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PROSPECTIVE STUDY

Contrast-enhanced ultrasound: Improving the preoperative staging of hepatocellular carcinoma and guiding individual treatment

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Abstract

AIM: To investigate the clinical role of contrast-enhanced ultrasound (CEUS) combined with contrast-enhanced computed tomography (CE-CT) or magnetic resonance imaging to improve the preoperative staging of hepatocellular carcinoma (HCC) and guide surgical decision-making.

METHODS: Sixty-nine patients who underwent liver resection for HCC in our center were enrolled prospectively in the study. CEUS and CE-CT/MRI were performed before surgery. Intraoperative ultrasound (IOUS) was carried out after liver mobilization. Lesions depicted by each imaging modality were counted and mapped. To investigate the impact of tumor size on the study, we divided the patients into two groups, the "Smaller group"(S-group, $\leqslant$ 5 cm in diameter) and the "Larger-group" (L-group, > 5 cm in diameter). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of CE-CT/MRI, CEUS, IOUS, CEUS+CE-CT/MRI and the tumor node metastasis staging of tumors were calculated and compared. Changes in the surgical strategy as a result of CEUS and IOUS were analyzed.

RESULTS: One hundred and twenty-seven nodules, comprising 94 HCCs confirmed by histopathology and 33 benign lesions confirmed by histopathology and follow-up, were identified in 69 patients. The overall diagnostic sensitivity rates of CE-CT/MRI, CEUS, IOUS and CEUS+ CE-CT/MRI were 78.7%, 89.4%, 89.4% and 89.4%, respectively. There was a significant difference between CEUS + CE-CT/MRI and CE-CT/MRI (P = 0.046). Combining CEUS with CT or MRI increased, the diagnostic specificity compared with CT/MRI, CEUS and IOUS, and this difference was statistically significant (100%, 72.7%, 97.0%, and 69.7%, P = 0.004, P = 0.002, P = 0.002, respectively). The diagnostic accuracy was significantly higher for CEUS + CT/MRI compared with CT/MRI (92.1% *vs* 77.2%, P = 0.001). The TNM staging of tumors based on CEUS + CE-CT/MRI approximated to the final pathological TNM staging (P = 0.977). There was a significant difference in the accuracy of TNM staging when comparing CEUS + CE-CT/MRI with CE-CT/MRI (P = 0.002). Before surgery, strategies were changed in 15.9% (11/69) of patients as a result of CEUS. Finally, only 5.7% (4/69) of surgical strategies were changed because of IOUS findings. In the S-group, CEUS revealed 12 false positive lesions, including seven false positive lesions that were diagnosed

by preoperative imaging examinations and five by IOUS. In contrast, in the L-group, IUOS revealed eight new malignant lesions; six of these lesions were true HCCs that were also identified by preoperative CEUS.

CONCLUSION: CEUS combined with CT or MRI improves the accuracy of preoperative staging for hepatocellular carcinoma and may help to guide individualized treatment for patients with HCC. CEUS may better identify non-malignant lesions in patients with small tumors and discover new malignant lesions in patients with large tumors.

Key words: Hepatocellular carcinoma; Contrast-enhanced ultrasound; Tumor node metastasis staging; Intraoperative ultrasound; Liver resection

Core tip: Contrast-enhanced ultrasound is a novel and promising technique. Contrast-enhanced ultrasound combined with computed tomography or magnetic resonance imaging improves the preoperative staging of hepatocellular carcinoma and may help guide treatment for patients with hepatocellular carcinoma, and may help to guide individualized treatments and assist surgeons in evaluating the safety and radicality of operation.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and is one of the most common causes of cancer-related death[1]. Hepatitis B virus (HBV) infections account for the majority of cirrhosis and primary liver cancer cases worldwide, especially in China[2,3]. Surgical resection is considered to be the primary curative therapy. Intraoperative ultrasound (IOUS) is used for navigation during hepatic resection[4-6]. However, IOUS also frequently leads to changes in the surgical approach because IOUS can detect new lesions, leading to inaccurate TNM staging before surgery.

Large regenerative nodules and dysplastic nodules (DN) are considered premalignant lesions of hepatocellular carcinoma[7-9] and are very difficult to differentially diagnose in early stage HCC. These cells may have already transformed to cancer cells, but no morphological methods are available to definitively prove this finding. However, the differential diagnosis implies different monitoring methods and different therapeutic approaches. In 2000, the European Association for the Study of Liver Diseases Conference proposed a set of criteria to establish the diagnosis of HCC in patients with cirrhosis[10]. To reduce the risk of false-positive diagnoses, the criteria require coincidental observation of two dynamic imaging techniques [contrast-enhanced computed tomography (CE-CT); contrast-enhanced magnetic resonance imaging (CE-MRI); angiography; contrast-enhanced ultrasound (CEUS)],; the noninvasive criteria were restricted to tumors larger than 2 cm that are present in a cirrhotic liver.

