Review

Clinical Impact of Ultrasound-Related Techniques on the Diagnosis of Focal Liver Lesions

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Alma Mater Studiorum-University of Bologna, Bologna, Italy**Key Words**B-mode ultrasonography · Contrast-enhancement ultrasonography · Elastasonography ·
Focal liver lesions · Pulsed and color Doppler ultrasonography**Abstract**

Since its introduction in clinical practice, ultrasound technology has greatly impacted patient management, particularly in the case of liver diseases, where hepatologists usually perform ultrasound examinations. Clinicians are increasingly aware of the great potential of ultrasound waves and of the recent innovations that exploit the mechanical properties of ultrasound waves. Thus, at present, not only B-mode ultrasound but also contrast-enhanced ultrasound and, more recently, elastasonography are used worldwide in various settings. This review aims to describe why clinicians should be aware of ultrasound-based techniques, how they should use these techniques for assessing focal liver lesions, and how these techniques impact patient management. We will review the clinical potential of ultrasound-related techniques, starting from lesion detection, moving to characterization, and concluding with their utility in guiding treatments and analyzing their effects.

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Introduction

Owing to its efficacy, safety, and low cost, ultrasonography (US) is widely used in many clinical settings, ranging from obstetrics and cardiology to thyroid or musculoskeletal examinations. Nevertheless, abdominal imaging still remains the leading application. In particular,

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US evaluation of focal liver lesions (FLLs) is routinely performed worldwide because of its accuracy in the detection and characterization of FLLs, particularly when US contrast agents (USCAs) are used, and its utility in guiding percutaneous treatments and in the assessment of tumor response. More recently, elastosonography, a new ultrasound-based technique, has been introduced, and its role in the evaluation of FLLs is emerging. Rather than describing the possible FLL patterns using different US-based techniques, the present review aims to focus on the utility of these techniques for clinicians, who can utilize an extremely useful tool with a wide range of applications.

Detection

“Gray-scale B-mode real-time US” is the first baseline US imaging technique that is currently used in many different clinical situations. Abdominal pain, jaundice, palpable mass, and fever of unknown origin are only few of the innumerable indications for abdominal gray-scale US, allowing the occasional detection of FLLs. In the Focused Assessment with Sonography for Trauma (FAST) examination, for example, FLL is detected in approximately 12 of 1,000 patients [1]. While in some patients, the identification of an incidental FLL does not change the immediate management [e.g., in cases of hemangioma and focal nodular hyperplasia (FNH)], in other patients, this finding can be extremely useful in the diagnostic framework. In patients with spontaneous rupture of hydatid cysts, hepatocellular adenomas, metastases, hepatocellular carcinomas (HCCs), or liver abscesses, treatment can be guided by US.

B-mode US is also recommended in the 6-month surveillance program for patients at a high risk of developing HCC, who are cirrhotic patients in Child–Pugh stage A and B (in stage C, if they are eligible for liver transplantation), noncirrhotic hepatitis B virus (HBV) carriers with active hepatitis B (or a family history of HCC), and noncirrhotic patients with chronic hepatitis C and advanced liver fibrosis (of stage F3 using the METAVIR classification) [2]. Despite conflicting results, a shorter follow-up interval of 3 months has been proposed by Japanese guidelines.

“Pulsed and color Doppler US” do not play a specific role in the detection of FLLs, whereas “contrast-enhanced US (CEUS)” has greatly impacted clinical practice. The use of microbubbles (MBs) is demonstrated to be extremely useful in the detection of malignancies because of the peculiar blood supply of the liver. Once MBs are injected, different overlapping vascular phases can be defined: the arterial phase, which starts approximately 15–20 s after contrast injection; the portal phase, which lasts until 2 min; and the venous phase, which lasts until the contrast has been cleared from the circulation. In the case of Sonazoid® (Daiichi-Sankyo, GE Tokyo, Japan), a CA approved only in Japan, the postvascular phase (also called the Kupffer phase because of MB phagocytosis by Kupffer cells) begins approximately 10 min after contrast injection and lasts for more than 1 h.

