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The diagnostic value of contrast-enhanced ultrasound in the management of HCC

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common gastrointestinal tumors and the third leading cause of cancer mortality [1]. Chronic hepatitis B and C, alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH) play a major role in the development of HCC. To reduce the mortality associated with HCC, early detection and initiation of curative therapy are essential.

While alpha-fetoprotein (AFP) levels and high resolution liver imaging are mainstays of monitoring programs for patients with chronic cirrhosis, contrast-enhanced ultrasound (CEUS) imaging visualizes HCC vascularity facilitating differential diagnoses. Being a dynamic real-time procedure, CEUS reflects both arterial wash-in and perfusion phases (portal venous and late phases) with high frame rates and outstanding spatial resolution. Since perfused (viable) and non-perfused (non-viable) areas are well distinguished, CEUS characterizes and differentiates liver tumors with high sensitivity and specificity [2]. CEUS can be used to select and monitor the most appropriate curative HCC therapy from the range available to best meet the needs of individual patients.

Diagnostic confirmation of focal liver lesions with CEUS

Ultrasound is a simple, inexpensive modality allowing differentiation of focal lesions from surrounding healthy tissue. Echogenic characteristics are varied and include lesions which appear echogenic, hypoechoic and/or inhomogeneous (Fig. 1). Fibrotic and cirrhotic liver parenchyma have different architecture to normal tissue because of the growth of

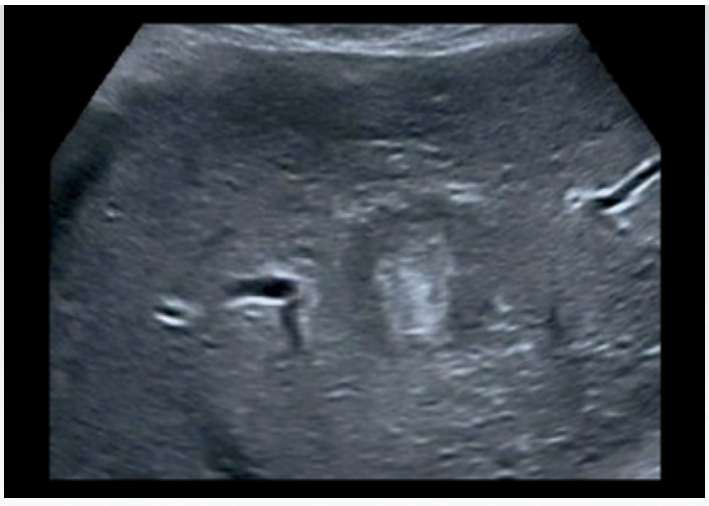

Fig. 1: B-mode representation of an HCC showing mixed echogenicity with both echogenic and hypoechoic areas.

connective tissue, subsequently the B-mode image is significantly more heterogeneous and hyperechoic than in normal liver, making the detection of focal lesions in this scenario more difficult. Moreover, regenerative processes in the cirrhotic liver appear heterogeneous, partly echogenic and partly hypoechoic in the B-mode image, making clear differentiation from tumor tissue with conventional ultrasound difficult.

The role of ultrasound is well established in the follow-up of patients with cirrhosis [3, 4]. It is well accepted by patients, is a low-cost procedure and reportedly offers reasonable diagnostic certainty with a sensitivity of up to 89 % and a specificity of 90 % [5, 6]. However the detection of small lesions (less than 2 cm diameter) depends to a great extent on operator experience and the quality of the ultrasound system [7]. The performance of low mechanical index (MI) contrast-enhanced ultrasound (CEUS) with SonoVue® (Bracco, Milan, Italy) allows greater characterization and diagnostic differentiation of focal lesions [2].

A typical HCC has a unique vascularization due to arterial neoangiogenesis. This vascularity can be visualized in CT, MRI and CEUS as contrast enhancement [8, 9, 10, 11]. Three distinct phases can be seen in HCC during CEUS evaluation. In the arterial phase the HCC is hyper-perfused compared to the surrounding tissue and presents as a region of hyper-echogenicity (Fig. 2). During the portal venous phase the contrast agent is washed out as portal venous blood supply in the HCC is less than that in the surrounding liver parenchyma (Fig. 3). In the late phase the wash-out increases and the HCC can be differentiated clearly from the surrounding parenchyma as a hypoechoic lesion. CEUS visualizes this vascularity with a sensitivity of up to 91 %, and a specificity of up to 92 % depending on operator experience [12, 13].