Recently, contrast-enhanced ultrasound techniques using second-generation contrast agents, such as SonoVue, have been developed[11]. CEUS has been introduced in most important guidelines and recommendations, such as those issued by the European Association for the Study of the Liver (EASL)[12], the 2008 European Federation of Societies for Ultrasound in Medicine and Biology guidelines[13], the Asian Pacific Association for the Study of the Liver[14] and the Japanese Society of Hepatology[15]. Like other contrast-enhanced radiological imaging techniques, CEUS can be used to evaluate tumor vasculature[16,17]. CEUS easily analyzes the details of intratumoral vasculature in real time, unlike angiography and contrast-enhanced computed tomography; this may help to distinguish between true HCCs, premalignant dysplastic nodules, and large regenerative nodules[18]. Alaboudy *et al*[19-21] reported that CEUS combined with CT or MRI improved the sensitivity and specificity of HCC diagnosis; however, few articles have focused on the role of preoperative contrast-enhanced ultrasound combined with CE-CT or MRI for staging of hepatocellular carcinoma in surgical patients; in surgical decision-making; or on the correlation between CEUS and intraoperative ultrasound. Therefore, we conducted this study to investigate the clinical role of CEUS combined with CE-CT or MRI.

MATERIALS AND METHODS

Ninety-six consecutive patients were admitted to our center. Of those, 69 HCC patients and eight ICC patients underwent liver resection. Eleven patients underwent radio frequency ablation; four patients had liver metastases, two patients had focal nodular hyperplasia and two patients had hemangiomas. We enrolled the 69 patients who underwent hepatic resection for HCC in our department in the interval from March 2013 to October 2013. All of the HCCs were proven histopathologically. After CE-CT was performed in 48 patients, CE-MRI was performed in 19 patients, and both CE-CT and MRI were performed in two patients), preoperative CEUS was performed in all patients. Intraoperative ultrasound was performed conventionally after mobilization of the liver. Lesions depicted by each imaging modality were counted and mapped. The arterial, portal and late phases of contrast enhancement were recorded and analyzed. To investigate the effects of tumor size, we divided the patients into two groups, the "Smaller group"(S-group, $\leqslant$ 5 cm in diameter) and the "Larger-group" (L-group, > 5 cm in diam-

eter). The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of CE-CT/MRI, CEUS, IOUS, CEUS + CE-CT/MRI and TNM staging were calculated and compared. Changes in surgical strategy as a result of CEUS and IOUS were analyzed.

CE-CT or MRI

CE-CT and CE-MRI were performed as previously published[22,23]. Data was acquired in the hepatic arterial, portal venous and equilibrium phases, and the images were stored for retrospective analysis.

CEUS and IOUS

Four sonographers with approximately 6, 8, 10, and 30 years of experience in abdominal US performed the ultrasonography. The sonographers were aware that the patients were at risk of developing HCC, but did not have access to additional information, *e.g.*, alpha-fetoprotein (AFP) levels. In cases of disagreement, the sonographers engaged in joint discussions until a consensus was reached.

CEUS was performed to characterize lesions that were identified by CT or MRI, and to detect the presence of latent new nodules. An iU22 ultrasound system (Philips Royal Electronic Corporation, The Netherlands) with a C5-1 transducer was used during the preoperative CEUS examinations, to start the mode of CEUS, to display clear of the lesions and to quickly push SonoVue (Bracco of Italy; 2.4-4.8 mL) through the antecubital vein. The pipe was washed with 5 mL of 0.9% sodium chloride solution. A timer began at the same time the contrast agent was injected, and continuous observations occurred for at least five minutes. All phases of contrast enhancement, including the arterial phase (10-20 s to 25-35 s after injection), the portal phase (30-45 s to 120 s) and the delay phase (> 120 s) were recorded and analyzed. HCCs were characterized by the mode of enhancement, which showed hyper-enhancement in the arterial phase and wash-out of microbubbles during the portal or late phase. If the lesion did not exhibit wash-out during the portal and late phases, the lesions were defined as benign solid lesions.

We used the VIVID4 unit (GE, United States) with an I-shaped 10-4 MHz intraoperative probe for the IOUS scans. After mobilization of the liver, IOUS was performed to search for nodules; suspected lesions were counted and mapped.

