

How Often Hepatocellular Carcinoma Has a Typical Pattern in Contrast Enhanced Ultrasound?

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ABSTRACT

Objectives: Contrast Enhanced Ultrasound is an imaging method that can evaluate immediately focal liver lesions discovered by ultrasound.

The aim of this study is to demonstrate if Contrast Enhanced Ultrasound can be reliable as a diagnostic method for hepatocellular carcinoma.

Material and methods: We included in our retrospective monocentric study all patients evaluated in our Department during 2 years, which had hepatocellular carcinoma as final diagnosis (using Contrast Enhanced Ultrasound, Contrast Enhanced Computed Tomography, Magnetic Resonance Imaging or biopsy). 91 patients with chronic liver diseases were evaluated, with a total of 114 liver nodules. The enhancement pattern of the nodules was evaluated according to the 2008 guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology. The lesions with arterial enhancement and washout in the portal or late phase were considered hepatocellular carcinoma. The nodules were classified according to their size in ≤ 3 cm and >3 cm.

Outcomes: Of all nodules, 103 had hyperenhancing arterial pattern and washout was observed in 79 cases. In our study, this method established the diagnosis of hepatocellular carcinoma in 45 of 55 cases with liver nodules larger than 3 cm (81.8%) vs. 34 of 59 cases with nodules smaller than 3 cm (57.6%) ($p < 0.001$).

Conclusions: 69.3% of all hepatocellular carcinoma had a typical enhancement pattern on Contrast Enhanced Ultrasound, performing better in nodules larger than 3 cm, than in smaller nodules ($p < 0.001$).

Keywords: hepatocellular carcinoma, Contrast Enhanced Ultrasound, vascular phases

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INTRODUCTION

Contrast Enhanced Ultrasound (CEUS) has become a reliable imaging method for the evaluation of incidental focal liver lesions (FLLs) (1). It is a safe method; there is no ionizing radiation and no risk of nephrotoxicity. Also, it has been demonstrated that CEUS can achieve the sensitivity and specificity of Contrast Enhanced Computed Tomography (CE-CT) and Contrast Enhanced Magnetic Resonance Imaging (CE-MRI), for detection and characterization of liver tumors (2). Hepatocellular carcinoma (HCC) accounts for 70-85% of primary liver cancer cases (3). Early diagnosis of HCC by an imaging method is very important, 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 (4). Depiction of the lesion's vascular architecture is a critical issue for HCC as it is helpful in the diagnosis (5).

The first set of Guidelines for the application of CEUS in clinical practice were issued in 2004 (6), than revised in 2008 (7) and latter in 2011, by The European Federation of Societies for Ultrasound in Medicine and Biology (EF-SUMB). During a CEUS examination the enhancement behavior of a hepatic lesion is observed in three vascular phases, i.e. the arterial phase (starting 10-20 s after injection of contrast agent and lasting for about 10-15 s), followed by the portal venous phase (up to 120 s post-injection) and late parenchymal phase (up to 4-6 min after injection). The arterial phase assess the vascularity pattern and density, while the portal and late phases are helpful in determining the nature of a lesion, as most malignant lesions are hypo-enhancing following contrast, while benign lesions are iso- or hyper-enhancing (7).

A hyperenhancing pattern during the arterial phase and "washout" in the portal or late phase are typical findings for HCC on CEUS (5). The arterial enhancement in HCC is usually homogeneous, but it can also be heterogeneous, due to fatty degeneration or tumor 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 is to demonstrate if CEUS can be reliable as a diagnostic method for hepatocellular carcinoma (HCC), based on typical enhancement pattern. On the other hand, we wanted to find if the size of the tumor modifies CEUS sensitivity for the diagnosis of HCC. □

MATERIAL AND METHODS

We included in our study patients with a final diagnosis of HCC, established by an imaging method. A total of 91 patients with chronic liver disease met the inclusion criteria (63 men, 28 women; age ranging from 25 to 85 years). We examined 114 liver nodules (in 91 subjects) detected by gray-scale ultrasound (US). 69 patients had liver cirrhosis and 22 of them presented chronic hepatopathy. All the nodules were finally diagnosed as HCCs, based on the enhancement pattern after CEUS or/and contrast CT/MRI examinations or biopsy.

