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Diagnostic value of contrast-enhanced ultrasound versus computed tomography for hepatocellular carcinoma: a retrospective, single-center evaluation of 234 patients

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Abstract

Objective: Hepatocellular carcinoma (HCC) is the most common cause of primary liver cancer. A major part of diagnostic HCC work-up is based on imaging findings from sonography, computed tomography (CT), or magnetic resonance imaging (MRI) scans. Contrast-enhanced ultrasound (CEUS) allows for the dynamic assessment of the microperfusion pattern of suspicious liver lesions. This study aimed to evaluate the diagnostic value of CEUS compared with CT scans for assessing HCC.

Methods: We performed a retrospective, single-center study between 2004 and 2018 on 234 patients with suspicious liver lesions who underwent CEUS and CT examinations. All patients underwent native B-mode, color Doppler and CEUS after providing informed consent. Every CEUS examination was performed and interpreted by a single experienced radiologist (European Federation of Societies for Ultrasound in Medicine and Biology level 3).

Results: CEUS was performed on all included patients without occurrence of any adverse effects. CEUS showed a sensitivity of 94%, a specificity of 70%, a positive predictive value of 93% and a negative predictive value of 72% for analyzing HCC compared with CT as the diagnostic gold standard.

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Conclusions: CEUS has an excellent safety profile and shows a high diagnostic accuracy in assessing HCC compared with corresponding results from CT scans.

Keywords

Hepatocellular carcinoma, liver, contrast-enhanced ultrasound, computed tomography, lesion, microperfusion

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Introduction

Hepatocellular carcinoma (HCC) is the most common cause of primary hepatic cancer, the sixth most common neoplasm, and the second most lethal tumor entity.[1–3] HCC mainly develops in patients with underlying chronic liver diseases, with varying risks depending on the geographical area. The benefit of HCC surveillance in cirrhotic patients is diagnosing HCC at early stages and thus offering potential curative therapeutic options, as shown in multiple clinical trials.[4,5] Surveillance of patients with chronic liver disease and at relevant risk for development of HCC, especially with cirrhosis, is recommended by leading hepatology societies.[6,7] The preferred imaging modality for liver cancer surveillance is ultrasonography with a diagnostic sensitivity up to 80% and a specificity of more than 90%.[8] Semiannual screening is more beneficial than screening at a 12-month interval. Additionally, a 3-month interval does not show increased survival rates or higher detection rates for small HCC lesions ($\leq$3 cm) and there are higher costs.[9,10] A disadvantage of sonographic surveillance is its operator dependency. Additionally, tumor markers, such as alpha-fetoprotein, have been evaluated for HCC surveillance.[11–13] The combination of a sonographic examination and detection of alpha-fetoprotein shows increased detection rates for HCC.[11] However, valid new biomarkers for early detection of HCC need to be established.

Malignant liver lesions show altered vascularization compared with adjacent unaffected liver parenchyma, while the healthy liver is dominantly supplied by portal venous branches. This results in a typical enhancing pattern of hyperenhancement during the early arterial phase and hypoenhancement/wash-out during the venous or delayed phases on computed tomography (CT) and magnet resonance imaging (MRI) scans. Multiple clinical studies have shown a high diagnostic accuracy for diagnosing HCC using the typical vascularization pattern.[14] The characteristic vascularization pattern can further dynamically be visualized via contrast-enhanced ultrasound (CEUS).[15–18] The advantage of non-ionizing CEUS is its safety, immediately availability, repeatability, and cost effectiveness.[19–23] Using the Liver Imaging Reporting and Data System allows for standardized screening, surveillance, diagnosing, and treatment response assessment of HCC by applying CT, MRI, or CEUS.[24] In indeterminate cases, biopsy and histopathological analysis need to complement the diagnostic work-up.

This study aimed to evaluate the diagnostic performance of CEUS in assessing HCC lesions compared with findings from corresponding CT scans.

Patients and methods

This retrospective, single-center study was approved by the ethics committee of the Medical Faculty, Ludwig-Maximilians-

University. All contributing authors followed the ethical guidelines for publication in the Journal of International Medical Research. All study data were gathered according to the principles expressed in the Declaration of Helsinki/Edinburgh 2002. Oral and written informed consent of all patients was provided before CEUS examinations and their associated risks and potential complications were carefully described.

