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Impact of European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines on the use of contrast agents in liver ultrasound

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Abstract The introduction of micro-bubble contrast agents and the development of contrast-specific techniques have opened new prospects in liver ultrasound. Over the past few years several reports have shown that contrast ultrasound can substantially improve detection and characterization of focal liver lesions with respect to baseline studies. The advent of second-generation agents and low mechanical index real-time scanning techniques has been instrumental in improving the easiness and the reproducibility of the examination. With the publication of the guidelines for the use of contrast

agents in liver ultrasound by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), contrast ultrasound enters into clinical practice. The guidelines define the indications and recommendations for the use of contrast ultrasound in focal liver lesion detection, characterization, and follow-up after tumor ablation procedures. We discuss the impact of EFSUMB guidelines on diagnostic protocols currently adopted in liver imaging.

Keywords Ultrasound contrast agents · Focal liver lesions · Liver neoplasms

Introduction

Detection and characterization of focal liver lesions is an important and challenging issue. Hepatocellular carcinoma (HCC) is the fifth most common cancer [1]. The liver is the organ most frequently involved by metastases. In addition, benign liver lesions such as hemangioma and focal nodular hyperplasia (FNH), have a high prevalence in the general population. Several imaging modalities and diagnostic protocols have been used to optimize detection and characterization of focal liver lesions.

Ultrasound is the most commonly used liver imaging modality worldwide. Unfortunately, ultrasound has limited sensitivity in the detection of small tumor nodules. Moreover, ultrasound findings are often nonspecific, as there is enough variability and overlap in the appearance of benign and malignant liver lesions to make a definite distinction problematic. Computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used to clarify

questionable ultrasound findings and to provide a more comprehensive assessment of the liver parenchyma.

Recently the introduction of microbubble contrast agents and the development of contrast-specific techniques have opened new prospects in liver ultrasound [2]. Contrast-specific techniques produce images based on nonlinear acoustic effects of microbubbles and display enhancement in gray-scale, maximizing contrast, and spatial resolution. The goal of improving the ultrasound assessment of focal lesions was initially pursued by scanning the liver with high mechanical index techniques. With these techniques the signal is produced by the collapse of the microbubbles. The main limitations of this destructive method is that it produces a transient display of the contrast agent. Thus it requires an intermittent scanning, and a series of sweeps must be performed in an attempt to cover the entire liver parenchyma. The advent of second-generation agents which have higher harmonic emission capabilities has been instrumental in improving the easiness and the reproduc-

ibility of the examination [3]. A lower, nondestructive mechanical index can now be used, thus enabling continuous real-time imaging. Over the past few years, several reports have shown that real-time contrast-enhanced ultrasound can substantially improve detection and characterization of focal liver lesions with respect to baseline studies [4].

With publication of the guidelines for the use of contrast agents in liver ultrasound by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) contrast-enhanced ultrasound has entered into clinical practice [4]. The guidelines define the indications and recommendations for the use of contrast agents in focal liver lesion detection, characterization, and post-treatment follow-up. This contribution discusses the impact of the EFSUMB guidelines on diagnostic protocols currently used in liver imaging with regard to four clinical scenarios: (a) characterization of focal liver lesions of incidental detection, (b) diagnosis of HCC in patients with cirrhosis, (c) detection of hepatic metastases in oncology patients, and (d) guidance and assessment of the outcome of percutaneous tumor ablation procedures.

Characterization of incidental focal liver lesions

Characterization of focal lesions of incidental detection is one of the most common and sometimes troublesome issues in liver imaging. Unsuspected lesions are frequently detected in patients who have neither chronic liver disease nor history of malignancy during an ultrasound examination of the abdomen. While a confident diagnosis is usually made on the basis of ultrasound findings in cases of simple cysts and hemangiomas with typical hyperechoic appearance, lesions with nonspecific ultrasound features require further investigation [5]. The patient is typically referred for contrast-enhanced CT or contrast-enhanced MRI of the liver.

The EFSUMB guidelines recommend the use of contrast agents to diagnose benign focal lesions not characterized in the baseline study. This statement is based on the ability of contrast ultrasound to carefully analyze lesion vascularity. The lesions that most frequently cause incidental findings, i.e., hemangioma and focal nodular hyperplasia, typically show contrast-enhanced ultrasound patterns that closely resemble those on contrast-enhanced CT or contrast-enhanced MRI [6]. Most liver hemangiomas show peripheral nodular enhancement during the early phase with progressive centripetal fill-in, leading to lesion hyperchogenicity in the late phase. Two recent series have shown this characteristic feature in 78–93% of hemangiomas [7, 8]. Focal nodular hyperplasia shows central vascular supply with centrifugal filling in the early arterial phase, followed by homogeneous enhancement in the late arterial phase. In the portal phase the lesion remains hyperechoic, relatively normal liver tissue and becomes isoechoic in the late phase. This pattern is observed in 85–100% of focal nodular hyperplasias [7, 9]. Therefore it appears that in

most liver lesions incidentally discovered in the baseline ultrasound study the detection of typical enhancement patterns after contrast injection may enable a quick and confident diagnosis, possibly avoiding the need for more complex and expensive investigations.

