5 Diagnosis and Staging: Contrast-Enhanced Intraoperative Ultrasound (CEIOUS) Using Intravascular Contrast Agents

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Tumor echogenicity and background liver appearance in IOUS (i.e., cirrhotic, steatotic) can affect our ability to recognize tiny lesions. It has been shown that small metastases can be better recognized if they are hypoechoic rather than isoechoic [1]. Another drawback of IOUS is its limitations in differentiating new lesions according to their echogencity. Based on these two well-known limitations, some authors have tried to find a solution by introducing additional analytical features, as, e.g., the modifications that can be induced on the ultrasound image by injecting a contrast agent.

In the early 1990s, attempts were made using carbon dioxide as a contrast agent for IOUS. However, the need for arterial catheterization made this technique too invasive [2]. The introduction of contrast agents injected intravenously generated new interest in this technique. The first generation consisted of gas-filled microbubbles with a galactose shell, which was both intravascular and somehow hepatospecific accumulating in Kupffer cells. For the ultrasonic visualization of this agent, insonation at a high acoustic pressure was applied intermittently to allow both a vascular and a hepato-specific phase. However, this resulted in collapse of the microbubbles and generated scattered ultrasound waves visualized on the US system in the vascular phase as flashes, not allowing a continuous ultrasound observation. Furthermore, in the postvascular phase, scanning of the liver was limited to one swing of the ultrasonic probe because all the microbubbles that accumulated in the hepatic parenchyma had collapsed by this time. The introduction of a second generation of pure intravascular contrast agents , providing real-time continuous monitoring of the contrast enhancement, has led to widespread use of this modality in ultrasound examination [3, 4].

The gas-filled microbubbles of these agents tolerate low acoustic pressures, enabling continuous observation during the arterial phase and repeated scanning during the late phase. We first introduced this new approach in an intraoperative pilot study on 20 patients [5], establishing their use by CEIOUS in surgery for both HCC and CLM. Recently, the introduction of contrast agents combining the intravascular features of second-generation contrast agents with the hepato-specific features of first-generation contrast agents taken up by Kupffer cells has shown further improvements in this technique, as discussed further in Chap. 6.

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5.1 Technique

Still, second-generation intravascular contrast agents are only available in the European countries. As described in Chap. 1, the major contrast agent available in Europe is composed of sulfur hexafluoride microbubbles stabilized by a phospholipid shell (SonoVue, Bracco Imaging, Milan, Italy). The machine is set to contrast mode (Fig. 5.1); preferably arranged side-by-side in order to simultaneously show the fundamental IOUS and CEIOUS so as not to loose any eventual targets found by IOUS (Fig. 5.2). The contrast is prepared as a solution by adding the powder and shaking gently to be injected intravenously by the anesthesiologist: 2.4–4.8 ml of SonoVue is rapidly infused per exploration through a peripheral vein advising the surgeons once the injection is started to let them initiate the timer of the ultrasound system and starting the registration of the enhancement process. The amount of contrast agent is established according to the preference of the operator; usually, half sample (2.4 ml), if properly prepared, is sufficient.

5.2 Indications

5.2.1 Hepatocellular Carcinoma

As mentioned for HCC, CEIOUS is now used for characterizing new lesions initially detected by IOUS [6]: the rationale is to check the vascular pattern during contrast enhancement of each new lesion. Since, in the case of HCC, it is very important to identify the arterial vascularization, which lasts from 20 to 30 s, each nodule has to be carefully evaluated, and that demands multiple injections in the presence of multiple nodules.

