

## Review Article

### A Review on ultra sound scan images of liver for the early detection of hepatocellular carcinoma

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#### ABSTRACT

##### Keywords

Hybrid imaging;  
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Visualization of tumor angiogenesis can facilitate non invasive evaluation of tumor vascular characteristics to supplement the conventional diagnostic imaging goals of depicting tumor location, size, and morphology. Hybrid imaging techniques combine anatomic [ultrasound, computed tomography (CT), and/or magnetic resonance imaging (MRI)] and molecular (single photon emission CT and positron emission tomography) imaging modalities. One example is real-time virtual sonography, which combines ultrasound (grayscale, colour Doppler, or dynamic contrast harmonic imaging) with contrast-enhanced CT/MRI. The benefits of fusion imaging include an increased diagnostic confidence, direct comparison of the lesions using different imaging modalities, more precise monitoring of interventional procedures, and reduced radiation exposure.

## I. Introduction

### Definition of ultrasonographic method

Ultrasound exploration (ultrasonography) is a very common diagnostic method. It is part of imaging procedures, without using ionizing radiations but ultrasounds (US) with usual frequencies of 2 - 5 - 12 MHz. Ultrasounds cross biological environments and are reflected at the demarcation limit between structures of different consistencies. The current procedure of ultrasound examination called "scanning"

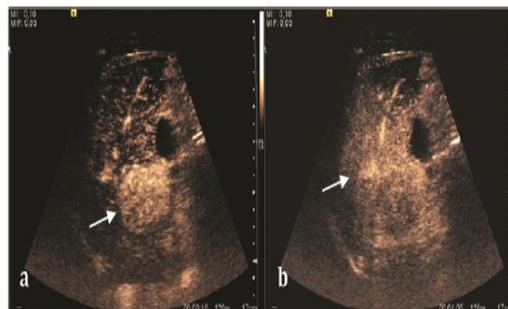
is based on the analysis of every plane from a region of interest in the human body. Each plane contains a high number of points with different brightness (within the limit of the grayscale used by the equipment) and their sum makes a defining "echo structure" for each organ. Ultrasound diagnosis is based on changes in tissue density due to pathological changes, resulting in echo structure transformation. Ultrasonography is an anatomical, hemodynamic and functional exploration.

## II.Hepatocellular Carcinoma (HCC):

It is the most common liver malignancy (Parkin *et al.*, 2005). It develops secondary to cirrhosis (in approx. 80% of cases) (Llovet *et al.*, 2003) therefore, ultrasound examination every 6 months combined with alpha fetoprotein (AFP) determination is an effective method for early detection and treatment monitoring for this type of tumor (Bruix and Sherman, 2005; Llovet and Bruix, 2008). Clinically, HCC overlaps with advanced liver cirrhosis (long evolution, repeated vascular and parenchymal decompensation, sometimes bleeding due to variceal leakage) in addition to accelerated weight loss in the recent past and lack of appetite. HCC appearance on 2D ultrasound is that of a solid tumor, with imprecise delineation, heterogeneous structure and uni- or multilobar (encephaloid form) (Fig.1). An "infiltrative" type is also described which is difficult to discriminate from liver nodular reconstruction in cirrhosis.

Typically HCC invades liver vessels, primarily the portal veins but also the hepatic veins (Badea and Badea, 1991). Doppler examination detects a high speed arterial flow and low impedance index (correlated with described changes in tumor angiogenesis). The spatial distribution of the vessels is irregular, disordered. (CEUS) contrast-enhanced ultrasonography examination shows hyper enhancement of the lesion during the arterial phase. During the portal venous phase there is a specific "wash out" of ultrasound contrast agent (UCA) and the tumor appears hypoechoic during the late phase. Poorly differentiated tumors may have a stronger wash out leading to an isoechoic appearance to the liver parenchyma during portal venous phase.

This appearance was found in approx. 30% of cases (Nicolau *et al.*, 2004). The described changes have diagnostic value in liver nodules larger than 2 cm.



**Fig.1** Encephaloid hepatocellular carcinoma (CEUS). Contrast tumor enhancement is observed on the left during arterial phase. The "wash-out" phenomenon can be seen on the right, during portal venous phase.