The inclusion criteria were as follows: patients with one or more liver nodules detected by conventional ultrasonography and confirmed to be HCC, based on imaging methods or biopsy.

We did not include in our study: 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.

The study was approved by the Local Ethical Committee.

The CEUS was performed with a Siemens Acuson S2000 scanner with incorporated Candence™ contrast pulse sequencing (CPS) contrast-specific software and a 3.5 MHz transducer. The CPS technology was applied with a low mechanical index (maximum 0.08 MHz), to avoid microbubbles disruption. Each liver nodule was scanned after bolus injection of 2.4 mL of the 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 [10]. The target lesion and the surrounding liver parenchyma were observed continuously 5-6 min following bolus injection, without exploration of the re-

maining liver areas. The sonographic examinations were digitally recorded and the enhancement pattern of the nodules was noted.

Enhancement pattern was studied during arterial (15-30 seconds), portal (30-120 seconds) and late phases (120-300 seconds), according to the EFSUMB Guidelines from 2008. On the basis of the enhancement characteristics, observed in the arterial, venous and late phases, the liver nodules were defined as either with typical pattern for HCC (according to the 2008 EFSUMB Guidelines) or with atypical pattern. A typical pattern for HCC was considered to be: a liver nodule hyperenhanced during the arterial phase with washout during the late phase on CEUS.

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

OUTCOMES

All nodules included in the study were examined by CEUS, contrast CT/RMN or biopsy. No side effects related to the contrast agent were reported.

Among the 91 patients enrolled in the study, 73 (80.2%) had a solitary nodule, 13 (14.3%) had two nodules and 5 patients (5.5%) had three or multiple nodules.

In the arterial phase, 103 (90.3%) of the 114 nodules were hyperenhanced, 8 (7%) were iso-enhanced, 1 nodule (0.9%) was hypo-enhanced as compared to the surrounding liver and 2 nodules (1.7%) had no clearly appreciable enhancement pattern (too deep for a good ultrasound evaluation).

In the venous phase, 34 (38.6%) of the 114 nodules presented rapid washout and became hypo-enhanced as compared to the surrounding liver, 10/114 of nodules (8.8%) presented a

mild washout, 3 (2.6%) of the liver nodules remained hyperenhanced (had no washout), 65 (57 %) were iso-enhanced with respect to the surrounding liver and 2 nodules (1.7%) had no appreciable enhancement pattern.

In the late phase 64 (56.1%) of the 114 nodules continued to washout, becoming more hypo-enhanced than the surrounding liver, 3 (2.6 %) liver nodules showed no further washout, remaining hypo-enhanced, 13 (11.5 %) were discreetly hypo-enhanced as compared to the surrounding liver parenchyma, 28 (24.6%) were iso-enhanced and 2 nodules (1.7%) had no appreciable enhancement pattern (Figure 1). Typical pattern for HCC with SonoVue®.

Finally, of all the 114 nodules washout was observed in 79 cases (69.3%). On the other hand, from the 103 nodules hyperenhanced in the arterial phase, 79 (76.7%) had a definite washout in the late phase (Table I).

At the end of the initial diagnostic work-up by CEUS, 79 of 114 nodules (69.3%) had a typical enhancement pattern for HCC. The rest of 35 liver nodules (30.7%) were considered indeterminate after CEUS examination.

When nodule size was taken into consideration, CEUS established the diagnosis of HCC in 45 of 55 cases with liver nodules larger than 3 cm (81.8%) vs. 34 of 59 cases with nodules smaller than 3 cm (57.6%) ($p < 0.001$) (Table II). □

DISCUSSIONS

The use of second-generation microbubble ultrasound contrast agents improved the ability of CEUS in detecting and evaluating FLLs, offering new perspectives for its use in clinical hepatology (11).

