

Contrast Enhanced Ultrasound for the characterization of hepatocellular carcinoma

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Abstract

Aim: Contrast-Enhanced Ultrasound (CEUS) is an imaging method that can discriminate between hepatocellular carcinoma (HCC) and other liver lesions. The purpose of this study is to present our experience concerning the use of CEUS in the characterization of HCCs. **Material and method:** We included in our study all the patients evaluated in our Department from September 2009 to October 2010, with focal liver lesions (FLLs) on abdominal ultrasound (US) that were diagnosed as HCCs after CEUS examination, also patients with chronic liver disease with focal liver lesions highly suspected to be HCCs but with an inconclusive pattern on CEUS. One hundred patients with 148 HCCs were included. The enhancement pattern of the nodules was evaluated according to the 2008 EFSUMB Guidelines. Nodules displaying arterial hyperenhancement with “washout” in the portal/venous phase on CEUS were considered diagnostic for HCC. Nodules considered indeterminate after CEUS were evaluated by contrast-enhanced CT or MRI for diagnosis. **Results:** Among the 100 patients included, 96 were patients with chronic liver disease and 4 were patients without known liver disease. 71 patients had a solitary nodule, 16 patients had two nodules and 13 patients had three or more nodules. 112 HCCs had a typical enhancement pattern and 36 nodules were considered indeterminate after CEUS and were sent to CT/ MRI for diagnosis. **Conclusions:** 75.7% of the studied liver nodules were diagnosed by CEUS as HCCs, thus CEUS is an easy method, convenient to perform, avoiding other expensive examinations.

Keywords: hepatocellular carcinoma, Contrast Enhanced Ultrasound, SonoVue

Rezumat

Scop: Ecografia cu substanță de contrast (CEUS) este o metodă imagistică care poate face diferențierea între carcinomul hepatocelular și alte tipuri de leziuni hepatice. Scopul acestui studiu a fost prezentarea experienței noastre în ceea ce privește folosirea CEUS pentru caracterizarea hepatocarcinomelor (HCC). **Material și metodă:** Am luat în studiu pacienții examinați în clinica noastră în perioada Septembrie 2009-Octombrie 2010 cu leziuni hepatice circumscrise descoperite prin ecografie abdominală și la care s-a stabilit diagnosticul de HCC în urma examinării prin CEUS precum și pe cei cu hepatopatie cronică la care a existat suspiciunea majoră de HCC, dar la care pattern-ul nodulilor a fost necaracteristic. Am inclus 100 de pacienți cu 148 de hepatocarcinoame. Pattern-ul de captare al nodulilor a fost evaluat în conformitate cu ghidurile EFSUMB din 2008. Nodulii care au fost hipercaptanți în faza arterială cu spălare în faza portală/venoasă au fost considerați patognomonici pentru diagnosticul de HCC. Nodulii care au fost considerați necaracteristici după CEUS au fost evaluați prin CT sau RMN cu contrast pentru stabilirea diagnosticului. **Rezultate:** Din cei 100 de pacienți incluși în studiu, 96 au avut hepatopatie cronică, iar 4 nu. 71 de pacienți au avut un singur nodul, 16 pacienți au avut 2 noduli, iar 13 pacienți au avut trei sau mai mulți noduli. 112 noduli hepatici au avut comportament tipic de HCC la CEUS, iar 36 de noduli au avut comportament necaracteristic și au fost examinați și prin CT/RMN pentru diagnostic. **Concluzii:** 75,7% din nodulii hepatici studiați au fost diagnosticați prin CEUS ca HCC-uri, astfel că metoda este una facilă, convenabil de efectuat, evitându-se astfel alte metode costisitoare de diagnostic.

