II.8

European Guidelines in Liver Contrast Ultrasound

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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 in attempts to optimize detection and characterization of focal liver lesions.

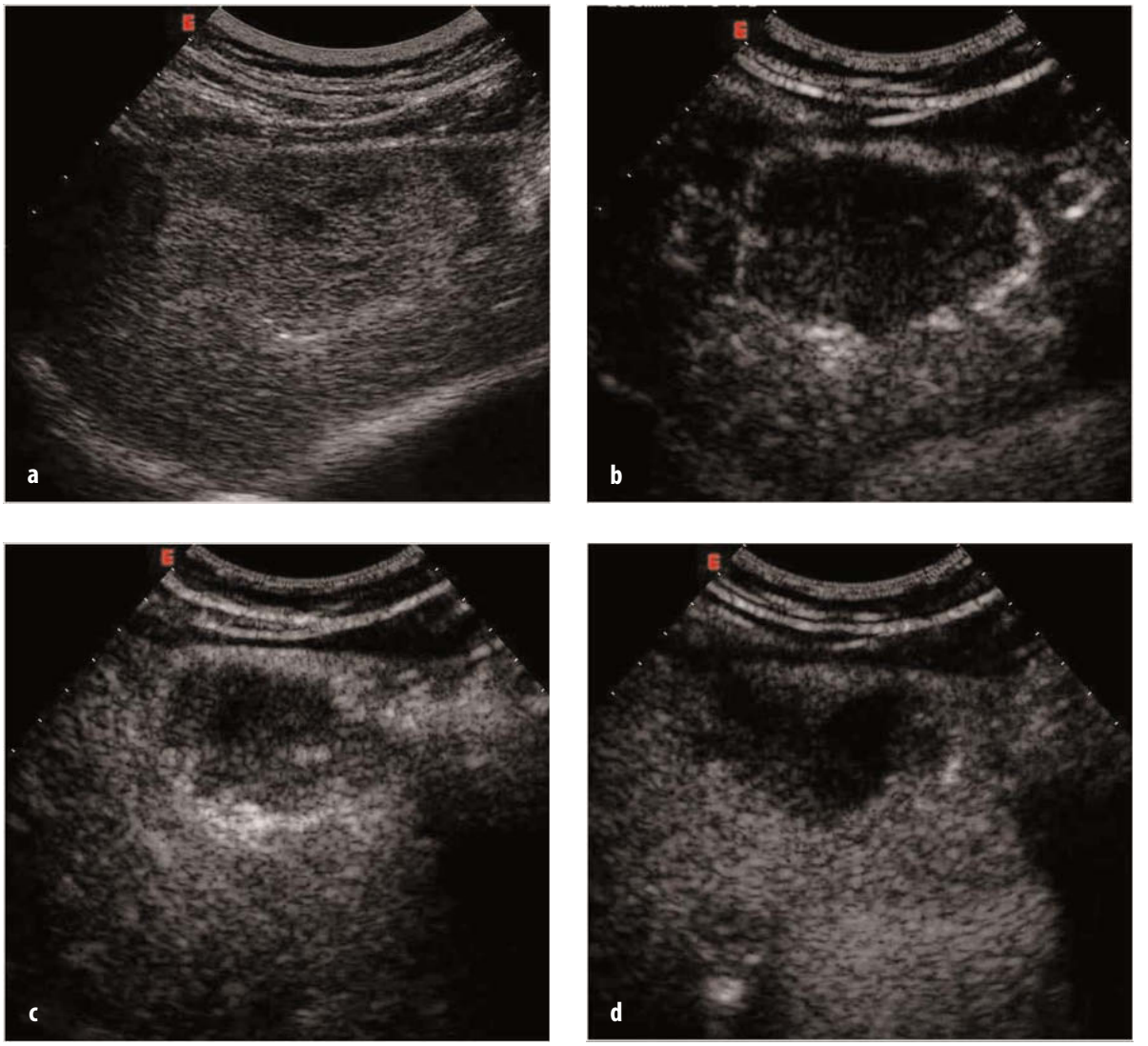
Ultrasound (US) is the most commonly used liver imaging modality. Unfortunately, US has limited sensitivity for the detection of small tumor nodules. Moreover, US findings are often non-specific, as there is enough variability and overlap in the appearance of benign and malignant liver lesions to make a definite distinction problematic. Computed tomography (CT) and magnetic resonance (MR) imaging are commonly used to clarify questionable US 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 up new prospects in liver US [2]. Contrast-specific techniques produce images based on non-linear acoustic effects of microbubbles and display enhancement in gray-scale, maximizing contrast and spatial resolution. The goal of improving the US assessment of focal lesions was initially pursued through 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 intermittent scanning, and a series of sweeps have to be performed in an attempt to cover the whole liver parenchyma. The advent of second-generation agents - that have higher harmonic emission capabilities - has been instrumental in improving the ease and the reproducibility of the examination [3]. In fact, a lower, non-destructive mechanical index can be used, thus enabling continuous real-time imaging. Over the past few years, several reports have shown that real-time contrast-enhanced US can substantially improve detection and characterization of focal liver lesions with respect to baseline studies [4].

With the publication of the guidelines for the use of contrast agents in liver US by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), contrast-enhanced US 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. In this paper, we discuss the impact of EFSUMB guidelines on diagnostic protocols currently adopted in liver imaging with regard to four clinical scenarios: (1) characterization of focal liver lesions of incidental detection; (2) diagnosis of HCC in patients with cirrhosis; (3) detection of hepatic metastases in oncology patients; and (4) guidance and assessment of the outcome of percutaneous tumor ablation procedures.

