and the patients were informed and they signed a formal authorization.

Instruments and methods. Patients fasted for 5 h before the test, and the corresponding allergy test was performed, Sequoia 512 Siemens diagnostic ultrasound system with real-time contrast pulse sequence CEUS technology was adopted, contrast agent was Sono Vue (GE, USA). Sono Vue was diluted with 5 ml of normal saline, and 2.4 ml of diluted contrast medium was drawn. The bolus was injected through the anterior left elbow vein followed by bolus injection of 5 ml of normal saline. The injection was simultaneously timed to observe the liver lesions. The time of contrast imaging was 5-7 min. The LightSpeed 16-slice spiral CT manufactured by GE Healthcare Life Sciences (Waukesha, WI, USA), was used and high-quality scanning mode was applied. The scanning parameters were 7.5 mm layer thickness, 1.25 mm resolution, 1.375I pitch, 120 kV voltage and 280 mA tube current.

Image analysis. Combined with the clinical data of patients, the diagnostic accuracy of the three diagnostic methods were evaluated by taking pathological sections as the gold standard of diagnosis. The characteristics of CEUS and CT scanning of lesions were observed, the focus of observation was the lesion density, number, and marginal conditions. The CEUS and CT images of all patients were analyzed by double blind method and analyzed by four experienced imaging physicians, the clinical values were also observed.

Statistical analysis. Using SPSS 22.0 data analysis system (Boyi Information Technology Co., Ltd., Guangzhou, China) for data analysis, the enumeration data are expressed as percentage, the comparison among groups used Chi-square test, the sensitivity and specificity of diagnosis was analyzed using ROC curve analysis.

Table II. Clinical symptoms of 426 patients (n, %).

Parameters	CEUS group (n=222)	CT group (n=204)	CEUS+CT group (n=102)	F-value	P-value
Pathological types				3.249	0.327
Block	19 (8.6)	17 (8.3)	7 (6.9)		
Large block	39 (17.6)	41 (20.1)	16 (15.7)		
Nodular	81 (36.5)	74 (36.3)	43 (42.2)		
Diffuse	36 (16.2)	29 (14.2)	10 (9.8)		
Small cancer	6 (2.7)	5 (2.5)	3 (2.9)		
T staging				3.467	0.458
TX	1 (0.5)	0 (0.0)	1 (1.0)		
T0	8 (3.6)	7 (3.4)	2 (2.0)		
T1	25 (11.3)	19 (9.3)	14 (13.7)		
T2	48 (21.6)	40 (19.6)	23 (22.5)		
T3	62 (27.9)	50 (24.5)	22 (21.6)		
T4	46 (20.7)	37 (18.1)	21 (20.6)		
N staging				2.277	0.390
NX	5 (2.3)	3 (1.5)	3 (2.9)		
N0	97 (43.7)	83 (40.7)	41 (40.2)		
N1	85 (38.3)	75 (36.8)	34 (33.3)		
M staging				2.915	0.379
MX	7 (3.2)	5 (2.5)	2 (2.0)		
M0	90 (40.5)	78 (38.2)	33 (32.4)		
M1	92 (41.4)	79 (38.7)	40 (39.2)		
Clinical manifestations				3.391	0.426
Fever and edema	42 (18.9)	39 (19.1)	22 (21.6)		
Weight loss	56 (25.2)	47 (23.0)	28 (27.5)		
Bloating, nausea, vomiting	39 (17.6)	27 (13.2)	17 (16.7)		
Right upper quadrant dull pain	74 (33.3)	66 (32.4)	39 (38.2)		
Liver pain	51 (23.0)	59 (28.9)	34 (33.3)		
Jaundice	86 (38.7)	74 (36.3)	44 (43.1)		
Dyspnea	124 (55.9)	110 (53.9)	56 (54.9)		
Cavity effusion	154 (69.4)	139 (68.1)	64 (62.7)		

CEUS, contrast-enhanced ultrasonography; CT, computed tomography.

Results

Clinical data of patients. According to the clinical data of patients, there was no significant difference in age, sex, ethnicity, marital status, living area, smoking index, alcohol drinking and pathological classification, TNM staging and clinical manifestations among patients receiving CEUS, CT and the two combined detection (p>0.05), further reducing the experimental error (Tables I and II).