Diagnosis of hepatocellular carcinoma in cirrhosis

The second clinical scenario is that of patients with hepatic cirrhosis. In view of the high risk of developing HCC these patients are carefully followed with ultrasound examinations repeated at 6-month intervals [10]. While the detection of a focal lesion in cirrhosis should always raise the suspicion of HCC, it is well established that the pathological changes inherent in cirrhosis may simulate HCC in a variety of ways, especially because nonmalignant hepatocellular lesions such as regenerative and dysplastic nodules may be indistinguishable from a small tumor. One of the key pathological factors for differential diagnosis that is reflected in imaging appearances is the vascular supply to the nodule. Through the progression from regenerative nodule to dysplastic nodule to frank HCC, one sees loss of visualization of portal tracts and development of new arterial vessels, termed nontriadal arteries, which become the dominant blood supply in overt HCC. It is this neovascularity that allows HCC to be diagnosed by contrast-enhanced CT or dynamic MRI [11].

According to EFSUMB guidelines, performing a contrast-enhanced ultrasound study is recommended for characterizing any lesion or suspect lesion detected at baseline ultrasound in the setting of liver cirrhosis [4]. Because of its ability to display contrast enhancement in real-time, contrast ultrasound can show arterial neoangiogenesis associated with a malignant change and therefore help to establish the diagnosis of HCC [12, 13]. HCC typically shows strong intratumoral enhancement in the arterial phase (i.e., within 25–35 s after the start of contrast injection) followed by rapid wash-out with isoechoic or hypoechoic appearance in the portal venous and delayed phase. In contrast, large regenerative nodules and dysplastic nodules usually do not show any early contrast uptake and resemble the enhancement pattern of liver parenchyma. Selective arterial enhancement on contrast ultrasound has been observed in 91–96% of HCC lesions, confirming that this may be a tool to show arterial neoangiogenesis of HCC [12, 13]. A recent study taking findings on spiral CT as the gold standard reported the sensitivity of contrast ultrasound in detecting arterial hypervascularity to be 97% in lesions larger than 3 cm, 92% in those of 2–3 cm, 87% in those of 1–2 cm, and 67% in those smaller than 1 cm [13]. Hence performing a contrast-enhanced study may be recommended in all lesions or suspected lesions 1 cm or larger in diameter detected in the baseline ultrasound in patients with cirrhosis or chronic hepatitis undergoing surveillance programs.

Detection of hepatic metastases in oncology patients

Metastatic disease involving the liver is one of the most common issues in oncology. CT and positron emission tomography are used in oncology protocols to provide objective documentation of the extent of the liver tumor burden and to assess extrahepatic disease. Nevertheless, ultrasound is widely used in posttreatment follow-up to monitor tumor response and to detect the emergence of new hepatic metastatic lesions. One of the major points addressed by the EFSUMB document is the use of contrast agents in this patient population. The use of contrast agents is recommended not only to clarify a questionable lesion detected at baseline examination. Performing a contrast-enhanced ultrasound study is recommended in every oncology patient referred for liver ultrasound unless a clearly disseminated disease is detected in the baseline study. This means that all liver ultrasound examinations performed to rule out liver metastases should include a contrast-enhanced study, even if the baseline scans show no abnormality. This strong statement is based on the substantially greater ability of contrast-enhanced studies than baseline to detect liver metastases [14]. Even small metastases stand out as markedly hypoechoic lesions against the enhanced liver parenchyma throughout the portal venous and delayed phases. The earlier the detection of liver metastatic disease, the earlier the therapeutic intervention can begin.

Guidance and monitoring of tumor ablation procedures

Several percutaneous techniques have been developed to treat nonsurgical patients with liver malignancies. These minimally invasive procedures can achieve effective and reproducible tumor destruction with acceptable morbidity. Radiofrequency ablation is increasingly accepted as the best therapeutic choice for patients with early-stage HCC when resection or transplantation are precluded and has also become a viable treatment method for patients with limited hepatic metastatic disease from colorectal cancer who are not eligible for surgical resection [15, 16]. When ultrasound is used as the imaging modality for guiding ablations, the addition of contrast agent can provide additional important information throughout all the procedur-

al steps: it improves delineation and conspicuity of lesions poorly visualized on baseline scans, facilitating targeting; it allows immediate assessment of the outcome of treatment by showing disappearance of any previously visualized intralésional enhancement; and it may be useful in the follow-up protocols for early detection of tumor recurrence [17].

Conclusions

The EFSUMB recommendations for the use of contrast agents in liver ultrasound may have a great impact on daily practice. We have outlined four clinical scenarios in which the EFSUMB guidelines may change the standard diagnostic imaging protocols. Other applications are currently under investigation, and these could possibly expand the indications for contrast-enhanced ultrasound in liver imaging [18–20]. However, despite the improvement in detection and characterization of focal liver lesions that can be achieved by using contrast-enhanced ultrasound, several issues are still unresolved. First, contrast ultrasound will hardly replace CT or MRI for preoperative assessment of patients with liver tumors, as these techniques still offer a more comprehensive assessment of the liver parenchyma, which is mandatory to properly plan any kind of surgical or interventional procedure. Second, the daily schedule of each ultrasound laboratory carrying out liver examinations will have to be reformulated, and many ultrasound laboratories must update their equipment and to provide proper training for their physicians. Finally, the cost of introducing contrast-enhanced ultrasound in daily practice will have to be taken into account. It can be argued that cost saving associated with patients who will no longer need a CT or an MRI of the liver after contrast-enhanced ultrasound could largely counterbalance the cost of the examination. However, an optimal use of contrast-enhanced ultrasound will require the definition of precise diagnostic flow charts for each clinical situation. Nevertheless, contrast-enhanced ultrasound has the potential to become the primary liver imaging modality for early detection and characterization of focal lesions. Early diagnosis of primary and secondary liver malignancies greatly enhances the possibility of curative surgical resection or successful percutaneous ablation, resulting in better patient care and improved patient survival.

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