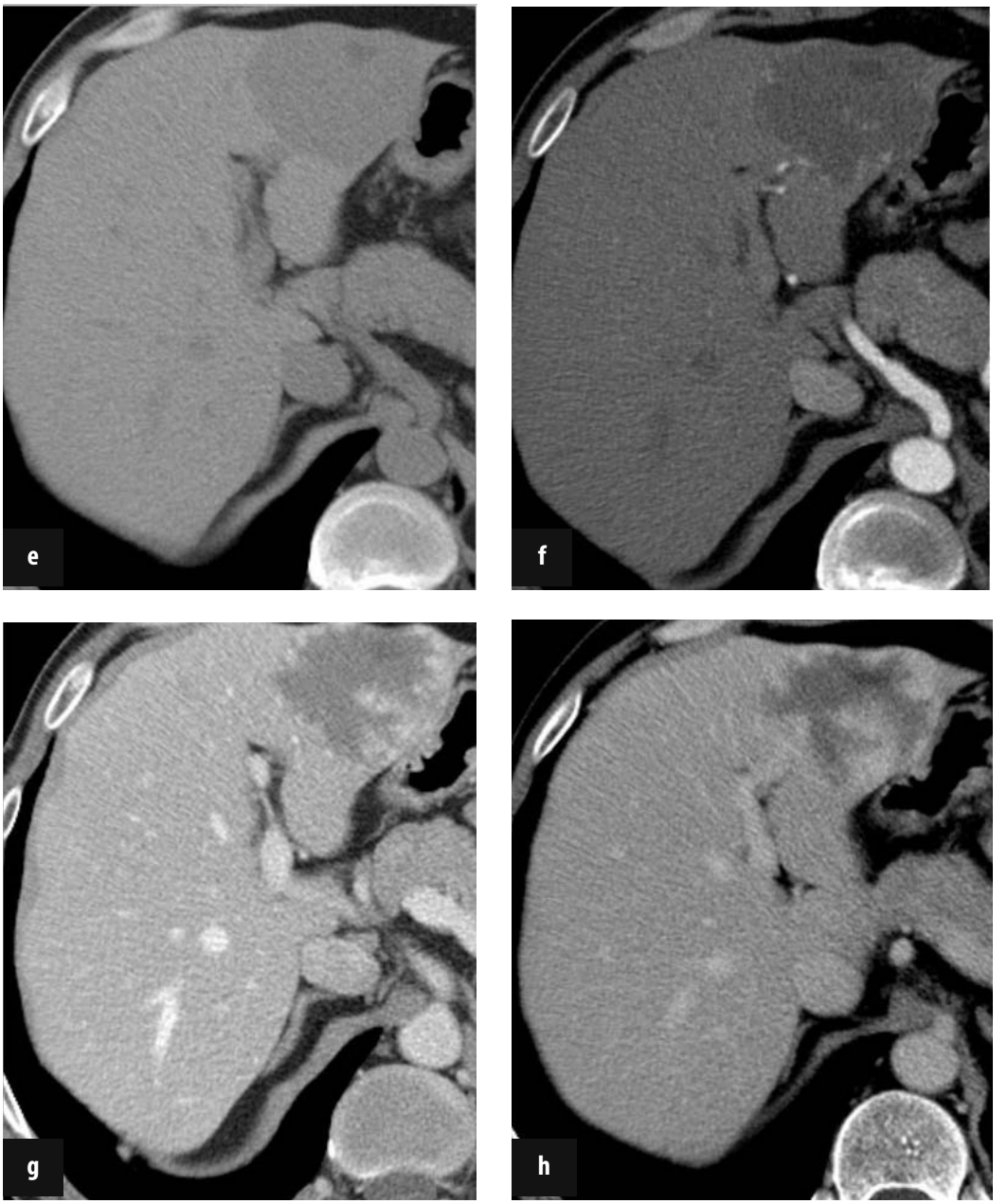
Characterization of Incidental Focal Liver Lesions

Characterization of focal lesions of incidental detection is one of the most common and sometimes troublesome issues in liver imaging.