The intensity and speed of the wash-out correlate to the differentiation of the HCC, in well differentiated HCC (G1) wash-out is late and low, in less well differentiated HCC (G2 and G3) wash-out is early and strong [14].

CEUS real-time visualization of vessel architecture and vascularization allows recognition of different pathologic patterns greatly facilitating diagnosis (Fig. 4). Additional ultrasound data processing can lead to color-coded vessel patterns to represent arrival time of contrast (Fig. 5) or display 3D

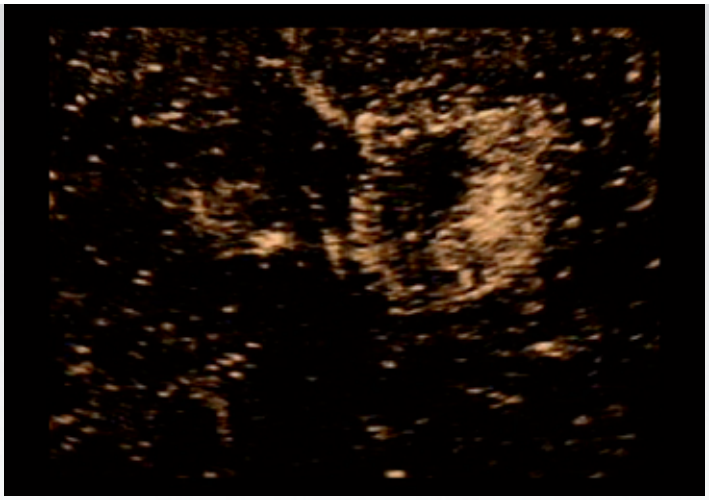

Fig. 2: CEUS image of an HCC showing the hyperechoic contrast agent during the wash-in phase.

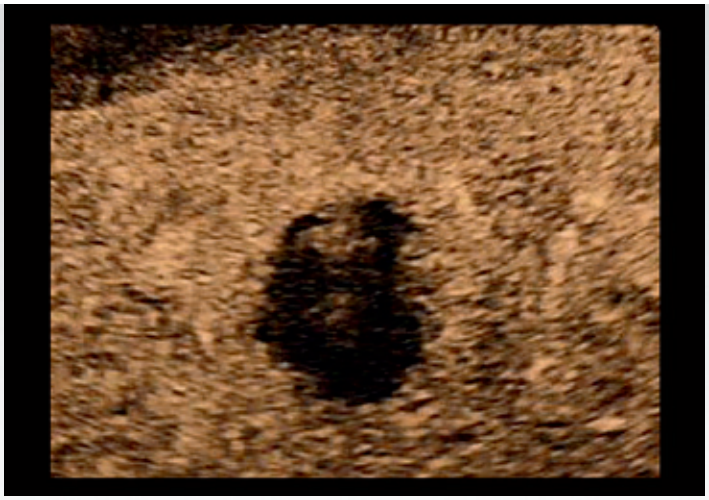

Fig. 3: CEUS image of an HCC depicted as anechoic region during the wash-out phase (portal venous and late phase).

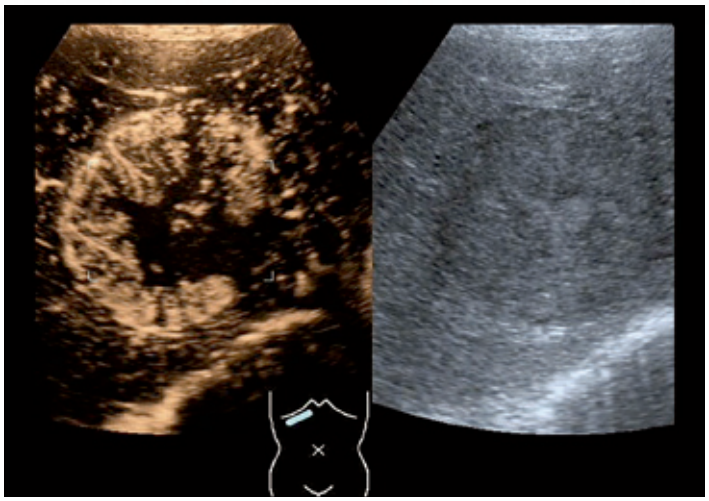

Fig. 4: Micro-architecture of the tumor blood supply can be visualized by CEUS.