All CEUS examinations were performed and analyzed by a single skilled radiologist with experience since 2000 (European Federation of Societies for Ultrasound in Medicine and Biology level 3). All included patients underwent native B-mode, color Doppler, and CEUS scans. Up-to-date, high-end ultrasound systems with adequate CEUS protocols were used (LOGIQ L9; GE Healthcare, Chicago, IL, USA; Ultrasound Sequoia, ACUSON Sequoia; Siemens, Mountain View, CA, USA; Philips Ultrasound iU22, EPIQ 7, Philips, Seattle, WA, USA). A low mechanical index was used to avoid early destruction of microbubbles (<0.2). For all CEUS examinations, the second-generation blood pool contrast agent SonoVue® (Bracco, Milan, Italy) was used.[19] 1.2 to 1.5 mL of SonoVue were applied. SonoVue is a purely intravascular contrast agent that does not diffuse into the interstitial space, thus allowing for dynamic assessment of the microcirculation. After the contrast agent was applied, a bolus of 5 to 10 mL of sterile 09% sodium chloride solution was provided. Hepatic lesions of interest were analyzed during the early arterial phase (10–45 s), portal venous phase (30–120 s), and late venous phase (120 s to 4–6 minutes) at intermittent imaging to reduce destruction of microbubbles. All patients were scanned for at least 5 minutes to guarantee thorough visualization of the sonomorphological appearance upon intravenous application of SonoVue. No adverse side effects upon administration of SonoVue® were observed. All CEUS examinations were successfully performed and the image quality was sufficient in every case. The patients' files and imaging records were collected from the archiving system of our institution.

A total of 385 patients underwent a CEUS examination of the liver between 2004 and 2018. Of these, 234 also underwent a CT scan in our Department and were included in this retrospective, single-center study. CEUS and CT data were retrieved from the Picture Archiving and Communication System of our institution. Rapid, homogenous, and intense early arterial contrast enhancement following late venous wash-out of the hepatic lesions of interest during CEUS or/and CT was required for establishing the diagnosis of HCC. Contrast-enhanced CT scans were performed using established scanning protocols for evaluation of HCC as follows: native, arterial and portal venous phases of the upper abdomen; and a delayed venous phase of the abdomen at axial, coronal, and sagittal reformation. The extracellular contrast agent Ultravist® 300 mg/mL was used for contrast-enhanced CT scans. Different CT scanners used included Siemens SOMATOM Force, Siemens SOMATOM Definition Flash, and Siemens SOMATOM Definition AS (Siemens Healthcare, Erlangen, Bavaria, Germany).

We analyzed diagnostic sensitivity, specificity, the positive predictive value, the negative predictive value, and the kappa coefficient for assessing interrater reliability of CEUS with CT as the gold standard. Analysis was performed using Graph Pad Prism (GraphPad Software Inc., La Jolla, CA, USA).

Results

Between 2004 and 2018, 234 patients underwent a CEUS examination with a predilection in men (164 male vs. 58 female patients, 74% vs. 26%, respectively). The mean age of the patients at the time of the CEUS examination was 63 years (range: 20–89 years). We further subdivided HCC lesions into four subtypes depending on the lesion size: $<$1.0 cm (range: 0.6–0.9 cm; mean: 0.7 cm), 1.0 to 3.0 cm (mean: 2.0 cm), 3.1 to 5.0 cm (mean: 4.1 cm), and $>$5.0 cm (range: 5.5–18.0 cm, mean: 6.7 cm), which comprised 5%, 48%, 24%, and 23% of the included cohort, respectively.

For the entire cohort, CEUS showed a sensitivity of 94%, a specificity of 70%, a positive predictive value of 93%, and a negative predictive value of 72% for assessing HCC compared with corresponding findings from CT scans as the reference imaging modality. The kappa coefficient between CEUS and CT showed a value of 0.704 ($p<0.001$). For the subgroups of HCC lesions at sizes of $<$1.0 cm, 1.0 to 3.0 cm, 3.1 to 5.0 cm, and $>$5.0 cm, CEUS had a sensitivity of 80%, 92%, 98%, 98%, a specificity of 75%, 57%, 40%, and 67%, a positive predictive value of 80%, 84%, 93%, and 98%, and a negative predictive value of 75%, 57%, 67%, and 67%, respectively.

The HCC-specific contrast enhancement pattern of HCC lesions in CEUS and CT is shown in Figures 1 and 2.

Discussion

Conventional ultrasonography, comprising native B-mode and color Doppler, still is the imaging modality of first choice for HCC surveillance in patients with chronic liver disease. The major hepatology societies recommend surveillance of high-risk patients semiannually. CEUS allows for effectively differentiating between various hepatic lesions, such as hemangioma, focal