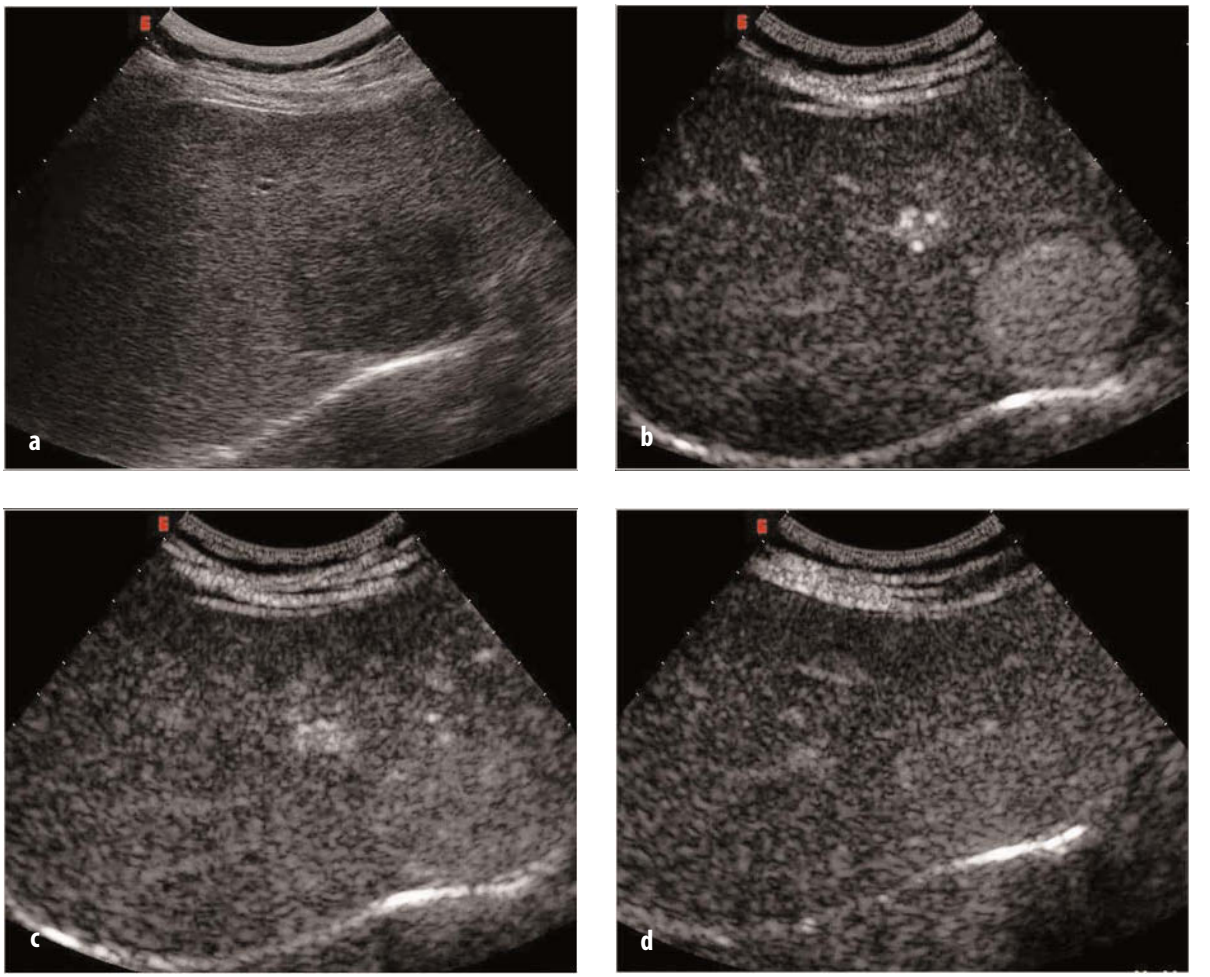


Unsuspected lesions, in fact, are frequently detected in patients who have neither chronic liver disease nor history of malignancy during an US examination of the abdomen. While a confident diagnosis is usually made on the basis of US findings in cases of simple cysts and hemangiomas with typical hyperechoic appearances, lesions with non-specific US features require further investigation [5]. The patient is typically referred for contrast-enhanced CT or contrast-enhanced MR imaging of the liver.

EFSUMB guidelines recommend the use of contrast agents to diagnose benign focal lesions not characterized at baseline study. This statement is based on the ability of contrast US to allow analysis of lesion vascularity. In fact, lesions that most frequently cause incidental findings – such as hemangioma and focal nodular hyperplasia – typically show contrast-enhanced US patterns that closely resemble those at contrast-enhanced CT or contrast-enhanced MR imaging. Most liver hemangiomas



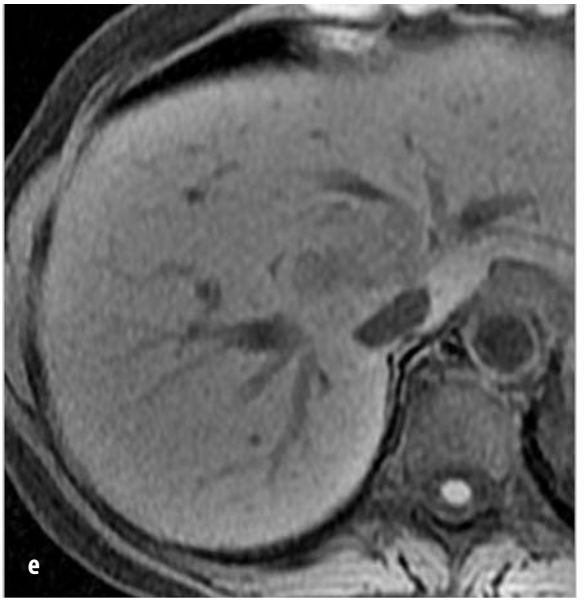
show peripheral nodular enhancement during the early phase, with progressive centripetal fill-in, leading to lesion hyperechogenicity in the late phase (Fig. 1). In two recent series, this characteristic features have been shown in 78-93% of hemangiomas [6, 7]. Focal nodular hyperplasia shows central 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 relative to normal liver tissue, and becomes isoechoic in the late phase (Fig. 2). This pattern has been observed in 85-100% of focal nodular hyperplasias [6, 8]. Therefore, it appears that in most liver lesions incidentally discovered at the baseline US study, 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.

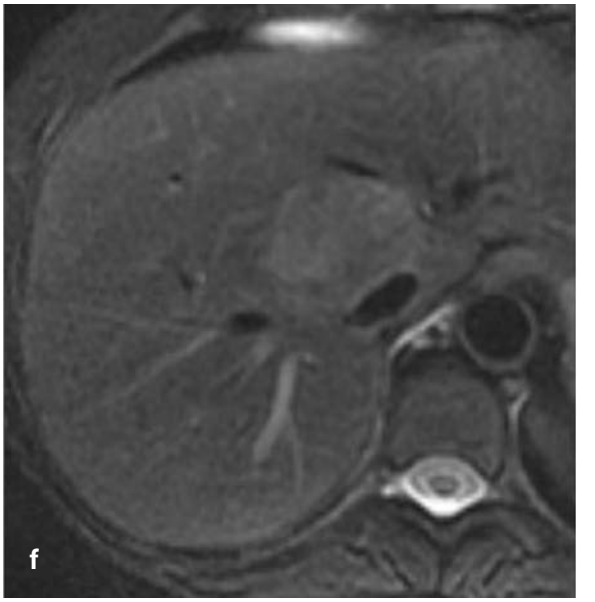


Diagnosis of Hepatocellular Carcinoma in Cirrhosis

The second clinical scenario is represented by patients with hepatic cirrhosis. In view of the high risk of developing HCC, these patients are carefully followed with US examinations repeated at six month intervals [9]. While the detection of a focal lesion in cirrhosis should always raise the suspicion of HCC, it is well established that the pathologic changes inherent to cirrhosis may simulate HCC in a variety of ways, especially because non-malignant hepatocellular lesions, such as regenerative and dysplastic nodules, may be indistinguishable from a small tumor. One of the key pathologic 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 non-triadal arteries, which become the dominant blood supply in overt HCC. It is this neovascularity that allows HCC to be diagnosed with contrast-enhanced CT or dynamic MR imaging [10].