CT results. The features of plain scan in 204 patients undergoing CT scan were: Low density in 92.6% of patients (189 cases), low and high density in 6.4% (13 cases), calcification in 2.5% of patients (5 cases), and 3.4% (7 cases) showed bleeding. Lesions: 76.5% (156 cases) of patients with multiple type, 23.5% (48 cases) with single type. In 80.9% (165 cases), the boundary of the lesions was blurred, and in 19.1% (39 cases) the boundaries of the lesions were clear. Dynamic contrast-enhanced features in 204 patients: 56.4% (115 cases) patients showed progressive enhancement. In 22.1% (45 cases) patients showed no significant enhancement. In 11.8% (24 patients), the patients showed marginal anadem-like enhancement. In 9.8% (20 cases) of patients fast-in, fast-out type was seen. Dynamic enhanced scan feature classification criteria are shown in Table III.

CEUS imaging results. In 222 patients undergoing CEUS, the imaging results were as follows: 53.2% (118 patients) showed overall enhancement, 16.7% (37 patients) showed heterogeneous enhancement, 18.9% (42 patients) showed peripheral enhancement, and 11.3% (25 cases) patients showed necrosis with liquefaction. In 65.3% (145 cases) patients, the portal venous phase and the delayed phase showed a low enhancement, while 34.7% (77 cases) showed no enhancement.

Table III. Dynamic enhanced scanning feature classification criteria.

Classification	Criteria
Progressive enhancement	Mild enhancement in the margin of the lesion in arterial phase, obvious enhancement in portal venous phase
No significant enhancement	No obvious enhancement in the lesions or visible nodular enhancement at the edge
Marginal anadem-like enhancement	Visible anadem-like lesions observed at the edge of the lesions
Fast-in, fast-out enhancement	Obvious enhancement in arterial phase, lesion enhancement was significantly reduced in portal venous phase and delayed phase

Table IV. Accuracy of three diagnostic methods (n, %).

Methods	Diagnosed	Misdiagnosed	Accuracy (%)
CEUS	195 (87.8)	27 (12.2)	87.8
CT	180 (88.2)	24 (11.8)	88.2
CEUS+CT	96 (94.1)	6 (5.9)	94.1
χ^2	12.54	13.47	13.87
P-value	0.041	0.037	0.032

CEUS, contrast-enhanced ultrasonography; CT, computed tomography.

Table V. ROC curve analysis.

Methods	AUC	95% CI	Sensitivity (%)	Specificity (%)
CEUS	0.724	0.211-2.534	76.8	78.9
CT	0.784	0.617-1.232	81.2	85.5
CEUS+CT	0.846	0.146-4.643	90.4	92.7
χ^2			13.51	12.74
P-value			0.037	0.041

CI, confidence interval; CEUS, contrast-enhanced ultrasonography; CT, computed tomography.

Diagnostic accuracy. Of the 222 patients who underwent CEUS examination, 195 were diagnosed with liver cancer, with a diagnostic accuracy of 87.8%. Of the 204 patients who underwent CT examination, 180 were diagnosed with liver cancer and the diagnostic accuracy was 88.2%. Of the 102 patients who underwent CEUS combined CT examination, 96 cases were diagnosed as liver cancer, the diagnostic accuracy was 94.1%. The accuracy of joint detection was better than single detection (p<0.05; Table IV).

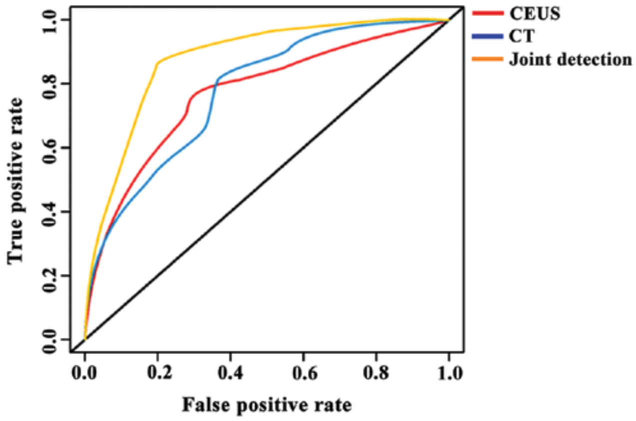

Figure 1. ROC curve analysis. The sensitivity and specificity of CEUS in the diagnosis of liver cancer were 76.8 and 78.9%, respectively. The sensitivity and specificity of CT were 81.2 and 85.5%, respectively. The sensitivity and specificity of CEUS and CT were 90.4 and 92.7%, respectively. CEUS, contrast-enhanced ultrasonography; CT, computed tomography.