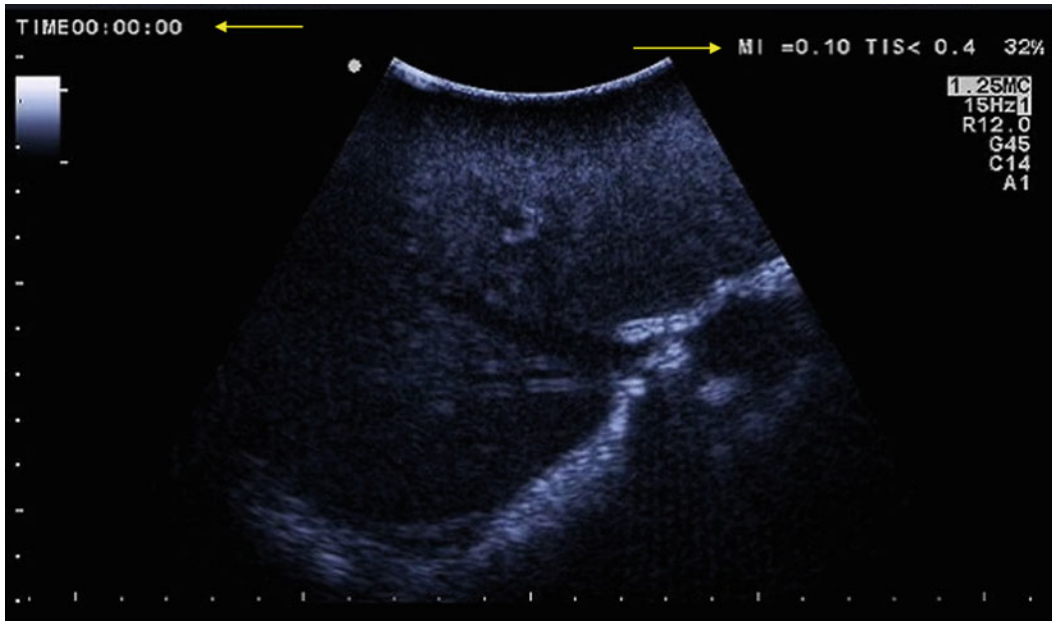

Fig. 5.1 Screen of the ultrasound system regulated by contrast preset. In the *upper right corner*, MI (*yellow arrow*) means mechanical index, which corresponds with the power at which the ultrasound waves intercept the microbubbles composing the contrast agent, which should be below 1, in order not to break the microbubbles and providing the contrast effect of real-time enhancement in ultrasound. In the *upper left corner*, the time (*yellow arrow*) elapsing from injection of the contrast agent by the anesthesiologist into a peripheral vein

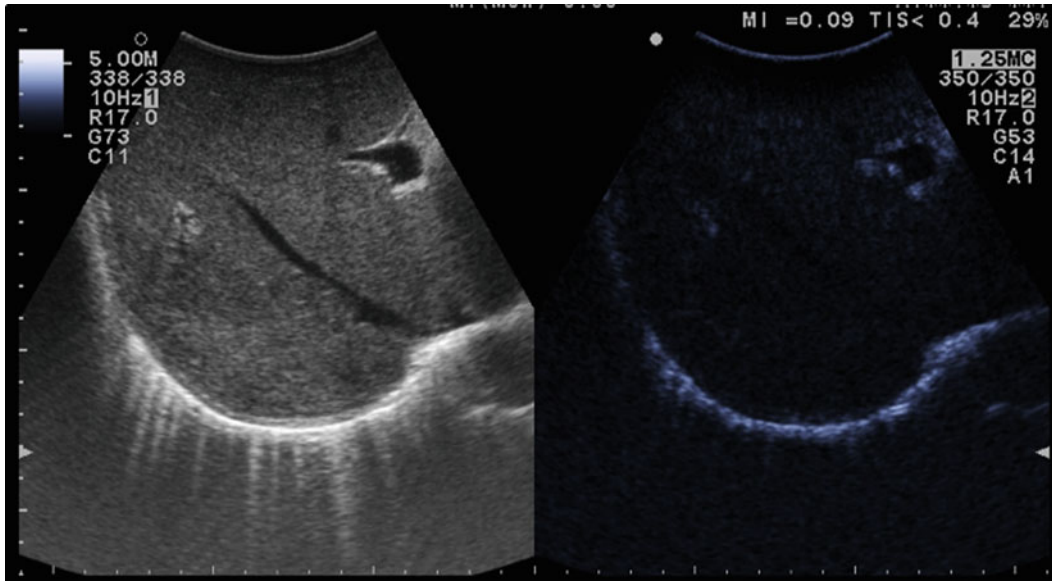

Fig. 5.2 The screen of the ultrasound system can be set to combine on the same image the preset for B-mode (*left*) and contrast (*right*)

This may no longer be necessary with the use of hepato-specific contrast agents (see Chap. 6).