Nodules that displayed arterial hyper-enhancement and/or hypo-enhancement in the delayed phase of CEUS and were hypoecho on IOUS were removed surgically. Radiofrequency ablation and ethanol ablation were used as alternatives in cases where the nodule cloud not be surgically removed. Nodules with ISO enhancement (both in arterial and late phases) were considered benign and were removed only if they were located close to the main lesion. The others nodules were followed up with measurements of serum AFP levels, ultrasound, spiral CT or MRI at 3 mo after surgery.

Statistical analysis

Continuous variables were expressed as the median ± SD and were compared between groups with a t test or Mann-Whitney U test for variables with an abnormal distribution. The categorical data were compared using the chi-squared test/Fisher's exact test. A conventional P value of < 0.05 was considered statistically significant. Calculations were performed with the SPSS package (SPSS, Inc. 1989-1995, Chicago, IL).

RESULTS

A total of 127 nodules, comprising 94 HCCs and 33 benign lesions, were confirmed in 69 patients. Demographic and clinical data, and pathological findings for the patients included in the present report are shown in Table 1. CEUS revealed 85 focal hepatic lesions with malignant imaging patterns, including 84 true-positive nodules (10 of which were not identified by CT or MRI) (Figure 1), and one of which was a false-positive finding. Contrast-enhanced CT or MRI revealed 83 hepatic focal lesions (74 true HCCs and nine false-positive lesions) (Figure 2). IOUS identified 94 hepatic focal lesions (84 true HCCs and 10 false-positive lesions). The sensitivity, specificity, accuracy, PPV and NPV for each imaging modality were 78.7%, 72.7%, 77.2%, 89.2%, and 54.6% for CE-CT/MRI; 89.4%, 97.0%, 91.3%, 98.8%, and 76.2%for CEUS and 89.4%, 69.7%, 84.3%, 89.4%, and 69.7% for IOUS; 89.4%, 100%, 92.1%, 100%, and 71.4% for CEUS + CT/MRI, respectively (Table 2). CEUS (89.4%), IOUS (89.4%), and CEUS + CT/MRI (89.4%) had significantly different sensitivities ($P = 0.046$, $P = 0.046$, $P = 0.046$, respectively) than CT/MRI (78.7%). The specificity of CEUS + CT and/or MRI was significantly higher than the specificity of CT and/or MRI, CEUS, or IOUS ($P = 0.004$, $P = 0.002$, and $P = 0.002$, respectively). The diagnostic accuracy of CEUS + CT/MRI was higher than that of CT/MRI ($P = 0.001$). CEUS may more accurately identify non-malignant nodules than CT/MRI and IOUS ($P = 0.006$, $P = 0.003$, respectively). In addition, the TNM staging of tumors based on CEUS + CE-CT/MRI approximated to the final TNM staging by pathology ($P = 0.977$). The accuracy rates of TNM staging with CEUS + CE-CT/MRI and CE-CT/MRI ($P = 0.002$) are shown in Table 3.

There were 50 malignant lesions and 23 benign lesions in the S-group, and 44 malignant lesions and 10 benign lesions in the L-group. Sensitivity, specificity, accuracy, PPV, and NPV for the S-group and L-group are shown in Tables 4 and 5 respectively. In the S-group, CEUS revealed 12 false positive lesions, comprising seven false positive lesions diagnosed by preoperative imaging and five by IOUS. The Ishak scores of those patients were 3-6 (mean score: 5.3). In contrast, IUOS revealed eight new malignant lesions, comprising five false-positive lesions, which were also identified by CEUS, and three true HCCs (one identified by CEUS and two discovered by IOUS). In the L-group, IUOS revealed eight new ma-

Table 1 Demographic and clinical data of 69 patients and pathologic data of tumors