In a multicenter study coordinated by DEGUM that included 1.349 patients with FLLs discovered by standard US, CEUS was com-



FIGURE 1. Typical pattern for HCC with SonoVue.

pared 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 (12). The accuracy of CEUS for the diagnosis of FLLs 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 (13).

The diagnostic value of CEUS for the characterization of FLLs in clinical practice was evaluated in several studies, starting from the database of the DEGUM study. In one of them (14), CEUS was compared with spiral-CT (standard radiological method) and in another one (15) 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 so the radiation exposure and invasive biopsies can be avoided in a high number of cases (14). The authors of the second study also 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 (15).

In a published French study, it was shown that CEUS was more reliable than CT or MR techniques in the assessment of FLLs (16).

In our study, 90.3% of the nodules in patients with chronic liver diseases had a typical arterial enhancement, thus being suspected for HCC, but only 69.3% of them presented a washout in the late phase. Of all 114 liver nodules included in our study, we observed a typical vascular CEUS pattern of HCC in 69.3% cases.

Finally 69.3% of the nodules examined by CEUS had a typical enhancement pattern for HCC (hyperenhancement in the arterial phase followed by washout in the portal and late phases) and had been diagnosed as such. Since the strategy of performing CEUS first in cirrhotic with new nodules discovered on standard US was implemented in our Department, in more than 2/3 of cases the final diagnosis was obtained without the need of more expensive imaging methods. For the rest of the cases (in-

CEUS phases	Arterial hyperenhancement	Portal washout	Late washout
Total			
114 nodules	103 (90.3%)	44 (38.6%)	79 (69.3%)

TABLE 1. CEUS enhancement pattern of the nodules.

Total	≤ 3 cm	> 3 cm
114 nodules	59 nodules	55 nodules
Conclusive for diagnosis with CEUS	34 (57.6%)	45 (81.8%)
Inconclusive for diagnosis	25 (42.4%)	10 (18.2%)

TABLE 2. CEUS diagnosis of HCC according to the nodule size.

conclusive cases in CEUS) or when the acoustic window is not good enough, contrast CT or MRI is performed. This is a cost/efficient strategy as we demonstrated in a previously published study (17).

In the study of A. Giorgio et al, small HCCs (<20 mm) presented hyperenhancement pattern in the arterial phase in 53.6% cases, as compared to 91.3% of the HCCs larger than 20 mm (18). In our study, HCCs smaller than 3 cm were hyperenhanced in the arterial phase in 93.2% cases and HCCs larger than 3 cm showed the same pattern in 87.3% cases. Also, we demonstrated that larger liver nodules (>3 cm) are more likely to be diagnosed as HCC on CEUS alone than smaller ones (p<0.001). The nodules less than 3 cm were diagnostic conclusive on CEUS in 57.6%, while nodules larger than 3 cm had a typical pattern in 81.8% of cases (p<0.001) (Table 2).

In another study, the majority of lesions (87%) showed classic hypervascularity in the arterial phase; 43% showed washout in the portal phase (up to 90 seconds), while late washout (91-300 seconds) occurred in 47% of the hypervascular tumors (19).

A number of studies showed that 5% to 25% of FLLs remained indeterminate after CEUS (20-25), because a benign or malignant diagnosis could not be sustained due to an atypical enhancement pattern and needed to be characterized by other diagnostic investigations. In our study, 30.7% (35 nodules) of the 114 liver nodules did not satisfy the criteria for imaging-based diagnosis of HCC.

One of the limitation of CEUS versus CT and MR imaging is the fact that only one liver lesion can be examined at a time, since the transducer has to be kept still during the examination. Our study had some limitations. We were not able to evaluate the specificity and accuracy of this method in characterizing HCCs. The small number of tumors was another limitation. □

CONCLUSIONS

In our study 69.3% of all HCCs had a typical enhancement pattern on CEUS. 90.3% of the liver nodules diagnosed as HCCs were hyper-

enhanced in the arterial phase and 69.3% presented washout in the late phase. CEUS performed better in nodules larger than 3 cm than in smaller nodules ($p < 0.001$).

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