Ultrasound is useful in HCC detection, stabilization and assessing therapeutic efficacy. In terms of staging related to therapy effectiveness, the Barcelona classification is used (Llovet *et al.*, 1999) which identifies five HCC stages. Curative therapy is indicated in early stages, which include very early stage (single nodule <2 cm), curable by surgical resection (survival 50-70% five years after surgical resection) (Llovet *et al.*, 2003) and early stage (single nodule of 2-5 cm, or up to 3 nodules <3 cm) which can be treated by radiofrequency ablation (RFA) and liver transplantation.

Intermediate stage (polinodulars, without portal invasion) and advanced stage (N1, M1, with portal invasion) undergo Trans arterial chemoembolization (TACE) of liver metastases palliative therapies (TACE and sorafenib systemic therapy) and in the end stage only symptomatic therapy applies.

### III. Early Hepatocellular Carcinoma (Early HCC):

The suggestive appearance of early HCC on 2D ultrasound examination is that of hypoechoic nodule, with distinct pattern, developed on cirrhotic liver. Hypoechoic appearance is characteristic of moderate/poorly differentiated HCC, with low or absent fatty changes. Rarely, HCC may appear isoechoic, consist of a tumor type with a higher degree of differentiation and therefore with slower development. Another common aspect is "bright loop" or "nodule-in-nodule" appearance, hypoechoic nodules in a hyperechoic tumor. (Minami and Kudo, 2010). Spectral Doppler characteristics of early HCC overlap those of the dysplastic nodule, as they are represented by the presence of portal venous signal type or arterial type with normal RI (well differentiated HCC) or increased RI (moderately or poorly differentiated HCC) (Fig.2 a,b).

The cerebral function monitor (CFM) exploration identifies a chaotic vessels pattern. On CEUS examination, early HCC has an iso- or hypervascular appearance during the arterial phase followed by wash out during portal venous and late phase. There are studies showing that the wash out process is directly correlated with the size and features of neoplastic circulatory bed. Thus, highly differentiated HCC illustrates the phenomenon of late or even very late "wash out" while poorly differentiated HCC has an accelerated wash out at the end of arterial phase (Strobel *et al.*, 2005; von Herbay *et al.*, 2009; Jang *et al.*, 2009). It is therefore mandatory to analyze all these three phases of CEUS examination for a proper characterization of liver nodules. Tumor wash out at the end of the arterial phase allows the HCC diagnosis

with a predictability of 89.5%. Some authors consider that early pronounced contrast enhancement of a nodule within 1-2 cm developed on a cirrhotic liver is sufficient for HCC diagnosis (Jang *et al.*, 2009). These results prove that for a correct characterization of the lesions it is necessary to extend the examination time to 5 minutes or even longer (Von Herbay *et al.*, 2009).



**Fig.2 (a)** Early hepatocellular carcinoma (2D, CFM). The 2D examination reveals a solid, hypoechoic nodule in IVth liver segment, without encapsulation. CFM shows a central vessel with ramifications to the periphery. The underlying liver is cirrhotic.



**Fig.2 (b)** Early hepatocellular carcinoma (2D, CFM). "Nodule in nodule" image: small hypoechoic early HCC inside monitored dysplastic nodule.

### **The ultrasound value in HCC "screening":**

Baseline 2D ultrasound has an important role in surveillance programs for patients at risk to develop HCC (Bruix and Sherman, 2011). The examination has an acceptable sensitivity which increases with the tumor size. Sensitivity varies between 42% for lesions <1 cm and 95% for tumors larger than 1 cm, and specificity can reach 90% (Andreana *et al.*, 2009). Optimal time interval for ultrasound screening of "at risk" population is 6 months as it results from clinical trials that investigated the tumor size doubling time (Bruix, 2005; Maruyama *et al.*, 2008). For a recently developed nodule the dimensional criteria will be taken into account. Thus, for a nodule with a size of less than 10 mm the patient will be re-evaluated by ultrasound every 3 months, as the growth trend is an indication for completion of investigations with other diagnostic procedures; at a size between 10 - 20 mm two concordant imaging procedures are necessary, supplemented if necessary by an ultrasound guided biopsy; at a size over 20 mm one single dynamic imaging technique with characteristic appearance is enough for positive diagnostic.