Cuvinte cheie: hepatocarcinom, ecografie cu substanță de contrast, SonoVue

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Introduction

Incidental liver lesions discovered on standard US must be evaluated by means of different imaging methods, and, sometimes, this can be a stressful event for the patients, during the waiting time for a new method of evaluation (contrast CT or MRI) [1]. Hepatocellular carcinoma (HCC) is one of the most common malignant tu-

mors worldwide that accounts for 70%–85% of primary liver cancer cases, with the burden of disease expected to increase in coming years [2]. Early diagnosis of HCC has become a principal objective in abdominal imaging, because several potentially curative treatment options, such as liver transplantation, surgical resection, and local ablation therapy, can be successfully used to improve the outcome of the detected HCC [3]. Depiction of the intral-lesional vascular architecture is a critical issue for HCC as it is helpful in the diagnosis and prognosis evaluation [4].

In the latter years, Contrast Enhanced US (CEUS) has become a reliable imaging method for the assessment of incidental liver lesions [1]. It is a safe and easily performed technique, with no requirement for ionizing radiation and no risk of nephrotoxicity, that proved to be a method that can achieve the sensitivity and specificity of Multidetector Contrast Enhanced Computed Tomography (MD-CT) and Contrast Enhanced Magnetic Resonance Imaging (CE-MRI), for liver tumor detection and characterization [5]. The first set of Guidelines for the application of CEUS in clinical practice were issued in 2004 [6], than revised in 2008 [7] by The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB).

The characterization of a hepatic lesion with microbubbles depends on all phases of contrast enhancement, i.e. the hepatic arterial phase (starting from 10-20 s after injection of contrast agent and lasting for about 10-15 s), portal venous phase (up to 120 s post-injection) and late parenchymal phase (up to 4-6 min after injection). The arterial phase helps in predicting the degree and pattern of vascularity, while the portal and late phases are helpful in determining the nature of a lesion, as most malignant lesions are hypo-enhancing in contrast while the benign lesions are iso- or hyper-enhancing [7].

In general, a heterogeneous or homogeneous hyper-enhancement during the arterial phase and “washout” in the portal/late phase are typical findings for HCC on CEUS [4]. The arterial enhancement in HCC is usually homogeneous, but it can also be heterogeneous, due to fatty degeneration or intratumoral necrosis [8].

The heterogeneity of HCC, contributed by various factors including tumor burden, the presence and severity of underlying cirrhosis and performance status, contributes to the complexity of patient care and evaluation [9].

The aim of this study was to present our experience concerning the use of CEUS in the characterization and the diagnosis of hepatocellular carcinoma and to find if the lesion enhancement patterns on contrast ultrasound could provide enough information to enable clinicians to make the correct diagnosis of HCC, without enhanced CT or MRI.

Patients and method

We included in our study patients with FLLs on US diagnosed as HCCs after CEUS examination, also patients with chronic liver disease with focal liver lesions highly suspected to be HCCs but with inconclusive pattern on CEUS. A total of 100 patients met the inclusion criteria (69 men, 31 women; age ranging from 25 to 85 years). From the 100 patients, 80 (80%) had liver cirrhosis (diagnosed based on clinical, biological, ultrasound, endoscopic criteria – esophageal varices in a patient with chronic liver disease - and/or liver biopsy), 16 (16%) had chronic viral hepatitis and 4 (4%) were patients without known liver disease. We examined 148 liver nodules (in 100 subjects) incidentally detected by gray-scale ultrasound (US). All the nodules were finally diagnosed as HCCs based on the enhancement pattern after CEUS or/and contrast CT/MRI examinations.

Informed consent was obtained before enrolment and the study was approved by the Local Ethical Committee.

The inclusion criteria were as follows: patients with one or more liver nodules detected by conventional ultrasonography and suspected to be HCC, based on the clinical background of the patient (liver cirrhosis, blood tests for chronic viral hepatitis and tumor markers) and ultrasonographic aspect.

The exclusion criteria from this study were: patients with liver nodules treated by percutaneous methods, patients diagnosed with HCC previously investigated by CEUS, patients with acute coronary syndrome or clinically unstable ischemic cardiac disease and pregnant or lactating women.

Target lesions were first identified using B-mode ultrasound. Then color or power Doppler was carried out to study the vascularity of target lesions and the surrounding parenchyma.