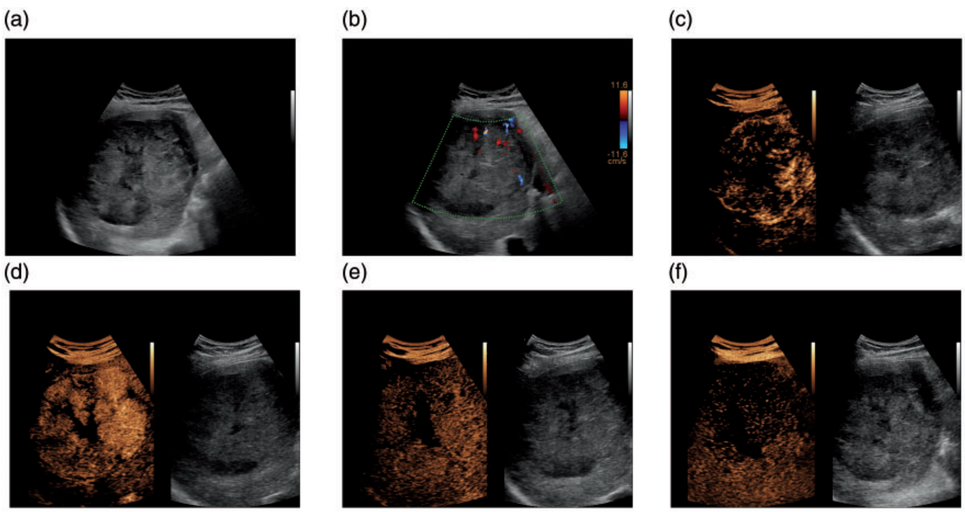

Figure 1. Representative sonomorphological features of hepatocellular carcinoma in contrast-enhanced ultrasound. a. Native B-mode shows an inhomogeneous hepatic mass in the right liver lobe. b. Intralesional hypervascularization is visualized in color Doppler. c. Early arterial hyperenhancement of the lesion in contrast-enhanced ultrasound (left) and the corresponding gray-scale mode (right). d. Increased contrast enhancement of the lesion in contrast-enhanced ultrasound with contrast-sparing central necrosis (left) in the arterial phase and corresponding gray-scale mode (right). e. Isoechogenicity of the lesion compared with adjacent liver tissue in the portal venous phase (contrast-enhanced ultrasound, left side; gray-scale mode, right side). f. Wash-out and resulting hypoechogenicity of the lesion in the delayed venous phase (contrast-enhanced ultrasound, left side, gray-scale mode, right side).

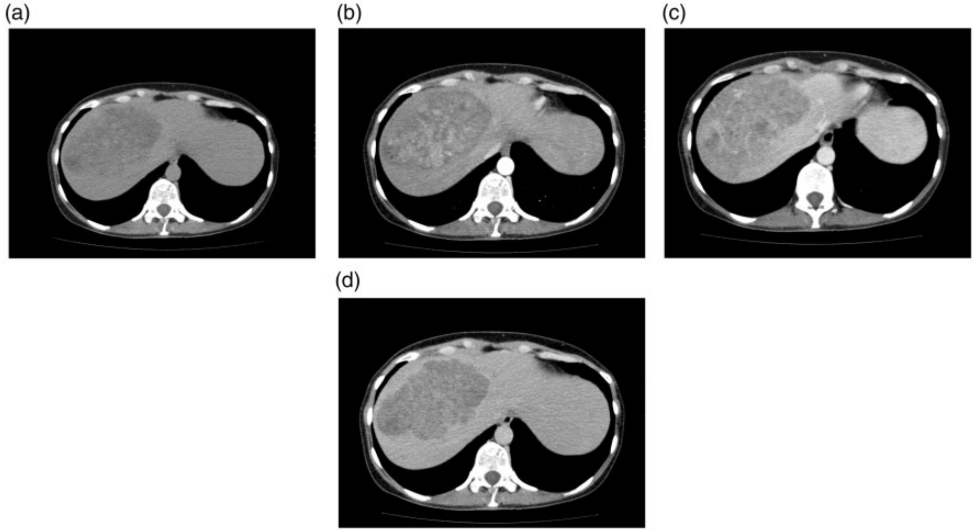

Figure 2. Computed tomographic morphological features of hepatocellular carcinoma. a. Inhomogeneous mainly hypodense mass in the right liver lobe in the native phase. b. Diffuse early arterial hyperenhancement of the mass in the arterial phase. c. Discrete partial wash-out in the portal venous phase. d. Marked wash-out in the delayed venous phase.

nodular hyperplasia, metastases, HCC, arteriovenous malformation, and echinococcal manifestations[25–31] at a lower rate of adverse effects compared with more elaborate imaging modalities. However, the limitations of CEUS must be considered over CT and MRI. These limitations include a restricted ability of staging, limited diagnostic accuracy in people with obesity and cirrhotic patients because of a poor sonic window, and a risk of misdiagnosing intrahepatic cholangiocarcinoma as HCC.[32,33]