	Total	S-group	L-group	*P* value
Clinical data				
Age (mean ± SD) (yr)	53.0 ± 11.8	52.69 ± 10.22	53.0 ± 13.88	0.82
Gender (Male/Female)	55:14	32:8	23:6	0.59
HBsAg (Positive/Negative)	63:6	37:3	26:3	0.69
AFP level (≤ 20/> 20 ng/mL)	19:50	14:26	5:24	0.17
Mean interval between two images (mean ± SD) (d)	7.88 ± 3.74	7.90 ± 3.36	7.86 ± 3.68	0.97
Mean MELD score (mean ± SD)	4.90 ± 2.81	4.92 ± 2.65	4.87 ± 3.06	0.94
Child-Pugh				
Class A	69	40	29	
Pathologic data				
Mean nodule size (mean ± SD) (cm)	5.49 ± 3.48	3.07 ± 1.12	8.80 ± 2.81	< 0.01
Tumor number (1/2/3)[1]				
Without CEUS	58:9:2	33:5:2	25:4	0.65
With CEUS	57:9:3	36:3:1	21:6:2	0.20
Tumor characteristics				
Degree of differentiation (Well/Moderate/Poor)	6:35:28	4:20:16	2:15:12	0.70
Micro-vascular invasion (Positive/Negative)	20:49	8:32	12:17	0.065
Mean Ishak score (mean ± SD)	4.94 ± 1.31	5.30 ± 1.14	4.45 ± 1.38	0.007

[1]Indicates that tumor number was documented before surgery. S-group: The "Smaller group" (≤ 5 cm in diameter); L-group: The "Larger-group" (> 5 cm in diameter). HBsAg: Hepatitis B surface antigen; AFP: Alpha-fetoprotein; CEUS: Contrast-enhanced ultrasound.

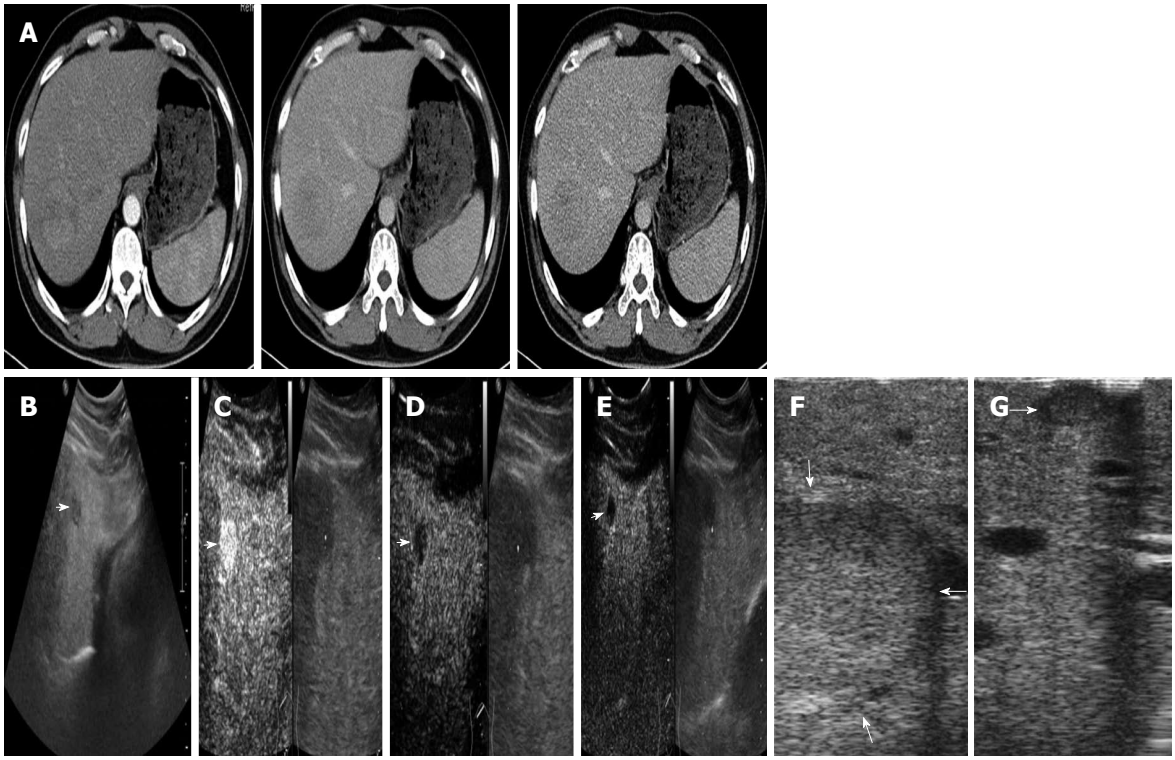

Figure 1 A 50-year-old man underwent right hepatic partial resection and left hepatic partial resection. A: CT just revealed the right HCC, not the left HCC which was identified by CEUS; B: Left HCC was discovered by conventional ultrasound; C-E: The left HCC was identified by CEUS in the arterial phase, portal phase and delayed phases; F: Right HCC identified by IOUS; G: Left HCC identified by IOUS. HCC: Hepatocellular carcinoma; CT: Computed tomography; CEUS: Contrast-enhanced ultrasound; IOUS: Intraoperative ultrasound.

lignant lesions, comprising six true HCCs, which were also diagnosed by CEUS, and two false positive lesions (one also incorrectly identified by CEUS and one discovered by IOUS). The false-negative case was a small lesion located under the right diaphragm that was difficult for CEUS to identify.