According to EFSUMB guidelines, a contrast-enhanced US study is recommended to characterize any lesion or suspect lesion detected at baseline US in the setting of liver cirrhosis [4]. Owing to the ability to display contrast-enhancement in real-time, contrast US appears to be a tool to show arterial neoangiogenesis associated with a malignant change, and, therefore, to help establish the diagnosis of HCC [11, 12]. HCC typically shows strong intratumoral enhancement in the arterial phase (i.e., within 25-35 seconds of the start of contrast injection) followed by rapid wash-out with isoechoic or hypoechoic appearance in the portal venous and delayed phases (Fig. 3). 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 at contrast US has been observed in 91-96% of HCC lesions, confirming





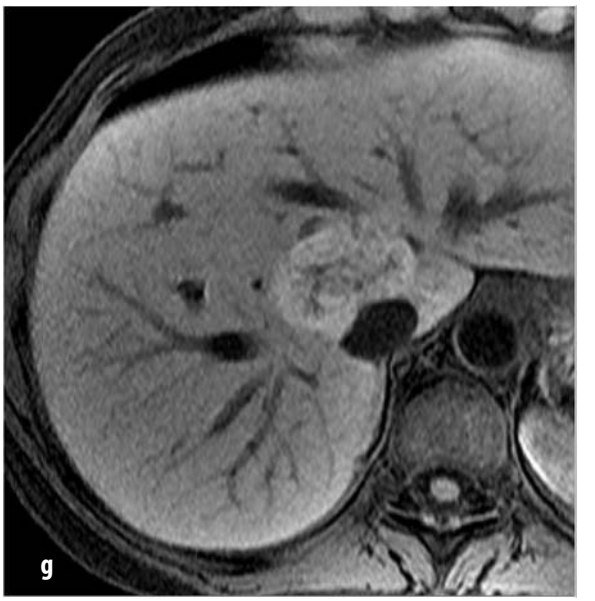
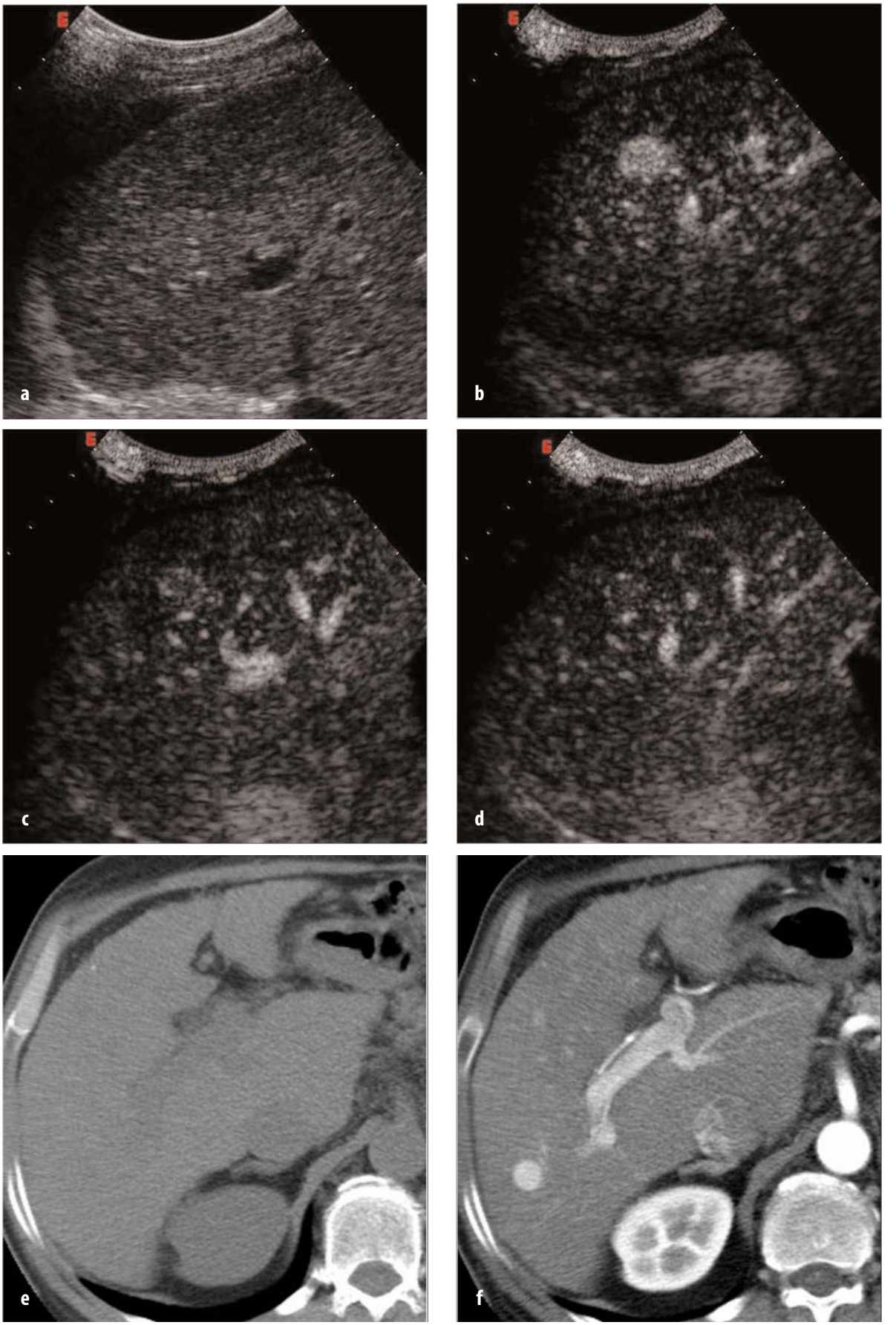


Fig. 2a-g. *Focal nodular hyperplasia.* Baseline US shows a hypoechoic lesion on segment VIII (**a**). At contrast-enhanced US the lesion shows homogeneous enhancement in the arterial phase (**b**) with isoechoic appearance in the portal and delayed phases (**c**, **d**). At MR imaging, focal nodular hyperplasia appears slightly hypointense on the T1-weighted image (**e**), slightly hyperintense on the T2-weighted image (**f**), and hyperintense on the T1-weighted image acquired 1 hour after the injection of an hepatospecific contrast agent (**g**)

that contrast US may be a useful tool to show arterial neoangiogenesis of HCC [11, 12]. In a recent study, in which findings at spiral CT were assumed as the gold standard, the sensitivity of contrast US in the detection of arterial hypervascularity was 97% in lesions larger than 3 cm, 92% in lesions ranging 2-3 cm, 87% in lesions ranging 1-2 cm, and 67% in lesions smaller than 1 cm [12]. Hence, performing a contrast-enhanced study may be recommended in all lesions or suspected lesions - 1 cm or larger in diameter - detected at baseline US in patients with cirrhosis or chronic hepatitis undergoing surveillance programs.