Malignancies are characterized by hypoenhancement in the portal and venous phases as well as in the postvascular phase using Sonazoid®, making their detection with CEUS possible. Therefore, CEUS was shown to be a reliable imaging technique for follow-up examinations of oncological patients with known extrahepatic tumors, with an accuracy of 91% [3]. In the case of HCC, the most frequent primary liver tumor usually occurring on cirrhosis, detection with CEUS is more complicated. The multistep carcinogenesis of HCC implies a progressive decrease in portal vessels and an increase in abnormal arterial vessels. However, well-differentiated HCC lesions are isoenhancing in the late phase in 51% of cases [4], making CEUS unreliable for the detection of lesions not seen on US. In contrast, the marked

hypoenhancement of intrahepatic cholangiocarcinoma (ICC) in the portal and late phases allows its detection with CEUS, as seen in the case of secondary liver tumors.

To improve the detection of malignancies, new MBs with a long-lasting late phase have recently been proposed. In a phase IIa study, BR14, a new CA with a mean terminal half life of 12.9 min, showed no significant difference in lesion detection compared with contrast-enhanced magnetic resonance imaging (CEMRI) [5]. Although this study included patients with known malignancies on CEMRI (including HCC) and the detection rate using BR14 was not compared with that using approved MBs with shorter late phases (e.g., SonoVue), it raises the possibility of the use of CEUS in the detection of HCC, where washout to hypoechogenicity, if present, may occur even after 180 s, particularly in well-differentiated nodules. As mentioned previously, Sonazoid is a relatively new USCA that deserves attention for its peculiar behavior. FLLs without Kupffer cells appear as hypoenhanced holes surrounded by enhanced tissue. BR14 has demonstrated a higher HCC detection rate than B-mode US and occasionally higher than contrast-enhanced computed tomography (CECT) in perfectly explorable livers [6]. Regarding liver metastases that lack Kupffer cells, CEUS with Sonazoid has a sensitivity comparable with that of CECT and CEMRI for detecting lesions >1 cm. Intraoperative US (IOUS) is the most accurate imaging technique for detecting FLLs and has contributed to the increase in the rate of radical and conservative resections in patients with hepatic colorectal metastases. Its sensitivity has been impacted by the introduction of USCA, reaching a diagnostic accuracy superior to that of CECT/CEMRI (96.3% vs. 73.8%), particularly because of its ability to identify smaller lesions [7]. Therefore, contrast-enhanced IOUS (CEIOUS) may be used to increase the detection rate of malignant lesions because of their hypoenhancement in the late phase, leading to a change in surgical planning.

“Real-time (RT) elastography” is a new technique that can estimate the strain modules from radiofrequency signals in response to external compression and provide an estimation of tissue elasticity. This technique has been studied for the characterization of nodules in superficial structures such as the breast, thyroid, and prostate. Few studies are available concerning its application to the liver, particularly for the evaluation of liver fibrosis. Apart from its use for characterization, discussed below, RT elastography has been studied for the detection of liver nodules in animal models [8] and during surgery [9]. In the latter setting, it has been demonstrated to have a higher diagnostic accuracy than B-mode IOUS in detecting lesions surrounded by a heterogeneous background or with an isoechoic pattern (96% vs. 89%). Nevertheless, its role in the detection of FLLs is yet to be definitively assessed.

Characterization

The role of “B-mode US” in the characterization of FLLs in a healthy liver is limited to few entities, of which hemangioma is the most common. In case of a homogeneous, hyper-echoic lesion with well-defined margins, usually close to vessels and with posterior acoustic enhancement, hemangioma can be confidentially diagnosed without the use of additional imaging modalities. In the same manner, the finding of a completely anechoic and rounded lesion, with posterior acoustic enhancement and thin walls, allows accurate diagnosis of a simple cyst, which can be confused only with type I echinococcosis, a very rare entity in Western countries.