Surgery

Among the nine malignant lesions newly detected by IOUS, three were from one patient and the other six were from six patients. The size of lesions was 5-23 mm in diameter (mean 14.3 mm). Surgical strategies were changed in 15.9% (11/69) of patients because of the preoperative CEUS

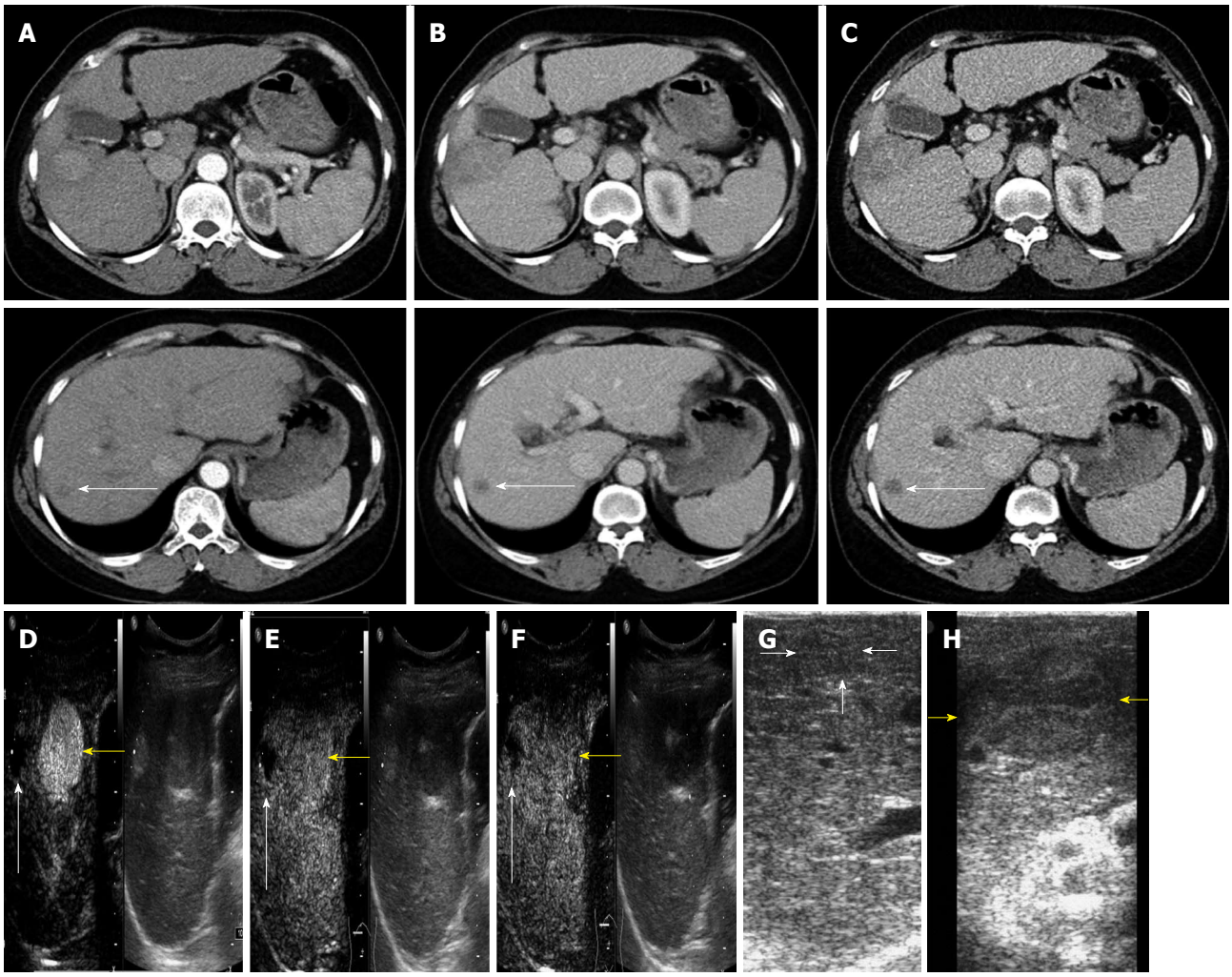

Figure 2 A 55-year-old woman underwent right hepatic partial resection. A-C: both lesions, displayed in the arterial, portal venous and equilibrium phases, were diagnosed as HCC by CT (white arrow); D-F: the HCC (yellow arrow) displayed wash-in in arterial phase and wash-out in late phases *via* CEUS; another lesion (white arrow), diagnosed as necrosis by final histopathology, displayed iso-enhancement in the three phases; G: the HCC identified by IOUS; H: the necrosis also falsely diagnosed as HCC by IOUS. HCC: Hepatocellular carcinoma; CT: Computed tomography; CEUS: Contrast-enhanced ultrasound; IOUS: Intraoperative ultrasound.