The use of contrast US as a reliable alternative to CT or MR imaging for characterizing nodular lesions detected by US surveillance has been recently endorsed by the American Association for the Study of Liver Diseases [13]. The diagnostic protocol is structured according to the actual risk of malignancy and the possibility of achieving a reliable diagnosis. Since the prevalence of HCC among US-detected nodules is strongly related to the size of the lesion, the work-up depends on the size of the lesion (Fig. 4) [13]. Lesions smaller than 1 cm in diameter have a low likelihood of being HCC, and only need to be followed-up in order to detect growth suggestive of malignant transformation. When the nodule exceeds 1 cm in size, the lesion is more likely to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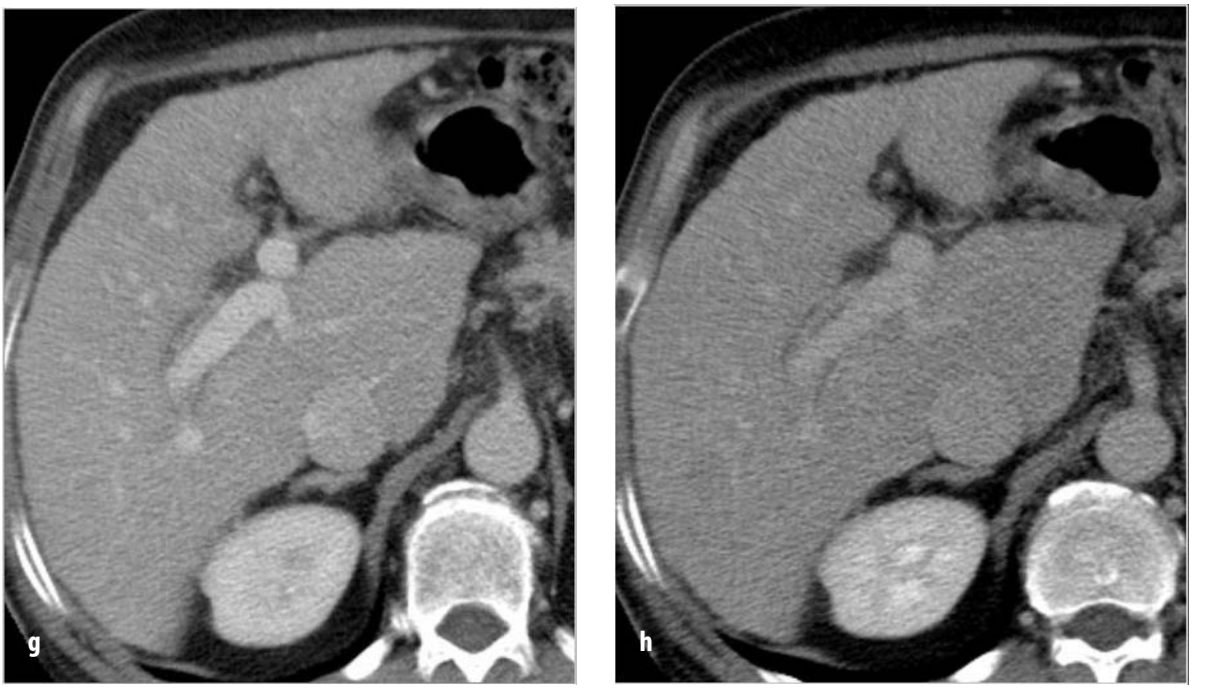


Fig. 3a-h. *Hepatocellular carcinoma.* At baseline US examination the lesion appears as an iso-hypoechoic nodule (**a**). At contrast-enhanced US, the lesion shows early enhancement in the arterial phase (**b**) with rapid wash-out in the portal-venous and delayed phases (**c**, **d**). At multidetector CT (**e**, baseline; **f**, arterial phase; **g**, portal-venous phase; **h**, delayed phase) the same enhancement pattern is observed