In uncertain cases complementary dynamic imaging techniques or biopsy should be performed. When Doppler exploration is not enough, CEUS examination will be performed (Gaiani *et al.*, 2001). One should always keep in mind the risk of false positive results for HCC in case of cholangio carcinoma masso complementary diagnostic procedures should be considered (Bruix and Sherman, 2011). The effectiveness of screening programs is proved by an increase in detection rate of HCC <2 cm

(from <5% in the 90s in Europe to > 30% today in Japan) with curative therapy options (Llovet and Bruix, 2008). The main problem of ultrasound screening is that, in order to be cost-effective, it should be applied to the general population and not in tertiary hospitals. This raises the importance of the operator and equipment dependent part of the ultrasound examination (Bruix *et al.*, 2001).

The efficiency of such a program is linked to the functional liver parenchyma of the cirrhotic patient. Therefore, some authors argue that screening should be excluded in patients with etiologies that prevent curative treatment or in patients with advanced liver disease (Child-Pugh class C) (Zapata *et al.*, 2010). After curative therapies (surgical resection, local ablative therapies) continuing ultrasound screening is recommended first at 1 month then at 3 months intervals after the therapy to assess the effectiveness of therapy and to detect other nodules.

### **Ultrasound monitoring ablative therapies:**

Ablative therapies are considered curative treatments for HCC together with surgical resection and liver transplantation and they are indicated for early tumor stages in patients with good liver function (Bruix and Sherman, 2005; Bruix and Sherman, 2011). Also they are successfully applied in the treatment of liver metastases, where surgical resection is contraindicated. They are chemical (intratumoral ethanol injection) or thermal (radiofrequency, laser or microwave ablation). They are applied in order to obtain a full therapeutic response, without affecting liver function. Complete response is locally proved by complete tumor necrosis with a safety

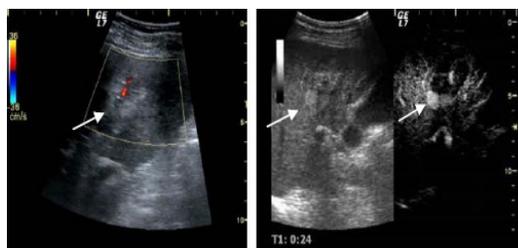
margin around the tumor. 2D ultrasound, Doppler ultrasound and especially CEUS can play an important role in pretherapeutic staging, particularly when sectional imaging investigations (CT, MRI) provide uncertain results or are contraindicated.

During the interventional procedure, ultrasound allows guidance of the needle into the tumor. CEUS allows guidance in areas of viable tissue and avoids intratumoral necrotic areas. CEUS also allows assessment of therapeutic effect immediately post-procedure (with the possibility of reintervention in case of partial response) (Claudon *et al.*, 2008). To accurately assess the effectiveness of treatment it is mandatory to compare the tumor diameter before therapy with the ablation area. The volume of damaged tissue must be higher than the initial tumor volume. CEUS appearance is that of central non enhanced area showing a peripheral homogeneous hyper enhanced rim due to post-procedure inflammation. 24 hours after the procedure the inflammatory peripheral rim is thinning and the necrotic area appears larger than at the previous examination.

Thus, a possible residual tumor may appear more evident. Residual tumor has poorly defined edges, irregular shape, and the tumor diameter is unchanged. Residual tumor tissue is evidenced at the periphery of the tumor as an eccentric area behaving as the original tumor at CEUS examination, with arterial hyperenhancement and portal and late wash-out. Ultrasound examination 24 hours after the procedure, including CEUS, can show apart from the character of the lesion any potential post-intervention complications (e.g. active bleeding).

In the first days after RFA both CEUS and spiral CT have low sensitivity in assessing therapeutic efficacy. CT sensitivity 24 hours post-therapy is reported to be even lower than CEUS (Vilana *et al.*, 2006). Difficulties in CEUS examination result from post-lesion hyperemia, presence of intratumoral air, ultrasound limitations (too deep lesion or the presence of fatty liver) or lack of patient's cooperation (immediately after therapy). For this reasons contrast imaging (CT or CEUS) control should be performed one month after ablation to confirm the result of the therapy (Sparchez *et al.*, 2009).

Local recurrence is defined as recurrence of a hyperenhanced area at tumor periphery in the arterial phase, with portal and late wash-out. Sometimes, especially for HCC treated by alcoholization (PEI) hyperenhanced septa or vessels can be shown inside the lesion (Spârchez *et al.*, 2009). In case of successful treatment, US monitoring using CEUS is performed every three months. Although CE-CT and/or MRI are considered the method of choice in post-therapy monitoring, CEUS can be used in follow-up protocols (Claudon *et al.*, 2008), its diagnostic accuracy being equivalent to that of CE-CT or MRI (Frieser *et al.*, 2011).