Tumor vascularity is a criterion for differentiating regenerative or dysplastic nodules from the HCC well correlated with the histological evidence of a progressive increase in unpaired arteries from dysplastic to neoplastic nodules in a cirrhotic liver [7]. However, the pattern of vascular enhancement is not sufficient for clearly differentiating malignant from nonmalignant nodules in a cirrhotic liver. Percutaneous contrast-enhanced ultrasound (CE-US) provides a 95 % specific differential diagnosis of focal liver lesions [4]; this rate is, however, referred to another type of lesion if compared to the target of CEIOUS. Intraoperative exploration profits from the higher resolution of US done in direct contact with the liver. Therefore, nodules detected by IOUS are usually smaller than 1 cm: here, vascularity as a criterion for differential diagnosis is less specific. However, some improvements compared with conventional IOUS can be expected. Our preliminary experience showed that CEIOUS can provide remarkable findings, either by the additional information on nodular vascularity in patients with HCC, or by detecting nodules that were not visible in IOUS in patients with CLM [5]. For patients with HCC, we introduced a classification of the pattern of enhancement by CEIOUS of the lesions detected in IOUS from which surgical decision-making can be established (Fig. 5.3) [6]. Briefly, any lesion with a pathologic behavior should appear as hypoechoic in the late phase and with an arterial phase in which it is fully enhanced prior to the remnant liver parenchyma (Fig. 5.4a), or with just inner vessels visualized in it (Fig. 5.4b): this kind of lesions are removed. Those lesions which disappear once the contrast enhances the liver are not considered neoplastic, and those are not removed (Fig. 5.5). With these criteria

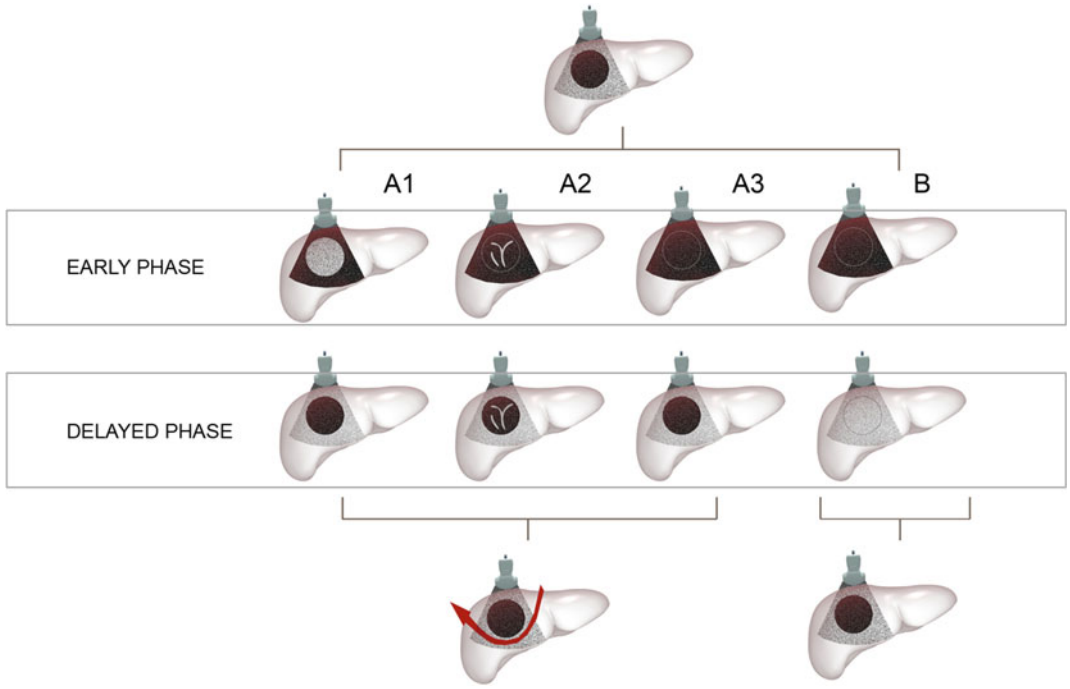

Fig. 5.3 Classification of patterns of enhancement in CEIOUS of those lesions detected in IOUS during surgery for HCC. Lesions having a class A pattern, featured by a hypervascular enhancement in early phase (*A1-2*), or any hypoechoic pattern in the delayed phases (*A1-3*), has to be resected; while lesions showing a class B pattern of enhancement are not removed