The CEUS examinations were performed for all patients with a Siemens Acuson S2000 scanner with incorporated Cadence™ contrast pulse sequencing (CPS) contrast-specific software and a transducer with 3.5 MHz transducer. The CPS technology was applied with a low mechanical index (0.08 MHz), to avoid microbubbles disruption. Each liver nodule was scanned after bolus injection of 2.4 mL of a sulfur hexafluoride-filled microbubble contrast medium SonoVue® (Bracco, Italy) via a 20-gauge intravenous catheter placed in the ante-cubital vein, followed by 10 ml saline flush. The contrast agent SonoVue® was provided as a sterile, lyophilized powder contained in a septum-sealed vial. The highly elastic bubbles are capable of both transpulmonary and trans-sinusoidal passage and are elimi-

nated from the blood through the lung: about 50% of the injected dose is removed within the first minute, and 80–90% is eliminated within 11 min after injection [10]. To diminish motion artifacts and avoid losing sight of the target tumor, investigators asked patients to hold their breath beginning 10 seconds after microbubble administration (when the first enhanced signal appeared in the liver). The target lesion and the surrounding liver parenchyma were then observed continuously for 5 min following bolus injection, without exploration of the remaining liver areas.

Enhancement patterns were studied during the vascular phase, including the arterial (15–30 seconds), portal (30–120 seconds), and late phase (120–300 seconds), according to the EFSUMB Guidelines from 2008. All CEUS examinations were then evaluated by level 2 or 3 investigators according to the EFSUMB classification, who formulated the final diagnosis. All sonographic examinations were digitally recorded and the pattern and enhancement of the nodules in each phase was noted. All patients were monitored for adverse events, until two hours after the procedure.

We classified the perfusion patterns on CEUS of each liver nodule during the arterial, portal and late phases. Lesions with higher, similar, or lower echogenicity compared with that of the adjacent liver parenchyma, were defined as hyperenhanced, iso-enhanced or hypo-enhanced, respectively. When the lesion began to appear hyperenhanced after injection, it was defined as enhancing. The enhanced lesion becoming hypo-enhanced was defined as having “washout”. On the basis of the appearance and enhancement characteristics, observed in the arterial, venous and late phase, the liver nodules were defined as either typical pattern for HCC or atypical pattern.

Liver nodules which appeared hyperenhanced by during the arterial phase and presented with contrast washout during the late phase on CEUS were diagnosed as hepatocellular carcinoma (HCC). The nodules that were considered indeterminate after CEUS examination, or atypical enhancement patterns, were sent to contrast-enhanced CT or MRI for diagnosis.

Summarized descriptive statistics were provided for continuous variables (mean and range) and percentages were calculated for categorical data.

Results

From all 100 patients included in the study 80 (80%) were patients with liver cirrhosis, 16 (16%) were patients with chronic viral hepatitis and 4 (4%) were patients without known liver disease.

All nodules included in the study were successfully studied during the arterial, portal and late phases with CEUS. No clinically significant side effects related to the sonographic contrast agent were experienced by patients. No patients were excluded from the study because of the inability to cooperate.

Among the 100 patients enrolled in the study, 71 (71%) of them had a solitary nodule, 16 (16%) had two nodules and 13 (13%) had multiple nodules.

At the end of the initial diagnostic work-up, the vast majority of the nodules, 112 of 148 nodules (75.7%) examined by CEUS had typical enhancement pattern for HCC and had been diagnosed as HCC. The remaining 36 liver nodules (24.3%) considered indeterminate after CEUS examination were sent to contrast-enhanced CT or MRI for diagnosis and were confirmed as HCCs.

In the arterial phase, 131 (88.5%) of the 148 nodules were hyperenhanced, 12 (8.1 %) were iso-enhanced, 1 nodule (0.7%) was hypo-enhanced with respect to the surrounding liver and 4 nodules (2.7%) were with no clear appreciable enhancement.

In the venous phase, 69 (46.6%) of the 148 nodules presented with a quick washout and become hypo-enhanced to the surrounding liver, 47 (31.8%) liver nodules remained hyperenhanced (did not washout), 28 (18.9%) were iso-enhanced with respect to the surrounding liver and 4 nodules (2.7%) were with no appreciable enhancement.