**Fig.3** Assessment of therapeutic efficacy on ultrasound (2D, CFM, CEUS). US exam shows vascular Doppler signal at CFM (left) and CEUS examination reveals incomplete therapy (right).

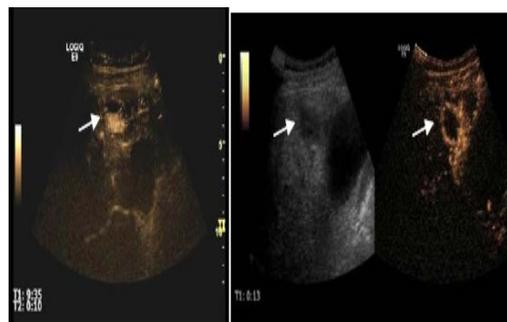
#### IV. Ultrasound Monitoring of TACE Therapy (Transarterial Chemoembolization):

Transarterial chemoembolization (TACE) is part of palliative therapies for HCC used in intermediate stages of the disease. It consists of selective angiographic catheterization of the hepatic artery and injection of chemotherapeutic agents (usually adriamycin, but other molecules are currently the subject of clinical trials), followed by embolization of hepatic artery with gelfoam, alcohol or metal rings (Bruix and Sherman, 2005). A similar procedure is transarterial embolization but without chemotherapeutic agents injection, used in the treatment of hypervascular liver metastases. These therapies are based on the predominantly arterial vasculature of HCC and hypervascular metastases, while the remaining liver parenchyma has a dual vascular intake, predominantly portal. Their efficacy is high only for lesions who are hyperenhanced during arterial phase.

The role of US is limited in the first few days after the procedure, and refers only to its complications, due to Lipiodol retention mainly intratumoral, but also diffusely intrahepatic. On ultrasound, Lipiodol appears intensely hyperechoic inside the tumor, with significant posterior attenuation which make US examination more difficult. On the other hand, CE-CT is also limited by the presence of Lipiodol (iodine oil), therefore the evaluation of therapeutic efficiency is currently made by indirect assessing Lipiodol binding to the tumor using nonenhanced CT (Maruyama *et al.*, 2008). CE-MRI is not influenced by the presence of Lipiodol, but it is an expensive method and still difficult to reach. Several studies have proved similar efficacy, even superior, of CEUS

compared to CE-CT and CE-MRI for the evaluation of post- TACE treatment results, while other studies have shown the limitations of CEUS especially for deep or small lesions (Fig.4).

Given the CEUS limitations, currently some authors consider CT as standard method for the evaluation of TACE and local ablative therapies and CEUS and CE-MRI as complementary methods (Lim *et al.*, 2006, Maruyama *et al.*, 2008). Monitoring TACE therapeutic results by contrast imaging techniques is performed as for ablative therapies initially after one month then after every 3 months post-TACE. Given that TACE is indicated only for hyperenhanced lesions during arterial phase, CEUS plays a very important role in monitoring the dysplastic nodules to identify the moment when changes occur in arterial vasculature, being able to have an early therapeutic intervention in order to limit tumor progression, to increase patient survival, and thus to create a bridge to liver transplantation.



**Fig.4** Small HCC is seen on the left (nodule in nodule). Efficient chemoembolization of the nodule (right). CEUS examination shows no circulatory signal within the nodule.

#### Ultrasound monitoring of systemic therapies:

Systemic therapies are procedures based on the affinity of certain molecules to

inhibit either tumor cell replication or multiplication of neoplastic vasculature (antiangiogenic therapies). They are intravenously administered and are indicated in advanced stages of liver tumor diseases, when there are no other effective therapeutic solutions. Among ultrasound techniques, CEUS is the one that brought a significant benefit not only by increasing the sensitivity and specificity of ultrasound in detecting liver metastases, but also by assessing the efficacy of systemic therapy for HCC and metastases.

The method has been adopted by oncologists since 2003, because it involves no irradiation and has no hepatic or renal toxicity, and it is now currently used in tumor therapeutic evaluation (Lassau *et al.*, 2011). It is currently used in large clinical trials aimed at determining the efficacy of different types of anti-angiogenic molecules by quantifying intratumoral perfusion based on the statistical analysis performed using specific software during post-processing in order to assess therapeutic efficacy as early as possible.