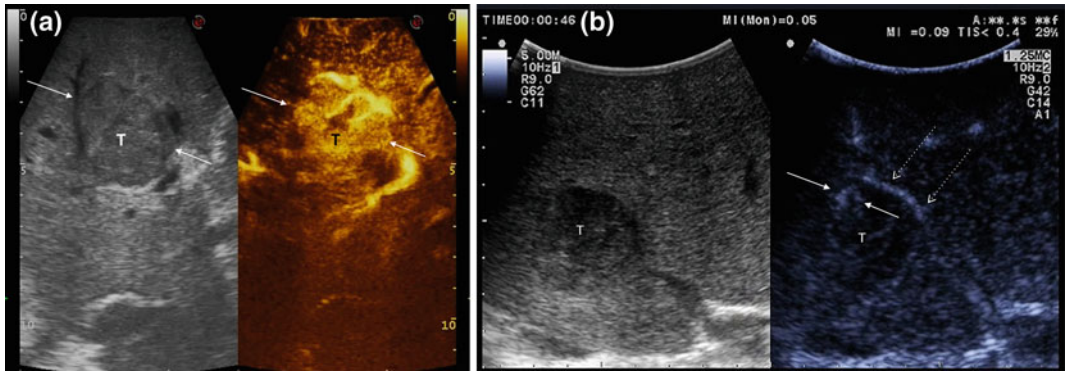

Fig. 5.4 **a** At an early stage, the lesion (*T*) on the right assumes contrast prior to the surrounding tissue showing a nodular arterial enhancement (A1 pattern); **b** while this lesion is not fully enhanced in the arterial phase but just shows inner vessels (*arrows*) originating from a perinodular basket of arteries (*dashed arrows*), and flowing into the nodule itself (A2 pattern)

we obtained a specificity of 69 % by CEIOUS [6]. This value is not very high especially when compared with that reported for CE-US [4]. However, as mentioned above, the small size of the lesions targeted by CEIOUS could explain this discrepancy: for these tiny nodules, there

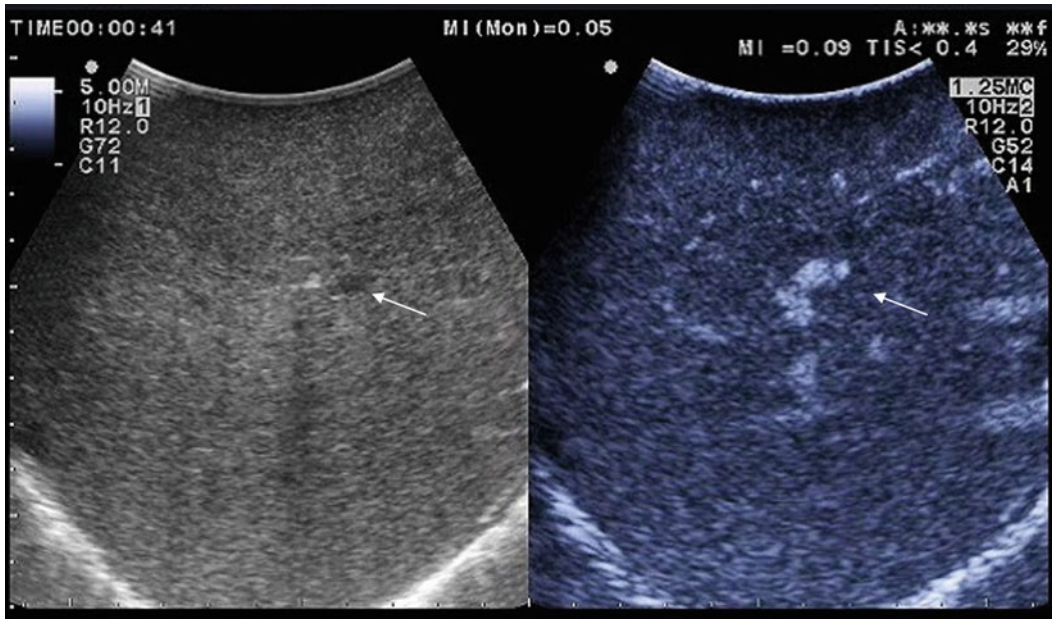

Fig. 5.5 In the delayed phase, the lesion visible on the left in B-mode exploration (*arrow*) is no longer detectable on the right by CEIOUS (*arrow*) (B pattern)

are limits to the use of neo-vascularity as a criterion for differentiating between malignant and benign lesions, which are independent from the method we use. Therefore, CEIOUS can be helpful in a certain percentage of nodules but not in all: in this respect the rate of 69 % of specificity is encouraging as it means that we can provide proper information with this new technique in seven out of ten lesions we detect at the time of laparotomy. For the remaining three, even histology may be lacking. Indeed, we are aware that there is no common agreement between pathologists in East and West on the definition of early HCC and dysplastic lesions [8]. The possible new perspective provided by the new contrast agent, is, as mentioned, still the object of extensive analyses (see Chap. 6).