The characterization of other FLLs with B-mode US is more challenging and not always possible. FNH, which usually affects young females, typically has an isoechoic pattern, calcifications, and a central scar; however, this latter peculiarity is absent in more than half of the patients with FNH. Similarly, hepatocellular adenoma (HCA) is frequently isohypoechoic with

Fig. 1. Typical Doppler and CEUS patterns of focal nodular hyperplasia. The presence of a low resistance index central artery on color and spectral Doppler US (a) and centrifugal arterial hyperenhancement at 22, 45, and 47 s (b, c, and d, respectively), with isoenhancement in the portal (e) and late (f) phases on CEUS.

respect to the surrounding parenchyma; however, it may also appear hyperechoic in case of fibrosis, fat, or even intralesional bleeding. In appropriate settings, i.e., including the US examination in the clinical background of the patient, hematomas (which typically appear hyperechoic if very recent or hypoechoic in their later stages), hydatid cysts, and abscesses can be conveniently identified with B-mode US. However, the finding of any characteristic different from those mentioned above in a healthy liver requires other modalities for precise characterization.

In case of steatosis, focal fatty sparing or infiltration is very common and usually involves typical areas such as the gallbladder fossa, the medial segment near the falciform ligament, and the porta hepatis. The finding of a hyperechoic area in a healthy liver or a hypoechoic area in a steatotic background, without mass effect and with a typical location and shape, allows correct classification of focal fatty diseases using only B-mode US. In a cirrhotic background, any newly detected FLL should raise the possibility of detecting HCC (usually isoechoic); however, differential diagnosis with regenerative nodules or ICC is not possible with B-mode US.

The utility of “pulsed and color Doppler US” is limited to FNH, in which the central artery with radial distribution is a characteristic element present in approximately 80% of cases. Typically, FNH has a low resistance index on spectral analysis because of arteriovenous shunts (fig. 1). In contrast, in the presence of arterioportal shunts, the finding of peritumoral hepatofugal portal flow may enhance the possibility of detecting hemangioma. Color Doppler US is not useful in the majority of these cases because the intratumoral flow velocity is below the sensitivity limits [10].

The abovementioned changes in vascularization that occur during the multistep carcinogenesis of HCC may be appreciable with Doppler US. Precancerous tissue generally has a

portal inflow, whereas advanced HCC frequently has an arterial inflow with a high resistance index (>1).

The introduction of USCAs has radically changed the approach to the characterization of FLLs, obviating the need for spectral and Doppler US in routine clinical practice. Indeed, CEUS allows the correct classification of the majority of FLLs with high diagnostic accuracy. The typical pattern of FLLs has been well described in the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines for CEUS, originally published in 2004, updated in 2008, and soon to be updated again [11, 12]. Excluding simple cysts (without enhancement in all phases), benign FLLs are generally characterized by an isoechoic pattern in the portal and late phases because of the persistence of USCA in the sinusoidal space, whereas malignant FLLs washout in these phases (as mentioned above). Discrimination between the different entities is based on the arterial pattern. The typical enhancement pattern of the most common FLLs is reported elsewhere (using ref [21]) and shown in fig. 1. Rarer entities with uneven patterns include angiomyolipomas (usually inhomogeneously hyperenhancing in all phases), cholangiocellular adenomas (where hypoenhancement in the late phase is reported) [13], and neuroendocrine metastases (with possible hyper- or iso-enhancement in the late phase). Theoretically, any FLL may arise on cirrhosis with the same pattern than in a healthy liver. The most frequent finding on a cirrhotic background, however, is HCC, typically characterized by hyperenhancement in the arterial phase, followed by hypoenhancement in the late phase. As mentioned above, an inconclusive pattern is present in a non-negligible number of HCCs, particularly in small nodules, where a false-negative rate of at least 20% in nodules 10–30 mm in diameter has been reported [14]. A correlation between contrast behavior and histological differentiation has also been suggested. HCCs that present a washout, usually slight, in the portal phase are more likely to be moderately or poorly differentiated, according to the Edmondson classification. In contrast, HCCs without washout in the late phase are more often well differentiated [3]. The histological grade may influence the washout time, leading to an earlier washout in poorly differentiated HCCs [15].