In the late phase 119 (80.4%) of the 148 nodules continued to “washout”, becoming more hypoechoic than the surrounding liver, 16 (10.8%) liver nodules did not “washout”, remaining hyperechoic, 10 (6.8%) were iso-echoic with respect to the surrounding liver and 3 nodules (2%) were with no appreciable enhancement.

In the figures 1 and 2 are presented examples of typical enhancement patterns of HCC at CEUS.

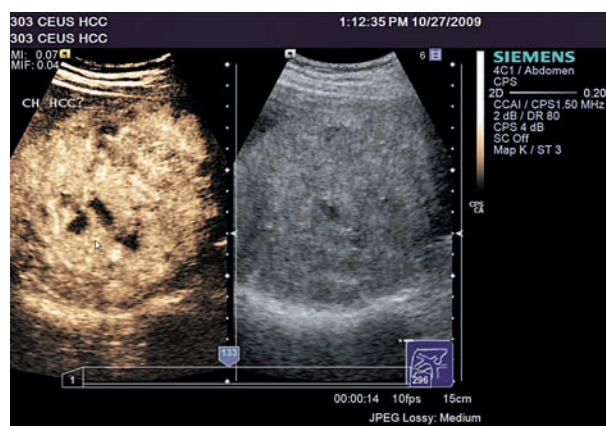


Fig 1. CEUS enhancement pattern of HCC in arterial phase

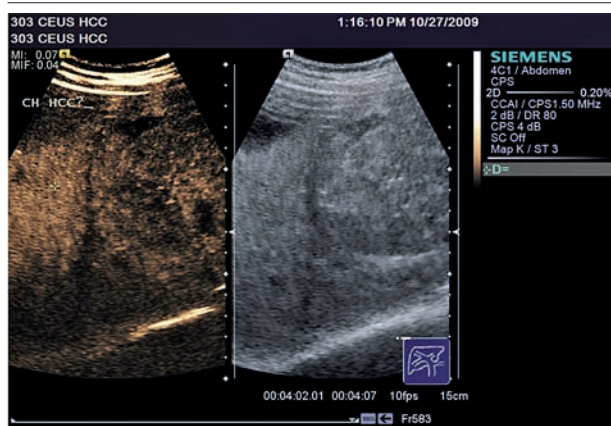


Fig 2. CEUS enhancement pattern of HCC in late phase

Discussions

The introduction of second-generation microbubble ultrasound contrast agents and the development of contrast specific ultrasound techniques have improved the ability of CEUS in detecting and characterizing liver lesions, offering new perspectives for its use in clinical hepatology [11]. Whereas the use of contrast agents has been established for CT or MRI, the value of contrast enhanced agents in the US (CEUS) of the liver is still under clinical investigation [12].

In the Guidelines for HCC management, issued by the American Association for the study of liver disease in 2005, CEUS was recommended as one of the noninvasive techniques in the demonstration of typical arterial hypervascularity and “washout” in the portal-venous phase (2 techniques mandatory) with a sensitivity of 92-94% and a specificity of 87-96% [13]. Furthermore, a lot of studies compared CEUS to other “gold standard” considered methods, for correctly diagnosing the liver tumors in clinical practice.

A DEGUM multicenter study included 1,349 patients with focal liver lesions discovered by standard US. CEUS was compared with a diagnostic “gold standard”: biopsy in more than 75% of the lesions, spiral contrast CT or contrast MRI in the rest of the cases [14]. The accuracy of CEUS for the diagnosis of focal liver lesions was 90.3%. Another German study showed that tumor-specific vascularity pattern could be assessed in most, but not in all cases studied, and that the diagnostic accuracy of CEUS was 83.1% for benign lesions, 95.8 % for malignant lesions, 91.4 % for liver metastases and 84.9 % for HCC [15]. Other, more recent, DEGUM prospective multicenter studies evaluated the diagnostic value of CEUS for the characterization of focal liver lesions in

clinical practice. In the first study CEUS was compared with the spiral-CT (standard radiological method) and in the second study, they compared CEUS with magnetic resonance imaging. The authors concluded that CEUS proved to be of equal rank to CT-scan in regard to the assessment of tumor differentiation and specification. The first study concluded that CEUS should be used before computed tomography for the differentiation of liver tumors, because therefore the radiation exposure and invasive biopsies can be avoided in a high number of cases [16]. The authors of the second study concluded that CEUS and MRI are of equal value for the differentiation and specification of newly discovered liver tumors in clinical practice and that CEUS and MRI are extremely reliable for the differentiation of benign and malignant lesions [17].