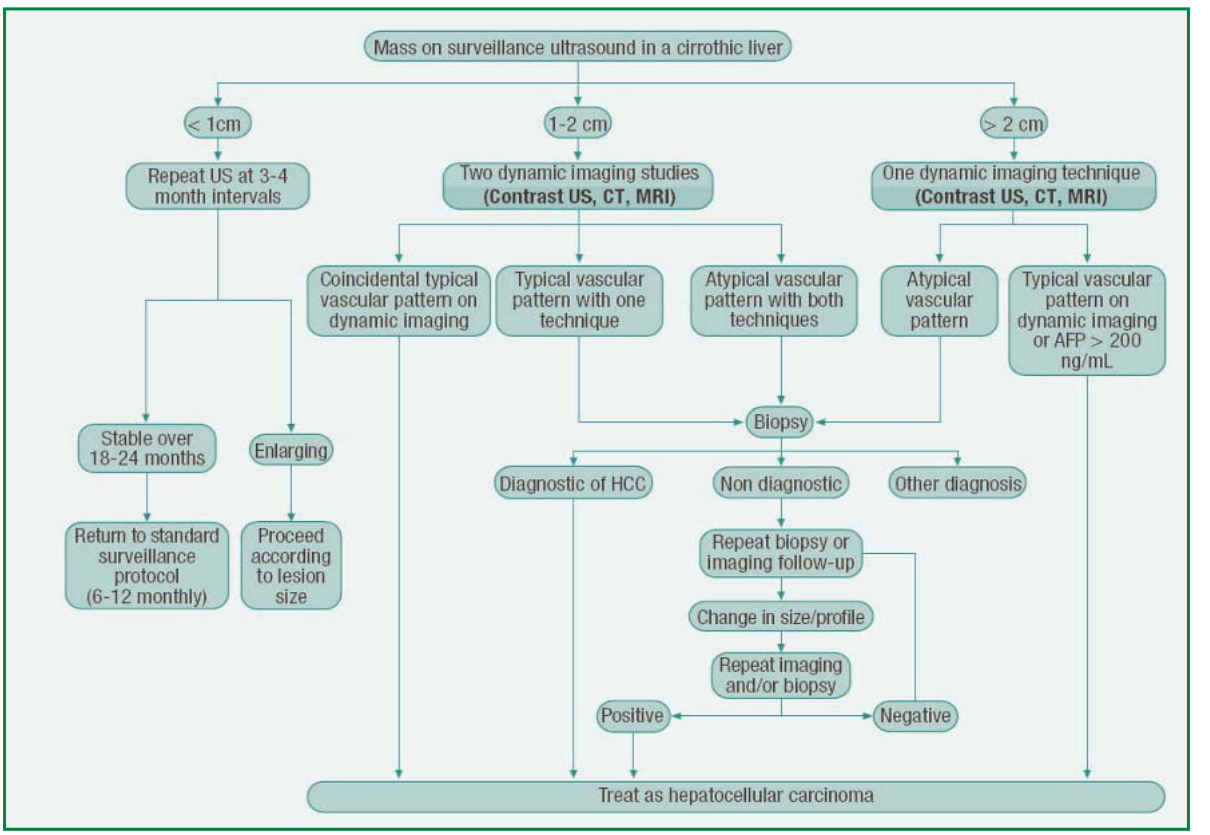
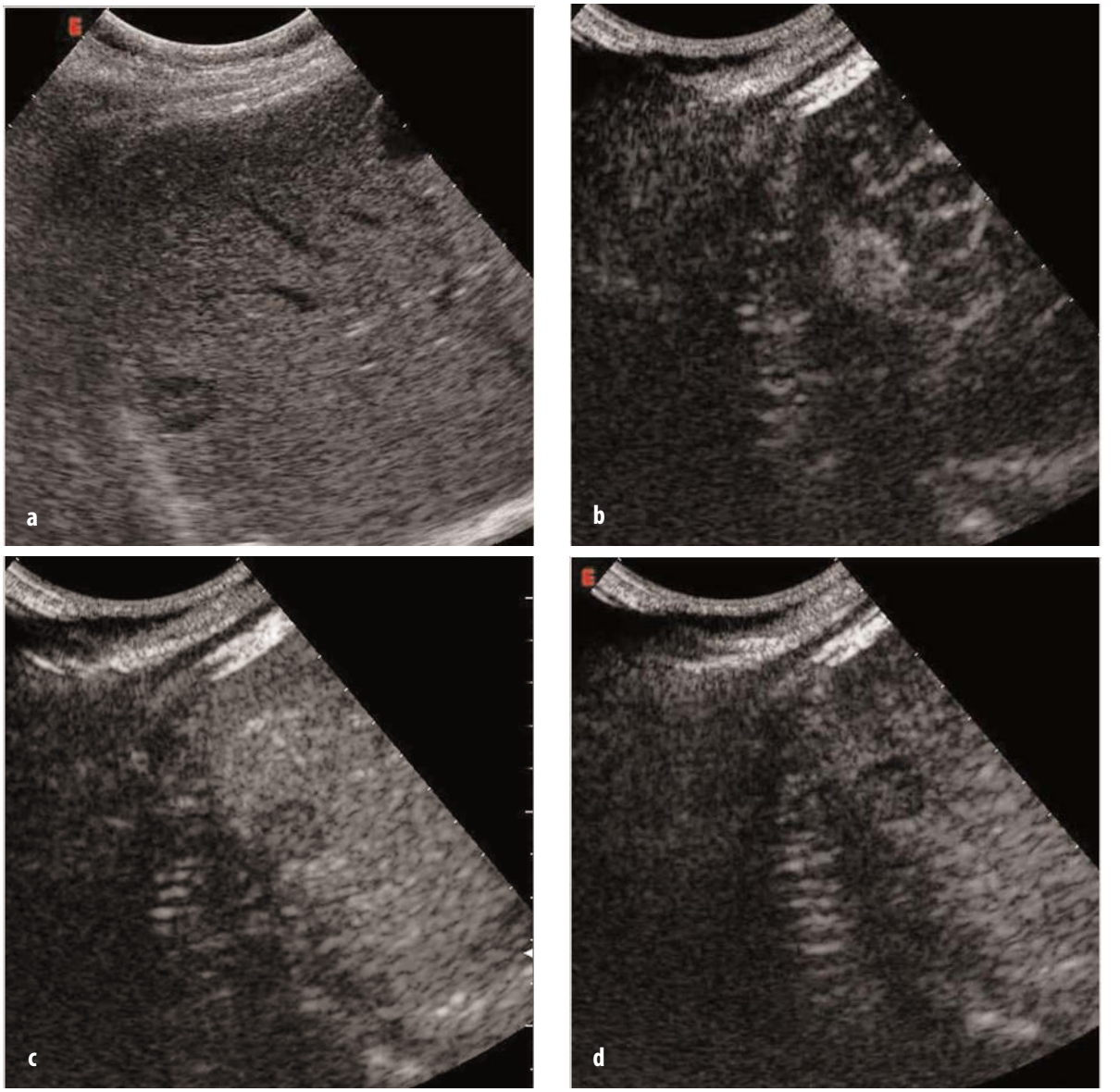


Fig. 4. Suggested algorithm for investigation of a nodule found on US during screening or surveillance. The typical vascular pattern means that the lesion is hypervascular in the arterial phase, and washes out in the portal/venous phase (Modified from [13])

be HCC and diagnostic confirmation should be pursued. It is accepted that the diagnosis of HCC in cirrhosis can be made without biopsy in a nodule larger than 1 cm that shows characteristic vascular features of HCC – i.e., arterial hypervascularization with wash-out in the portal venous or delayed phase - even in patients with normal alpha-fetoprotein values. For lesions ranging 1-2 cm, current guidelines require typical imaging findings to be confirmed by two coincident dynamic imaging modalities – out of contrast-enhanced US, contrast-enhanced multidetector CT, and contrast-enhanced MRI – to allow a non-invasive diagnosis [13]. If the imaging findings are not characteristic or the vascular profile is not coincidental among techniques, biopsy is recommended [13].