According to the American Association for the Study of Liver Diseases (AASLD) guidelines of 2005 [16], the diagnosis of HCC could be performed by CEUS alone in newly developed nodules >2 cm or in case of a coincidental finding of the typical pattern in at least 2 imaging techniques between CECT, CEMRI, and CEUS. In nodules >2 cm, a single imaging technique with a typical contrast pattern is sufficient to reach the diagnosis. The 2012 update of the AASLD guidelines [17] excluded CEUS from the HCC diagnostic flowchart because of the possible misdiagnosis with ICC, whose incidence is rising, particularly in HCV-related cirrhosis, and both entities are characterized by hyperechogenicity in the arterial phase followed by washout in the portal and late phases [18]. This raised an intense debate in the scientific community, and these recommendations were not well received in Europe and Asian countries, where CEUS is still included in HCC guidelines [19, 20]. The occurrence of an early and intense washout in the portal and late phases should suggest the diagnosis of ICC or metastases from nonhepatic primary tumors instead of HCC. Moreover, ICC frequently displays a heterogeneous and rim-like arterial enhancement. In this setting, the use of the potential of CEUS, namely the temporal resolution that allows appreciation of the rapidity of washout and the intensity of hypoenhancement, is a key factor, which is not available with other imaging modalities such as CECT and CEMRI [21].

Three-dimensional US is routinely used in obstetrics and cardiology; however, its use in the liver is limited by the slight difference between FLLs and the surrounding liver parenchyma. Combined use with USCA has been proposed to better visualize the intralesional vasculature; however, its influence on clinical outcomes seems to be negligible.

The utility of “RT elastography” in the characterization of FLLs is not yet well defined. In general, malignant tumors are stiffer than benign ones, a characteristic that has led to excel-

Fig. 2. Hemangioma in a healthy liver on shear wave elastography using Aixplorer (SuperSonic Imagine, Aix-en-Provence, France) (a) The B-mode US image is provided to better localize the lesion for quantification (22.4 kPa, in this case). (b) Brighter blue indicates stiffer tissue, as shown in the color scale at the upper right corner.

lent accuracy in the diagnosis of thyroid nodules. Few studies have investigated the role of color maps and shear wave velocity (SWV) in the differentiation between metastatic and primary liver tumors, with contrasting results. When only solid FLLs were evaluated, color maps showed an accuracy of 92.7% in defining FLL as metastatic, whereas when all types of nodules, including necrotic nodules, were included, only SWV had a positive predictive value (PPV) of 80% (using 2.5 m/s as cut-off) to discriminate between metastatic and nonmetastatic FLLs [22, 23]. Regarding FLLs occurring on cirrhosis, Gheorge et al. [24] demonstrated the utility of RT elastography in the discrimination between regenerative nodules and small HCC lesions by quantifying the resulting color map. However, in general, it is necessary to remark the influence of a cirrhotic background during elastography. When strain imaging techniques, which involve external compression by the operator, are used, variability of the measurements may be affected by the degree of cirrhosis (i.e., the measurement of the elasticity of a region of interest relative to that of the surrounding tissue). In contrast, SW modalities can quantify the absolute elastic properties of a region of interest. This makes the technique more suitable for characterizing FLLs, even if the results have not been encouraging till date (fig. 2).

Treatment

The utility of US is not limited to the diagnosis of FLLs, being extremely useful in guiding percutaneous treatments in the same way as that for guiding biopsies. In the majority of cases, gray-scale US is sufficient to localize FLL; however, when a lesion is isoechogenic with the surrounding parenchyma, the injection of USCA may be the only option for FLL identification. The hypoechogenicity in the late phase of malignant lesions, particularly if early and marked, allows the operator to insert the needle while the contrast is still in the bloodstream. In contrast, if the washout is only slight or even absent, a behavior not uncommon in early HCC, the possibility to appreciate the arterial enhancement may permit the clinician to aim for the enhanced area. This is also true during surgery, where US and CEUS can guide the treatment to achieve radical resections.