Table 2 Sensitivity, specificity, accuracy and positive predictive value, negative predictive value for contrast-enhanced computed tomography/magnetic resonance imaging, contrast-enhanced ultrasound, intraoperative ultrasound, contrast-enhanced ultrasound + computed tomography and/or magnetic resonance imaging

	Sensitivity	Specificity	Accuracy	PPV	NPV
CE-CT or MRI	78.7%[a]	72.7%[b]	77.2%	89.2%	54.6%
CEUS	89.4%	97.0%[b,d]	91.3%	98.8%	76.2%
IOUS	89.4%	69.7%[b]	84.3%	89.4%	69.7%
CEUS + CE-CT/MRI	89.4%	100%	92.1%[f]	100%	76.7%

[a]$P < 0.05$ *vs* CEUS, IOUS and CEUS + CE-CT/MRI; [b]$P < 0.01$ *vs* CEUS + CE-CT/MRI; [d]$P < 0.01$ *vs* CE-CT/MRI and IOUS; [f]$P < 0.01$ *vs* CT/MRI and IOUS. PPV: Positive predictive value; NPV: Negative predictive value; CEUS: Contrast-enhanced ultrasound; IOUS: Intraoperative ultrasound; CE-CT: Contrast-enhanced computed tomography; MRI: Magnetic resonance imaging.

findings (Table 6). Finally, surgical strategies were changed in four patients because of lesions that were newly detected by IOUS, and which were not in the same liver segments as the originally identified lesions (one patient with left lobe underwent an additional partial resection, two patients had lesions in other segments and underwent expanded resection, and, in the last patient, a lesion invaded the diaphragm and required partial-diaphragmatic-resection).

DISCUSSION

The safety and radicality of resection are key considerations in surgical decision-making and for the prevention of recurrence in cirrhotic patients with HCC. During

Table 3 Tumor node metastasis stage of tumors without contrast-enhanced ultrasound, with contrast-enhanced ultrasound and by pathology

	TNM					Pathology	
	Ⅰ	Ⅱ	ⅢA	ⅢB	ⅢC	Right	Wrong
Without CEUS	56	7	4	2		46	23
With CEUS[1,2]	50	4	8	7		61	8
Pathology	49	4	7	9	1		

[1]P = 0.002 *vs* without CEUS about accuracy of TNM stage; [2]P = 0.977 *vs* CEUS and pathology about TNM stage. CEUS: Contrast-enhanced ultrasound; TNM: Tumor node metastasis.

Table 4 Sensitivity, specificity, accuracy and positive predictive value, negative predictive value for contrast-enhanced computed tomography/magnetic resonance imaging, contrast-enhanced ultrasound, intraoperative ultrasound in the S-group

	Sensitivity	Specificity	Accuracy	PPV	NPV
CE-CT or MRI	84.0%	69.6%	79.5%	85.7%	66.7%
CEUS	90.0%	100.0%	93.2%	100%	82.2%
IOUS	94.0%	78.3%	89.1%	90.4%	85.7%
CEUS + CE-CT/MRI	90.0%	100%	93.2%	100%	82.2%

S-group: the "Smaller group" (≤ 5 cm in diameter). PPV: Positive predictive value; NPV: Negative predictive value; CEUS: Contrast-enhanced ultrasound; IOUS: Intraoperative ultrasound; CE-CT: Contrast-enhanced computed tomography; MRI: Magnetic resonance imaging.

Table 5 Sensitivity, specificity, accuracy and positive predictive value, negative predictive value for contrast-enhanced computed tomography/magnetic resonance imaging, contrast-enhanced ultrasound, intraoperative ultrasound in the L-group

	Sensitivity	Specificity	Accuracy	PPV	NPV
CE-CT or MRI	72.7%	80.0%	82.4%	89.2%	44.0%
CEUS	88.6%	90.0%	88.9%	98.8%	64.3%
IOUS	84.1%	50.0%	77.8%	88.1%	41.7%
CEUS + CE-CT/MRI	86.4%	100%	90.7%	100%	66.7%

L-group: the "Larger-group" (> 5 cm in diameter). PPV: Positive predictive value; NPV: Negative predictive value; CEUS: Contrast-enhanced ultrasound; IOUS: Intraoperative ultrasound; CE-CT: Contrast-enhanced computed tomography; MRI: Magnetic resonance imaging.