#### **Ultrasound monitoring of post-surgical resection status:**

Surgical resection is the treatment of choice for non-cirrhotic or cirrhotic patients with well preserved liver function with single liver lesion. After resection, recurrence rate exceeds 70% at 5 years and is mainly due to primary tumor dissemination.

The strongest predictors of tumor recurrence are the development of other tumors near the primary tumor scar and vascular micro invasion (Bruix and Sherman, 2005). 2D ultrasound is used

within screening programs. CEUS efficacy has not been proven so far in monitoring post resection patients.

#### **Ultrasound in liver tumor pathology, Technical progress:**

Ultrasound has known a great development arising from the need to increase patient access to advanced investigations while avoiding procedures using radiation (CT), contrast agents with allergic potential (iodine substances) and hepatic or renal toxic agents. Ultrasound exploration by maneuverability of the equipment and dynamic character of the image allows guided interventional procedures or intraoperative examination. Combining ultrasound with such procedures is necessary due to the lack of specificity of the method in case of tumors. Even if tumor markers for defining the nature of some masses are available, their accuracy is not good enough; therefore biological samples from the nodules detected by imaging is often required.

Accuracy of ultrasound guided puncture in the diagnosis of liver tumors is dependent on the operator's experience and can reach up to 87.5 - 99% (Horigome *et al.*, 1999). The extracted material can be either a histology fragment or cytology aspiration; in both cases the credibility of the method is sufficient to ensure optimal cancer therapies (Badea and Badea, 1991). Intraoperative ultrasound is also a complementary investigation that allows detection of very small nodules. In addition it allows the characterization of tumor using Doppler and CEUS procedure as well as guided interventional procedures such as intraoperative (PEI or RFA) radio frequency ablation or percutaneous ethanol injection.

### **Targeted therapy using contrast agents:**

The introduction of second generation contrast agents has been a great progress. Diagnostic performance is already proven. A step forward is tumor targeted therapy under ultrasound guidance. The principle is that of transporting chemotherapeutic agents to the target using microbubbles as vectors. Experiments have been made for binding different substances and/or genes to the lesion, with local release by "breaking" and intracellular penetration using the phenomenon of cellular membrane permeability called "sonoporation" (Lindner, 2004, Newman and Bettinger, 2007).

### **Image fusion:**

Techniques for image fusion obtained by different imaging procedures allow the correlation of real-time ultrasound examination with CT or MRI images, enabling positioning of the needle in relation to the exact position of the tumor. The technique allows a better guidance both for biopsies and percutaneous ablative procedures, replacing CT guidance and thus avoiding irradiation. Combination with CEUS allows a better characterization of lesions as well as successful monitoring of percutaneous procedures or TACE effects (Sandulescu *et al.*, 2011; Ewertsen *et al.*, 2011). Elastography was initially introduced in practice to assess the degree of fibrosis in chronic liver disease.

In liver tumors it allows detection of liver nodules due to the difference of elasticity between the hepatic nodule and the parenchyma. There are few studies that try to assess the benign or malignant character of the lesion based only on elasticity. By combination with CEUS the method could

be beneficial for early detection and characterization of HCC.

### **V. High Intensity Focused Ultrasound (HIFU):**

It is a new technique capable of destroying tumor tissue by hyperthermia, allowing percutaneous ablation without requiring tumor puncture. There are studies showing the efficacy of this technique in combination with TACE, with anti-tumor effect and better survival than using TACE alone (Wu, 2005). The method is expected to be an alternative to PEI and RFA because it avoids the puncture of the cirrhotic liver, but more studies are needed to prove its efficacy as a single therapy in the curative treatment of HCC (Maruyama *et al.*, 2008). Techniques for visualizing blood circulation independently from the angle of intonation based on transversal oscillation of red blood cells groups. This technique is now implemented on conventional transducers and can real time evidence different features of the blood flow visualized so far only on MRI angiography (Hansen *et al.*, 2011).

### **VI. Conclusions**

Ultrasound exploration using current technologies has excellent possibilities for practical use. Several elements related to the lack of standardization and reproducibility of ultrasound procedures as well as operator-dependent nature of the method require structured approach to its use in liver tumors pathology (Bolondi *et al.*, 2007). Structuring these applications and description of their actual performance are included in successive recommendations made by expert groups, known as "EFSUMB guidelines" (Albrecht *et al.*, 2004; Claudon *et al.*, 2008).

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