Detection of Hepatic Metastases in Oncology Patients

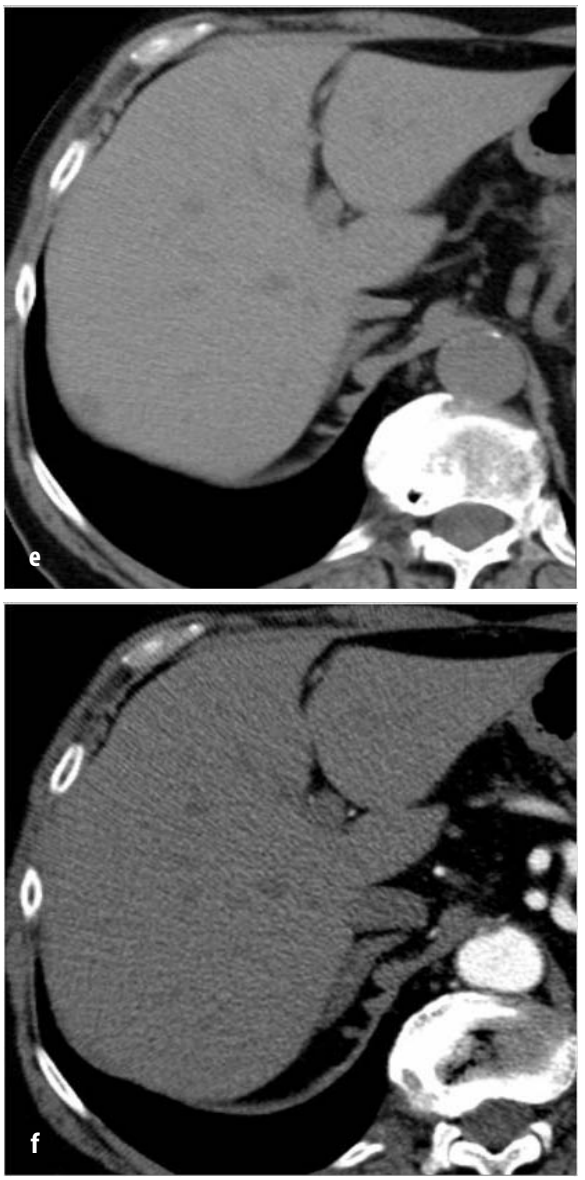
Metastatic disease involving the liver is one of the most common issues in oncology. CT and positron emission tomography (PET) are used in oncology protocols to provide objective documentation of the extent of the liver tumor burden and to effectively assess extrahepatic disease. Nevertheless, US is widely used in post-treatment 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. In fact, 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 clear-cut disseminated disease is detected at the baseline study. This means that all liver US examinations performed to rule out liver metastases should include a contrast-enhanced study, even if the baseline scans do not show any abnormality. This strong statement is based on a substantial increase in the ability to detect liver metastases in contrast-enhanced studies compared to baseline [14]. Even small metastases stand out as markedly hypoechoic lesions against the enhanced liver parenchyma throughout the portal venous and delayed phases (Fig. 5). The earlier the detection of liver metastatic disease, the earlier the therapeutic intervention.

Guidance and Monitoring of Tumor Ablation Procedures

Several percutaneous techniques have been developed to treat non-surgical patients with liver malignancies. These minimally invasive procedures can achieve effective and reproducible tumor destruction with acceptable morbidity. Radio-frequency ablation is increasingly accepted as the best therapeutic choice for



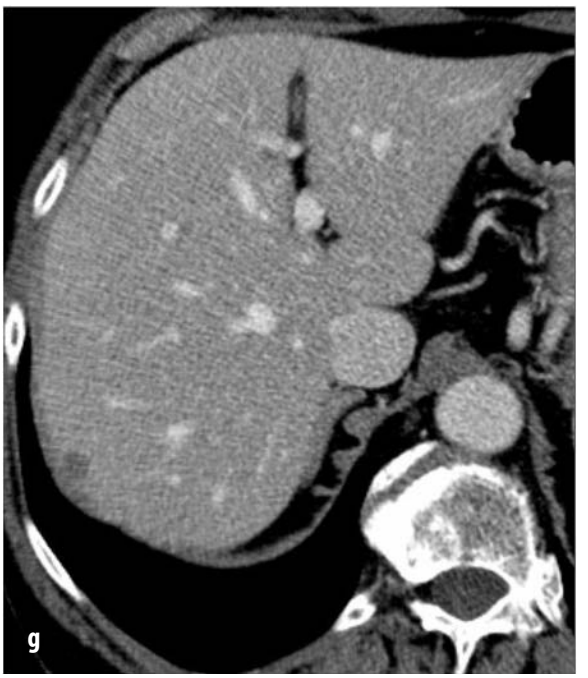


Fig. 5a-g. *Metastasis.* Baseline US examination shows a subcapsular hypoechoic nodule (**a**). At contrast-enhanced US the lesion shows rim enhancement during the arterial phase (**b**) with hypoechoic appearance in the portal-venous and delayed phases (**c**, **d**). At multidetector CT, the metastatic nodule appears hypodense in the baseline scan (**e**) as well as in the arterial (**f**) and the delayed phases (**g**)