In addition to its use during procedures, CEUS allows the identification of residual activity, i.e., enhancement in the arterial phase in a portion of a treated FLL, after nonsurgical treatments such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave ablation (MWA), high-frequency US (HIFU), transarterial chemoembolization

(TACE), and systemic drugs. The recognition of residual activity is crucial in patient management as long-term survival is greatly impacted by complete rather than partial effectiveness of the procedure. In case of contraindicated or inconclusive CECT or CEMRI, EFSUMB guidelines recommend the use of CEUS to assess therapeutic response because its sensitivity is comparable with that of CECT, with an accuracy ranging from 91 to 100% [12]. Regarding percutaneous treatments, The possibility of evaluating the treatment efficacy immediately after the procedure allows a potential retreatment in the same session, impacting patient outcome. Indeed, a decrease in incompletely ablated tumors, from 16 to 6%, has been demonstrated [25]. Notably, the presence of gas in RFA or alcohol in PEI may limit the visualization of the distal portion of a treated FLL, making immediate evaluation of residual activity impossible. However, a drastic reduction in artifacts usually occurs within a time span of approximately 10 min, making it suitable to treat FLL again in the same session. Misdiagnosis of tumor persistence is possible in the 1st week after the treatment because the hyperemic halo of newly developed fistulas is a frequent finding after thermal ablation procedures. However, in these cases, the hyperenhancement in the arterial phase is usually diffuse, homogeneous, and surrounds the lesion with a diameter larger than that of the nodule before the treatment. In contrast, the utility of CEUS for evaluating the response to TACE is not well defined, particularly because it is usually performed in patients with multifocal disease, implying the need for a panoramic view in the arterial phase that CEUS does not provide. Multiplicity, deep localization, pre-treatment hypoenhancing nodules, and diffuse growth patterns were reported as factors that reduce the “diagnostic” capability of CEUS till 38% in a study that included metastases and HCC lesions [26]. In contrast, in case of “diagnostic” examination, the authors reported a detection of residual activity at a rate comparable with that of CECT and CEMRI, making CEUS a supportive technique in difficult situations. Four-dimensional scanning (4DS; 3-dimensional reconstruction in real time) has also been proposed to enhance CEUS capabilities, although more studies are warranted. Its proposed utility is related to the possibility of better identifying a perfused area, even if only in the late phase (that lasts longer than the arterial phase), since a completely devascularized area is expected in complete necrosis. An expected decrease in the vascular supply is the basis of the potential role of pulsed and color Doppler US and, more recently, of CEUS in evaluating the response to antiangiogenic treatments, among which sorafenib is the only treatment approved for advanced HCC. Apart from sorafenib, many other antiangiogenic treatments are available for secondary FLLs, making this approach useful in many settings. The clinical need is based on the unreliability of dimensional criteria such as the World Health Organization (WHO) and the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines in evaluating the effectiveness of treatments whose aim is not a decrease in tumor dimension but the induction of necrosis by blocking neoangiogenesis. These criteria have already been amended for HCC and gastrointestinal stromal tumors (GISTs), the use of CEUS for which was endorsed by the European Society of Medical Oncology [27, 28].

To overcome the subjectivity of CEUS, great interest has arisen in recent years in the quantification of contrast enhancement through dedicated software for making results more objective and comparable [29]. A decrease in contrast enhancement >10%, together with stability of tumor volume, has been demonstrated as a predictor of progression free and overall survival in patients with metastatic renal cancer, including those with liver localizations [30]. Lastly, the use of targeted MBs in the near future would probably improve the evaluation of treatment efficacy, in addition to a potential application in the characterization of FLLs. Nevertheless, no targeted MBs have been approved for human use till date. In conclusion, the diagnostic workup of any FLL should include US techniques for correct characterization of the lesion and for the assessment of treatment efficacy. Other imaging techniques that are expensive and with ionizing hazards radiation, e.g., CECT or CEMRI, should be avoided unless they are absolutely necessary. Moreover, the possibility of the immediate use of US-based

techniques in many different clinical settings should encourage clinicians to deepen their knowledge of these techniques.

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