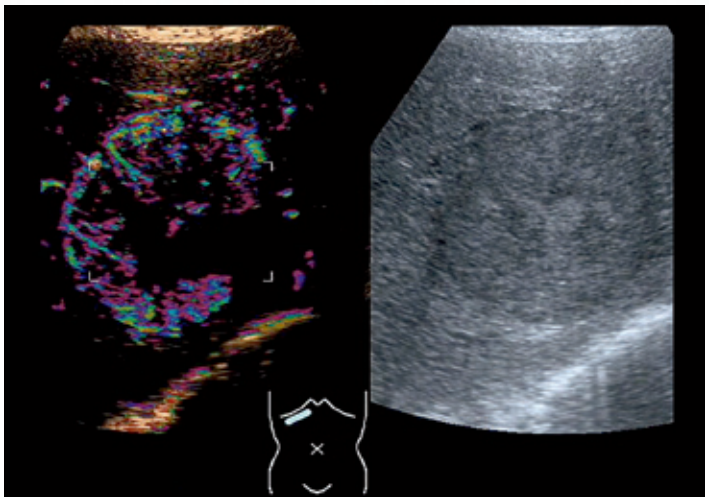

Fig. 5: Parametric imaging – color-coded representation of the “wash-in” phase in the tumor.

reconstructions (Fig. 6), aiding interpretation especially by inexperienced or non-imaging medical personnel. Raw data acquisition of CEUS enables to carry out a time curve analysis with graphical and numerical values for parameters such as time to peak, wash-in, wash-out and area under the curve.

Ultrasound and CEUS-assisted biopsy

In a non-surgical setting histological confirmation of HCC prior to any curative therapy is recommended. Ultrasound-guided biopsy is a safe and easy way to collect tissue samples. CEUS-assisted biopsy highlights the viable region of tumor tissue improving the sampling results [15].

Ultrasound and CEUS-assisted therapy

Sonography plays a vital role in the perioperative follow-up of HCC surgery. CEUS can incidentally also improve the diagnostic certainty in the diagnosis of hemorrhage, hematoma or abscess.

Local ablation procedures such as RFA (radio-frequency ablation) and PEI (percutaneous ethanol injection) are standard therapeutic options for inoperable patients [3, 16]. Such therapies require safe positioning of the probe. Ultrasound and specifically CEUS guidance supports the exact transcutaneous and intraoperative probe placement while allowing continuous monitoring of the ablation procedure [4] (Fig. 7).

The outcome of the ablation procedure is defined by the resultant extent of the coagulative necrosis – and thus tumor destruction. Tumor necrosis post ablation is visible in CEUS as a complete contrast defect at the ablated site in the arterial, portal venous and late phase (Fig. 8). Visible perfusion indicates viable tumor tissue requiring a repeat ablation (Fig. 9). Depending on tumor size and degree of the cirrhosis local ablation therapy can achieve a five-year survival rate of more than 70 % [17]. Hence optimization of the ablation outcome using CEUS has potential benefits for patient outcome.

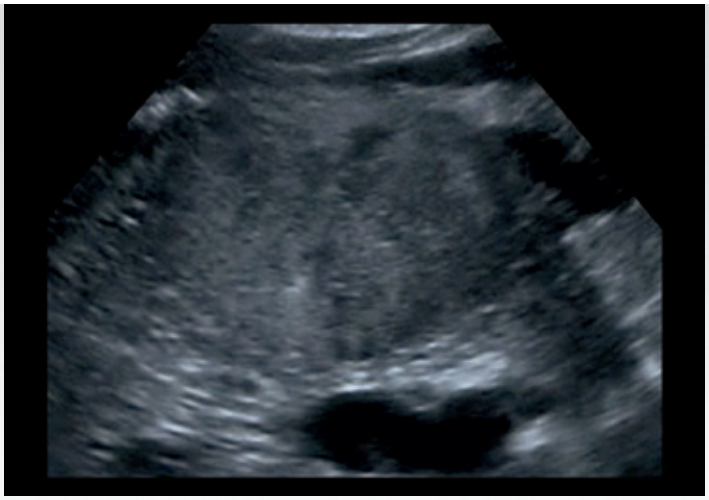

Fig. 6a: An HCC in the left hepatic lobe in the B-mode.