This retrospective, single-center study aimed to assess the diagnostic performance of CEUS in evaluating HCC compared with findings from corresponding CT scans as the reference imaging modality. We found that CEUS had a high diagnostic accuracy in assessing HCC. The kappa coefficient between CEUS and CT findings was 0.704, which is considered as a substantial degree of agreement between CEUS and CT findings. These data are in line with previous studies.[34–38] In a prospective, clinical study, CEUS showed comparable results with corresponding CT findings visualizing hypervascularization of HCC lesions and even showed superior diagnostic performance considering late venous wash-out.[39] Furthermore, a multicenter trial showed that the diagnostic performance of CEUS was equivalent to that of CT scans concerning tumor differentiation and specification.[17] The limited diagnostic power of elaborate imaging modalities in case of smaller HCC lesions was described in a retrospective study. This retrospective study showed that typical HCC features were less frequently detected by using MRI in HCC lesions of <1.5 cm in diameter.[40] This diagnosis of features might be improved by using CEUS, which allows for visualization with a striking spatial and temporal resolution. Our results are in line with previous studies showing that CEUS has a high diagnostic accuracy for detecting small HCC lesions.[41,42]

In the present study, in 22 indeterminate findings from CEUS versus CT, contrast-enhanced MRI or histopathology was performed to compare findings with these modalities. In 18/22 cases (82%), MRI/histopathology confirmed findings from CEUS examinations, whereas diagnosis as established by CT was validated in only 4/22 cases (18%). In other cases when results from CEUS strongly indicated HCC and CT, or even MRI scans were not able to visualize a suspicious lesion, a histopathological correlation eventually showed HCC. In one of our cases, CEUS suggested intrahepatic cholangiocellular cancer featuring moderate arterial enhancement in the periphery of the lesion and subsequent early venous wash-out. Corresponding findings from a CT scan suggested HCC. Histopathology finally validated suspected intrahepatic cholangiocellular cancer.[43,44] False-negative findings were either correlated with results from MRI or histopathological results and comprised vascular pseudolesions, hemangioma, and echinococcosis. In another of our cases, findings from CEUS and CT scans strongly suggested intrahepatic cholangiocellular cancer, which was histopathologically confirmed. However, CEUS is not recommended as a primary imaging modality by the leading hepatology societies.[6,7,45,46] Except for the American Association for the Study of Liver Diseases, CEUS is regarded as a secondary imaging option.

The incidence of HCC is increasing because of several reasons, such as advanced surveillance programs, a growing age of hepatitis C virus-infected patients because of advanced therapies and spread of the Western lifestyle, and the associated effect of non-alcoholic steatohepatitis.[47,48] An essential proportion of patients with non-alcoholic steatohepatitis shows progression to HCC without cirrhosis.[48,49] A large retrospective study showed that patients with non-alcoholic fatty liver disease underwent surveillance at less frequent intervals than alcohol- or hepatitis C virus-induced liver disease.[50] Patients with non-alcoholic steatohepatitis are unlikely be enrolled in surveillance programs without developing cirrhosis.

The performance of conventional ultrasound is of inferior value compared with CEUS.[51] Benign and malignant lesions might share sonomorphological features,[52] thus leading to potential misdiagnosis. Interestingly, CEUS has already been shown to be a cost-effective tool for HCC surveillance.[53] Despite the known diagnostic superiority of CEUS compared with conventional sonography, no recommendation for using CEUS in the context of HCC surveillance in patients with chronic liver disease has been pronounced by the leading hepatology societies. Therefore, further evaluation on whether CEUS might be a feasible diagnostic tool for HCC surveillance is required.

The availability, repeatability, excellent safety profile, and economic benefit of CEUS are attractive in the context of liver cancer surveillance. Patients with chronic liver disease have concomitant impaired renal function, and therefore, more elaborate CT and MRI scans are not feasible for these patients. In a recent meta-analysis, no definite recommendation for either extracellular contrast-enhanced CT/MRI or gadoxetate-enhanced MRI for HCC diagnosis was made.[14] Both modalities show limited accuracy for lesions of <1.0 cm in diameter. Therefore, there is diagnostic potential of CEUS allowing for real-time visualization of smaller hepatic lesions with high temporal resolution. Our results support this notion. CEUS was recently shown to be complementarily used when MRI results remain indeterminate and CEUS allows for detection of HCC.[54]

Advantages of CEUS include its capability of dynamically analyzing parenchymal and tumor microperfusion at a more accurate temporal and spatial resolution than CT and MRI. Notably, safe application of CEUS in pediatric patients has already been described in several clinical trials and eventually led to its approval for pediatric liver imaging by the Food and Drug Administration.[55] Consequently, CEUS is a powerful diagnostic instrument for evaluating HCC lesions and can be used with less hesitation in renal impairment, hyperthyroidism, pregnancy, and in pediatric patients compared with CT scans. The role of CEUS as a first-line diagnostic tool for characterizing HCC and in the context of cancer surveillance still needs to be determined in future clinical trials.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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