Table 6 Surgical strategies changed according to contrast-enhanced ultrasound findings

	1 segment	1 segments	3 segments	Right liver	Left liver	Right 3 segment	Left 3 segment	Liver transplantation
Without CEUS	7	22	8	13	5	12	1	1[1]
With CEUS	10	22	7	13	5	10	1	1[1]

[1]This patient accepted TACE, and then accepted liver transplantation 2 mo later. CEUS: Contrast-enhanced ultrasound; TACE: transcatheter arterial chemoembolization.

surgical procedures, IOUS plays a primary role in identifying lesions that were missed by preoperative imaging, and is helpful in mapping major vessels to identify clear surgical margins. In addition to assessing hepatic tumors and evaluating the relationship between tumors and major vascular structures, IOUS can also better characterize nonspecific lesions that are identified by cross-sectional imaging. However, IOUS has some drawbacks, such as a lack of accuracy in differentiating early-stage HCC from macronodules, including large regenerative and dysplastic nodules (the latter considered as the true HCC precursors)[8]. Otherwise, IOUS could not be performed before laparotomy. Newly identified lesions may require more extensive procedures than initially indicated, such as expanded resection or combined local therapies. In patients with very extensive disease, surgeons may be obliged to stop the operations. Thus, accurate staging of HCC before surgery is extremely important.

Contrast-enhanced ultrasound with a low mechanical index (MI), using second-generation contrast agents, can depict the vasculature of hepatocellular carcinoma and allows continuous real-time imaging of the whole liver to be performed with slow panoramic sweeps. CEUS can also be used for visualization in the arterial, portal and late phases. HCC is typically hypervascular[24-26]. In particular, a dramatic alteration in the arterial hypervascularity is observed in moderately and poorly differentiated HCCs[27,28]. The vascular phenotype of dysplastic nodules is complex and can reflect different grades of malignancy. Several histological features are predictive of malignant

transformation, including an abnormal number of capillary units, unpaired arteries, portal tract changes (including a reduction in both portal vein and normal hepatic artery branches) and a progressive increase in the number of abnormal hepatic arteries[18,29,30]. Typically, HCCs are hypervascular in the arterial phase and washout in the portal and late parenchymal phases, while benign lesions demonstrate ISO enhancement or hyper-enhancement in both the arterial and late phases[31,32].

Our previous studies showed that contrast-enhanced intraoperative ultrasound (CEIOUS) is a novel and promising technique that improves specificity and accuracy of IOUS and can influence surgical strategies and oncological radicality[22,23]. However, CEIOUS could not overcome the aforementioned flaws of IOUS. To confirm the presence of malignant tumors and identify potentially missed lesions, we wanted to use CEUS to qualitatively analyze these lesions before operation. Therefore, we conducted this study. We demonstrated that CEUS combined with CT/MRI improved the diagnostic accuracy for HCC preoperatively, not just after laparotomy. For patients with more than one malignant lesion, liver transplantation (instead of liver resection) should be the preferred treatment[33], as long as additional lesion can be identified preoperatively. In other words, individualized treatments are advisable for patients with HCC.

In the present study, the overall diagnostic sensitivity, specificity and accuracy rates of CEUS + CT/MRI were much better than those of CE-CT/MRI (89.4% *vs* 78.7%, $P = 0.046$; 100% *vs* 72.7%, $P = 0.004$; 92.1% *vs* 77.2%, $P = 0.001$, respectively). With the use of CEUS + CE-CT/MRI, the TNM staging of tumors approximated to the final pathological TNM staging ($P = 0.977$), which was more accurate than TNM staging based on CE-CT/MRI ($P = 0.002$), as shown in Table 3. With CEUS + CE-CT/MRI, more accurate staging can better meet clinical needs and help to make the most appropriate treatment decision. On the other hand, compared with IOUS, the combination of these two preoperative imaging modalities can provide the same sensitivity but higher specificity and accuracy, overcoming the disadvantages of IOUS and CEIOUS, which must be performed after laparotomy. This imaging strategy may help surgeons to choose patients who meet the indications for surgical intervention and to evaluate the safety and radicality of surgery. CEUS provided additional information for HCC staging. Several studies[4,6,34,35] have reported that IOUS affects the surgical approach in 11.5%-41.3% of patients with liver tumors. However, combining CEUS with CT/MRI changed the surgical approach in 15.9% (11/69) patients before surgery. Finally, only 5.7% (4/69) of the surgical strategies were changed because of IOUS detection of new lesions, which was lower than reported in previous studies. Thereafter, we suggest that preoperative CEUS should be a standard examination for patients undergoing liver resection.