ROC curve analysis. The ROC curve showed that the AUC of CEUS was 0.724 (95% CI, 0.211-2.534); the AUC of CT was 0.784 (95% CI, 0.617-1.232); the AUC of CEUS combined with CT was 0.846 (95% CI, 0.146-4.643). The sensitivity and specificity of CEUS in the diagnosis of liver cancer were 76.8 and 78.9%, respectively. The sensitivity and specificity of CT were 81.2 and 85.5%, respectively. The sensitivity and specificity of CEUS and CT were 90.4 and 92.7%, respectively. The specificity and sensitivity of combined detection were better than single detection (p<0.05) (Table V; Fig. 1).

Discussion

Liver cancer is a highly malignant disease with high incidence among the malignant tumors, early diagnosis and treatment of the disease is the most important and effective way to improve the prognosis of patients clinically (6). The early stage of liver cancer has no obvious clinical features, the rough assessment is mainly through the imaging method (7). Nowadays in clinic, MRI, CT, CEUS and other imaging methods can achieve a more accurate diagnosis of liver cancer (8). According to studies by Fischer *et al* (9), CT is the most accurate diagnosis of liver cancer. While Mishima *et al* (10) asserted that CEUS was more effective in showing the performance of liver cancer lesions, which is more widely recommended in the early diagnosis of liver cancer clinically. The imaging method of single examination, though short in time and radiation damage to patients, may often have some limitations due to disease differences (11). However, there are also some related research (12,13) showing that the sensitivity and specificity of combined imaging diagnosis of malignant tumors are better than single detection. Therefore, CEUS combined with CT is proposed for the diagnosis of liver cancer. By retrospective analysis of 426 patients with liver cancer, the imaging performances were compared and their clinical values were analyzed. The aim is to provide reference and guidance for patients with liver cancer in future clinical trials.

CT makes a more accurate assessment of the location, number, size of lesions in the liver and the surrounding tissue of the lesion, and the tissue characteristics inside the lesion can be presented by enhanced scanning (13). According to the experimental results of Farinati *et al* (14), the difference between the intensified levels of CT examination of each stage can be used as an indicator of the source of blood supply, suggesting that CT can be used as a detection method of liver cancer metastasis. However, CEUS is a new imaging diagnostic technique in clinical practice and has high ability to distinguish blood dynamic changes in malignant tumor tissues (15). CEUS is better than CT in echogenic changes in lesion area, and the detection is more economical. The main component of contrast medium used in CEUS detection is SF6 gas microbubbles, which is more applicable for patients with cardiovascular disorders, not prone to iodine reaction (16). In this study, CEUS sensitivity and specificity for the diagnosis of liver cancer were 76.8 and 78.9%. The sensitivity and specificity of CT were 81.2 and 85.5%, respectively. The sensitivity and specificity of CEUS and CT were 90.4 and 92.7%, respectively. The reason may be that the ultrasound microbubbles of CEUS detection can only be detected in the capillaries and blood pool, but not clearly in the extracellular space (17). Compared with CT, CEUS avoids the occurrence of misdiagnosis of peaks at intensified times and it shows real-time performance of overall liver lesions through dynamic performance (18). However, due to the weak ability of CEUS to detect lesions of atypical small hepatocellular carcinoma, the detection of differentiation and pathology of liver cancer is weaker than that of CT (19). CT scan reflects the characteristics of the lesions through the enhanced scanning of the liver and the use of liver function and cancer cell blood supply (20). CT can accurately show the situation of hepatic artery and blood vessels of patients, and the performance for hepatic arteriovenous fistula was significantly better than CEUS, CT also has better detection ability for small liver cancer (20). Therefore, CEUS more accurately show the 'whole' of liver cancer, CT is more subtle for the 'details'. The use of combined detection between the two makes up for each other's deficiencies, and provides higher accuracy of natural diagnosis. The results of Mauri *et al* (21) showed that the combined detection of CT and CEUS was superior to single imaging in the diagnosis of gastric cancer. This also proves the experimental results from the side.

In this study, through analyzing the CT and CEUS imaging results of 426 cases of liver cancer, it was proposed that CT combined with CEUS detection is more applicable for liver cancer. However, due to the lack of samples and more detailed analysis of the liver cancer type, we will conduct a more comprehensive analysis in future experiments.

In conclusion, CEUS combined with CT detection can make up for deficiencies in each other, effectively improving the diagnostic accuracy of liver cancer, which can be used as an effective detection method of liver cancer diagnosis.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

BS contributed to the conception and design of this study. YL and DX interpreted the data and drafted this manuscript. JL collected the data and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Yuhuangding Hospital (Yantai, China). Signed written informed consents were obtained from the patients and/or guardians.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

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