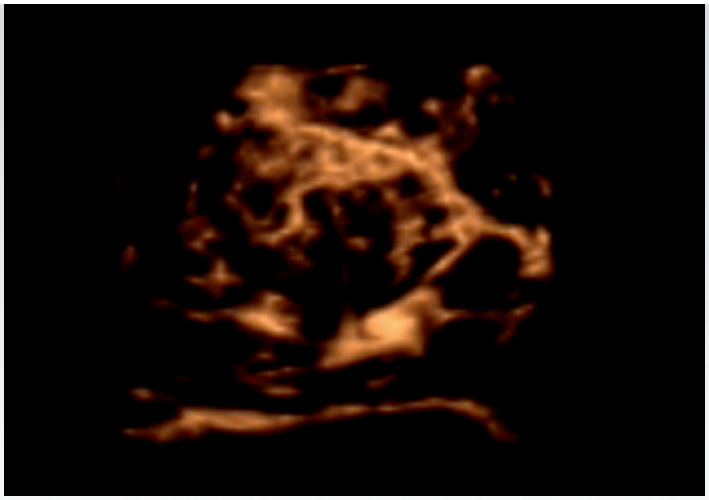

Fig. 6b: 3D visualization of CEUS in an HCC in the arterial phase.

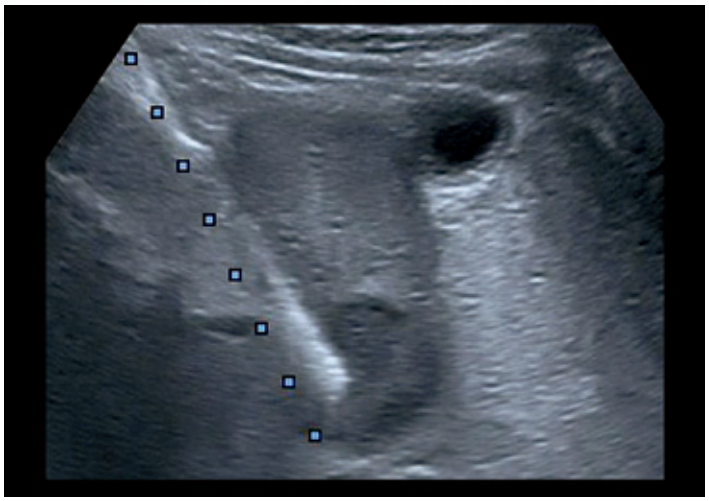

Fig. 7a: A small HCC in the left hepatic lobe (close to the gall bladder) which was inoperable due to a comorbidity. The biopsy guide (dotted line) and needle position can been seen in the image.

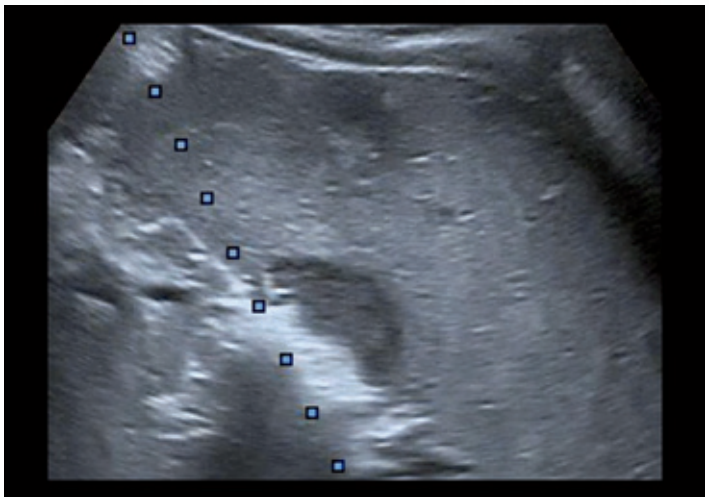

Fig. 7b: Ethanol injection during local ablation is visible as echogenic filling of the HCC.

Summary

CEUS is well suited for the detection and differentiation of HCC in the cirrhotic liver and increases diagnostic certainty compared to conventional B-mode imaging.

CEUS can support different therapies by visualizing tumor vascularity. This allows the assessment of the tumor response and improves the clinical outcome for the patient.

In local ablation procedures ultrasound is well suited for monitoring purposes both during intervention and follow-up.

Used by an experienced sonographer ultrasound and CEUS may be the modalities of choice for the diagnosis of HCC.