To investigate the impact of tumor size, we divided the patients into two groups, the "Smaller group"(S-group) and the "Larger-group" (L-group). In the S-group, CEUS revealed 12 false positive lesions, consisting of seven false positive lesions that were diagnosed by preoperative imaging and five by IOUS. In the L-group, IOUS revealed eight new malignant lesions, consisting of six true HCCs, which were also diagnosed by CEUS. The following reasons may account for this phenomenon. Firstly, the Ishak scores of the S-group patients (Ishak: 5.54 ± 0.90) were higher than those of the L-group patients (Ishak: 4.86 ± 1.25, $P < 0.05$). The more severe cirrhosis may have contributed to the difficulty of distinguishing malignant lesions from benign lesions using other contrast enhanced imaging techniques. In addition, the restricted follow-up in the S-group patients could have helped to diagnose small HCCs earlier than in the L-group patients, whose nodules were larger than 5 cm when discovered. Therefore, CEUS may be better at identifying non-malignant lesions in small HCCs ($\leqslant$ 5 cm), which is vitally important for patients awaiting a liver transplant who have more than one lesion noted by CT or MRI. If CEUS could better identify non-malignant lesions, more patients would have the opportunity to receive liver transplants. In our study, CEUS discovered six new malignant lesions in larger HCCs (> 5 cm). In larger and more advanced HCC, liver resection is considered the standard of care[36,37]. Discovering the presence of previously undetected, smaller malignancies plays a crucial role in ensuring that surgery is safe and appropriate. More studies are needed to confirm the influence of tumor size on the results of these imaging studies.

The limitations of the paper are as followed: first, the number of subjects in our study was relatively small, and more studies on the impact of tumor size are needed to confirm the results; secondly, although our study was a prospective study, it was still not a randomized controlled trial. The contrast-enhanced ultrasound also had certain disadvantages, such as a short arterial phase and the potential to be affected by the tumor's location and motion artifacts.

CEUS combined with CT or MRI improves the accuracy of preoperative staging for hepatocellular carcinoma and could help to guide individualized treatments for patients with hepatocellular carcinoma. CEUS may identify more accurately non-malignant lesions in patients with small HCC ($\leqslant$ 5 cm), and discover new malignant lesions in larger HCCs (> 5 cm).

COMMENTS

Background

Early stage hepatocellular carcinomas (HCCs) are very difficult to distinguish from premalignant dysplastic nodules. Contrast-enhanced ultrasound (CEUS) improves nodule characterization, which may help to differentiate HCCs from premalignant dysplastic nodules. Therefore, the authors investigated whether contrast-enhanced ultrasound could improve the preoperative staging of HCC and guide individual treatments.

Research frontiers

CEUS techniques using second generation contrast agents (SonoVue) can analyze the detailed intratumoral vasculature in real time, which may be helpful to distinguish between HCC and premalignant dysplastic nodules.

Innovations and breakthroughs

The use of CEUS combined with computed tomography (CT) or magnetic resonance imaging (MRI) improved the accuracy of tumor node metastasis staging for hepatocellular carcinoma, and may help to guide individualized treatments and assist surgeons in evaluating the safety and radicality of operation.

Applications

The study results suggested that a preoperative contrast enhanced ultrasound examination should be a standard for patients undergoing liver resection.

Terminology

Contrast-enhanced ultrasound with a low mechanical index, and using second-generation contrast agents, can depict vasculature of hepatocellular carcinoma and allows continuous real-time imaging of the whole liver to be performed with slow panoramic sweeps. This technique helps to differentiate malignant nodules from benign lesions.

Peer review

In this prospective study, the authors assessed the diagnostic efficacy and changes in treatment decision after adding contrast enhanced ultrasound to contrast enhanced CT or MRI in patients with hepatocellular carcinoma undergoing hepatic resection. The work has clinical significance and is of benefit to the patients and the medical community at large. The results are interesting and suggest that CEUS combined with CT or MRI can improve the staging of hepatocellular carcinoma, which could be helpful to guide individualized treatment for patients with hepatocellular carcinoma.

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