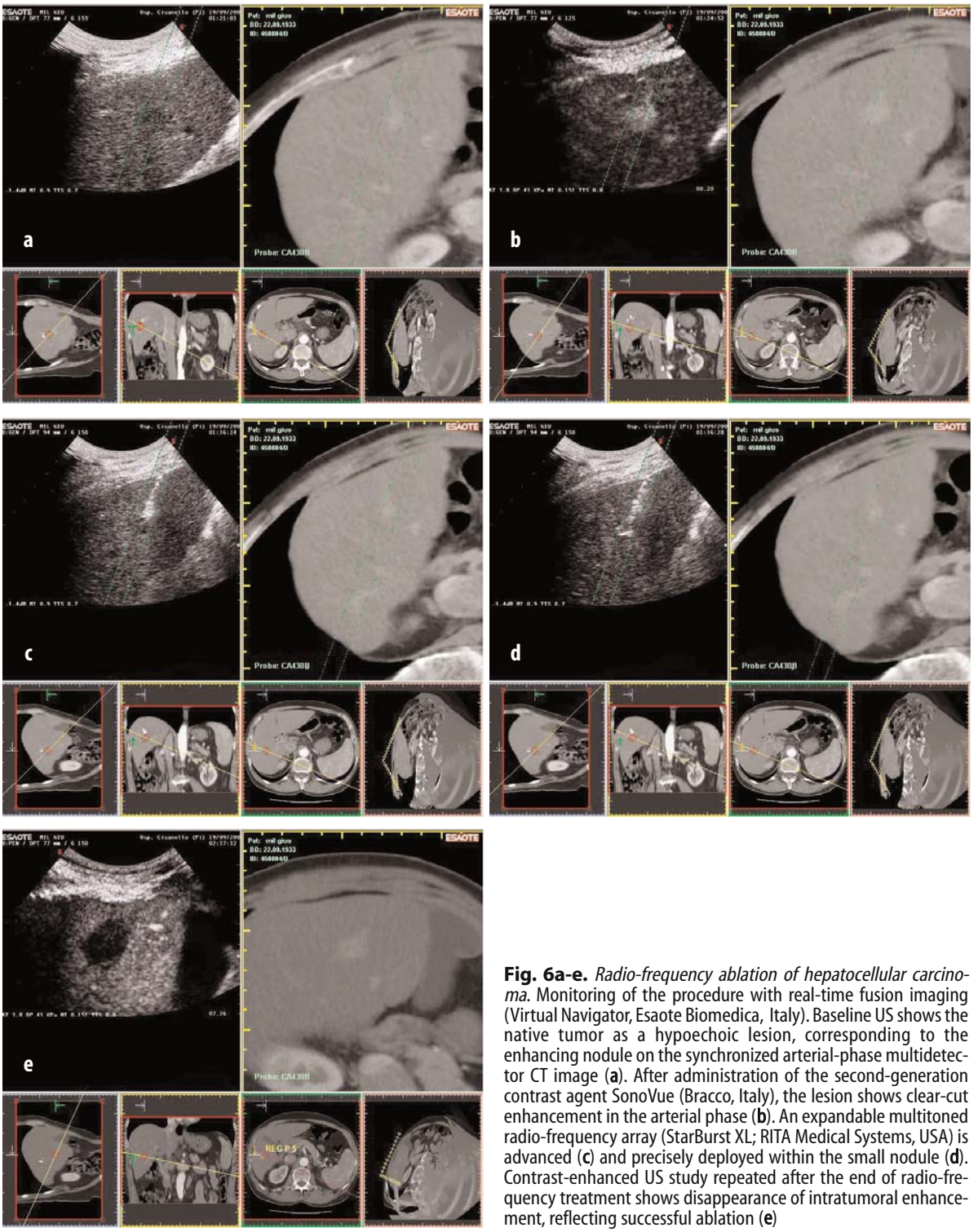


Fig. 6a-e. *Radio-frequency ablation of hepatocellular carcinoma.* Monitoring of the procedure with real-time fusion imaging (Virtual Navigator, Esaote Biomedica, Italy). Baseline US shows the native tumor as a hypoechoic lesion, corresponding to the enhancing nodule on the synchronized arterial-phase multidetector CT image (**a**). After administration of the second-generation contrast agent SonoVue (Bracco, Italy), the lesion shows clear-cut enhancement in the arterial phase (**b**). An expandable multitoned radio-frequency array (StarBurst XL; RITA Medical Systems, USA) is advanced (**c**) and precisely deployed within the small nodule (**d**). Contrast-enhanced US study repeated after the end of radio-frequency treatment shows disappearance of intratumoral enhancement, reflecting successful ablation (**e**)

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 US is used as the imaging modality for guiding ablations, the addition of contrast agent can provide additional important information throughout all the procedural steps: it improves delineation and conspicuity of lesions poorly visualized on baseline scans, facilitating target-

ing; it allows the immediate assessment of the outcome of treatment by showing the disappearance of any previously visualized intralesional enhancement (Fig. 6); and it may be useful in the follow-up protocols for early detection of tumor recurrence [17].

Conclusions

Despite the improvement in detection and characterization of focal liver lesions that can be achieved using contrast-enhanced US, several issues are still open. First, contrast US will hardly replace CT or MR imaging 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 US laboratory doing liver examinations will have to be reformulated, and many US laboratories will have to update their equipment and to provide proper training for their doctors. Last but not least, the cost of the introduction of contrast-enhanced US into 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 MR imaging of the liver after contrast-enhanced US could largely counterbalance the cost of the examination. However, an optimal use of contrast-enhanced US will require the definition of precise diagnostic flow charts for each clinical situation. Nevertheless, contrast-enhanced US 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 eventually in improved patient survival.

Key Points

- Several reports have shown that real-time contrast-enhanced US substantially improves detection and characterisation of focal liver lesions with respect to baseline US.
- The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) has issued guidelines that define the indications and recommendations for the use of contrast agents in liver US.
- EFSUMB guidelines are producing a major impact on diagnostic protocols for all the main clinical situations: (1) characterisation of focal liver lesions of incidental detection; (2) diagnosis of hepatocellular carcinoma in patients with cirrhosis; (3) detection of hepatic metastases in oncology patients; and (4) guidance and assessment of the outcome of percutaneous tumor ablation procedures.
- The use of contrast US as a reliable alternative to CT and MR imaging in characterising nodular lesions detected by US surveillance in patients with cirrhosis as hepatocellular carcinoma has been recently endorsed by the American Association for the Study of Liver Diseases.

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