In a recently published French study it was shown that CEUS was more reliable than CT or MR techniques in the assessment of focal liver lesions [18]. In our study, the majority of the nodules, 112 of 148 (75.7%) examined by CEUS had a typical enhancement pattern for HCC (hyperenhancement in the arterial phase followed by “washout” in the late phases) and had been diagnosed as such. On the other hand, 88.5% of the nodules had a typical arterial enhancement, 65.5% presented “washout” in the portal phase and finally, 80.4% presented “washout” in the late phase. Since the strategy of performing CEUS first in cirrhotics with new nodules discovered on standard US was implemented in our Department, in 3/4 of cases we obtain the final diagnosis without the need of more expensive imaging methods. For the rest of the cases or when the acoustic window was not enough good, contrast CT or MRI is performed. This is a cost/efficient strategy as we demonstrated in a previously published study [19].

A number of studies showed that between 5% and 25% of focal liver lesions remained indeterminate even after CEUS [12, 20-24], since a benign or malignant diagnosis cannot be proposed due to the atypical enhancement pattern and need to be characterized by other diagnostic investigations. In our study, 36 of the 148 liver nodules studied (24.3%), did not satisfy the criteria for imaging-based diagnosis of HCC and had to be evaluated by contrast CT/MRI for a definitive diagnosis.

Two studies showed that CEUS sensitivity in the diagnosis of HCC is directly related to the size of the tumor. For nodules ≤ 2 cm, Giorgio et al. [25] and Galiani et al. [26] observed 53.6% and 83.3% sensitivities respectively, while for nodules > 2 cm the sensitivities were found to be 91.3% and 94.5%, respectively. A study designed to evaluate the diagnostic efficacy of contrast-enhanced helical computed tomography (CE-CT) and

CEUS has been conducted in patients with small hepatic nodules, previously detected by surveillance programs [27]. The sensitivity, specificity and diagnostic accuracy were 91.1%, 87.2%, and 89.3%, respectively, for CEUS. For CE-CT, the sensitivity, specificity and diagnostic accuracy were 80.4%, 97.9%, and 88.4%, respectively. The authors of the study found no significant difference between CEUS and CE-CT in characterizing small (1-2 cm) hepatic nodules [27].

In our study, 4 liver nodules examined by CEUS had no enhancement in all arterial, venous and late phases and another 2 liver nodules were isoenhanced in all arterial, venous and late phases, probably because the tumors were located deep into the liver and CEUS could not detect them.

There are some intrinsic limitations in CEUS, in generally, e.g. obese patients with abundant flatulence, or deeply situated lesions. Compared with CT or MRI, the performance of CEUS is more strongly influenced by the experience of the investigator, by patient-related factors (cooperativeness), by nodules dimensions and by nodule location. Another limitation of CEUS in comparison to multiphase CT and MR imaging is the fact that only one liver lesion can be examined at a time as the transducer has to be kept still during the examination, and further contrast injections are necessary to characterize other additional primary liver tumors. Another limitation is that the arterial phase in CEUS examination is about 30 s, which make it challenging to scan the entire liver for detection of multiple hypervascular HCC lesions.

Our study had some limitations. We were not able to evaluate the sensitivity, specificity and accuracy of this method in characterizing HCC. The small number of tumors was another limitation. Further investigations including a larger number of lesions are required.

Conclusions

Our study showed that CEUS examination is an easy, convenient and efficient procedure to perform, 75.7% of the studied liver nodules being diagnosed as hepatocellular carcinoma. CEUS provided enough information to establish a final diagnosis in the majority of the studied liver nodules, thus avoiding other expensive examinations such as enhanced CT/MRI.

Conflict of interest: none

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