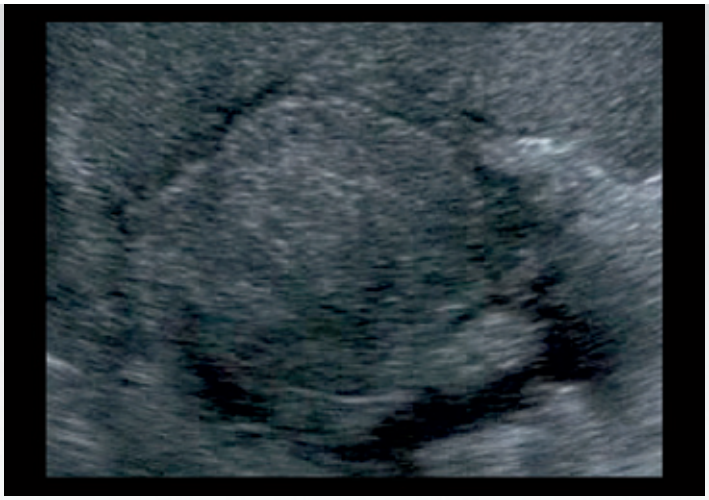

Fig. 8a: HCC post-RFA in the B-mode image.

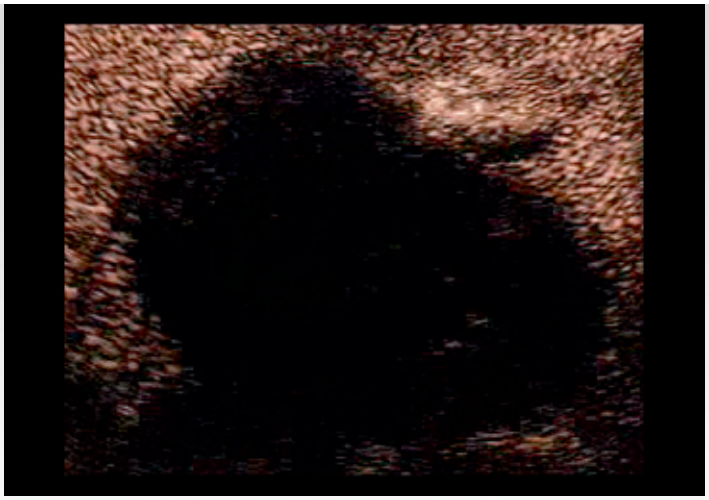

Fig. 8b: Complete contrast defect confirms successful complete ablation.

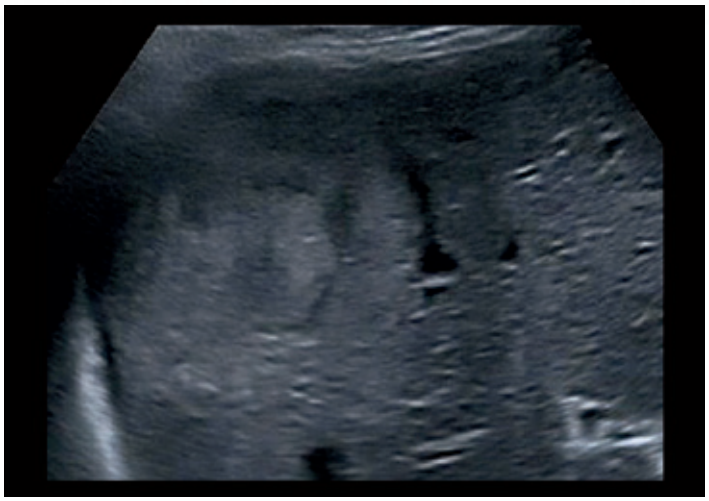

Fig. 9a: HCC post-SIRT (selective internal radiation therapy) in the B-mode image.

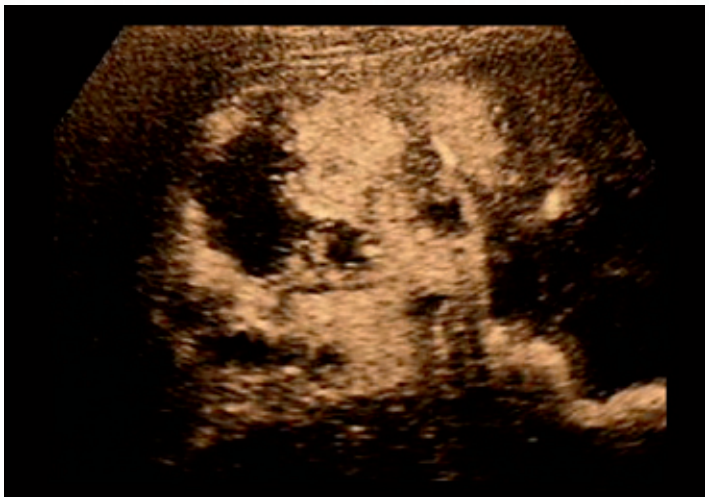

Fig. 9b: Incomplete necrosis after SIRT, suggesting viable tumor tissue is present.

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