5.2.2 Colorectal Liver Metastases

Echogenicity impacts detection of CLM [1], as previously mentioned. Therefore, a modality that would improve lesion visibility, and enhancing detection, was needed: CEIOUS addresses this main goal in the case of CLM. In the 1990s, in half of the patients undergoing surgery for CLM the surgical strategy was modified by IOUS findings [9]. However, more recently, progress in preoperative imaging has reduced this rate: in fact, some authors have recently reported that merely 4 % of operative decision-making has been modified by IOUS [10]. By adding CEIOUS to IOUS exploration, operation decision-making has been affected in 38 % of patients with CLM [11]: if this discrepancy in the rates of modified surgical

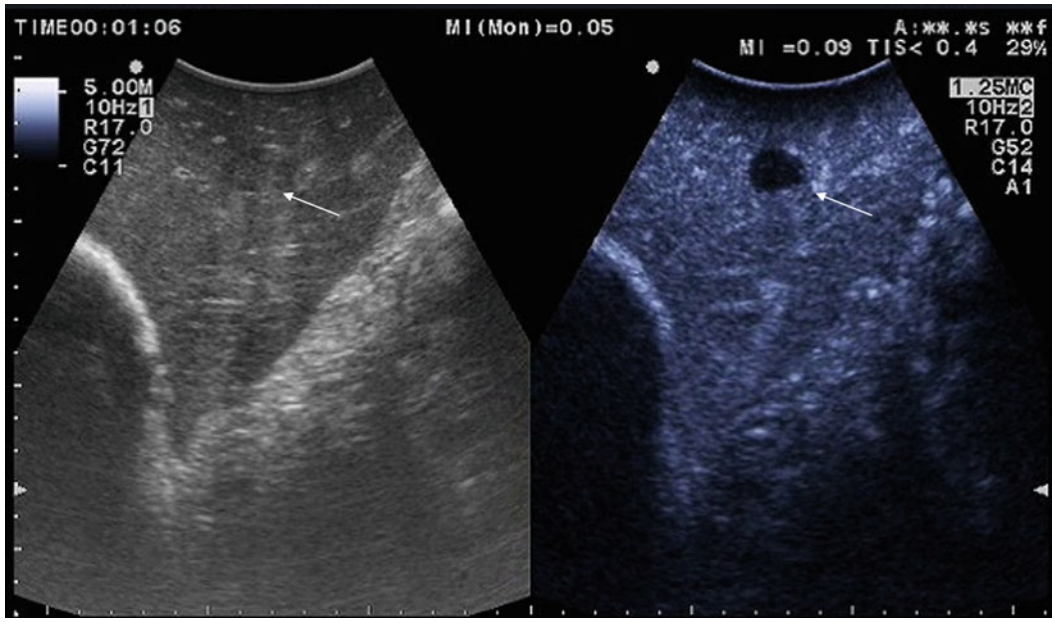

Fig. 5.6 In the delayed phase, the CLM visible as hypoechoic in B-mode exploration on the left (*arrow*) may lead to the assumption of a so-called ''black-hole'' pattern in CEIOUS (*arrow*)

strategy among series is partially motivated by the different surgical approach, which by latest experience is featured by more parenchymal sparing procedures (see Chap. 7), probably CE-IOUS is playing a role too. By using CE-US, CLM has shown a so-called ''black-hole'' effect (Fig. 5.6): the metastastic nodule in the late phase (2–5 min after injection) remains unenhanced and then becomes black in comparison with the surrounding enhanced liver parenchyma. Therefore, CEIOUS allows better nodule visibility. However, with growing experience, we paradoxically witnessed a decrease in the rate of detectable new lesions from 44–77 % in the first two reports [12, 13] to 17–19 % in the most recent reports [11, 14]. The clinical impact of CEIOUS thus seems to progressively decrease with the improvement of preoperative imaging. However, looking at the number of new lesions detected by IOUS, the latter explanation may not be convincing. Indeed, the 16 % of new lesions detected by IOUS in the first report [12] has been substantially confirmed by more recent experience [11, 14]. Technologically, the improvements in IOUS can explain the still high rate of new lesions detected intraoperatively. However, technological improvements in CE-IOUS have been observed in the last years, too, with the introduction of new contrast agents (see Chap. 6). However, initial data do not substantially differ from those mentioned above. Therefore, the decrease observed in the impact of CEIOUS in clinical practice probably means that a steady state has been reached for this method in the case of CLM: therefore, the definition of useful criteria for selective use of CEIOUS seems justified.

In our experience, multinodularity (Fig. 5.7) and isoechogenicity (Fig. 5.8) seem to affect the detection power of IOUS for CLM, and, the latter, as mentioned in Chap. 4, may even impact patient prognosis after surgery [1]. In this

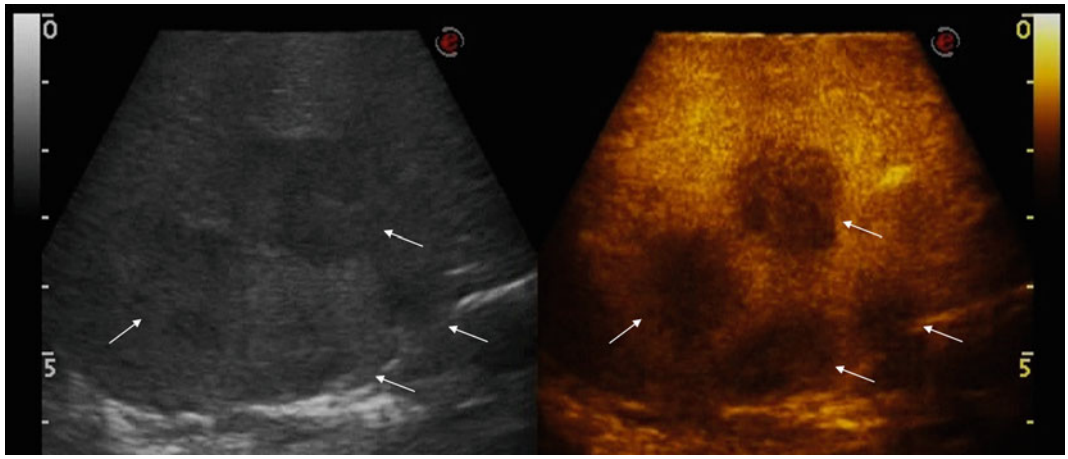

Fig. 5.7 In the delayed phase, the ''black-hole'' effect significantly increases the visibility of CLM (*arrows*) by CEIOUS (*right*) compared to the B-mode (*left*) even in the case of large nodules (*arrows*): this is very useful in case of multiple nodules, particularly when isoechoic, as shown here

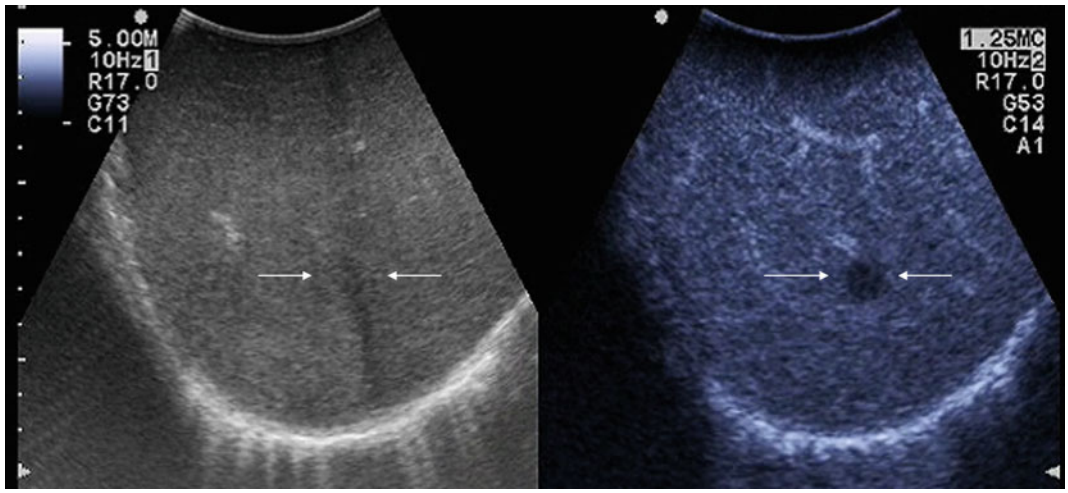

Fig. 5.8 In the case of a tiny isoechoic lesion in B-mode (*arrows on the left*), CEIOUS enhances significantly its detectability (*arrows on the right*)

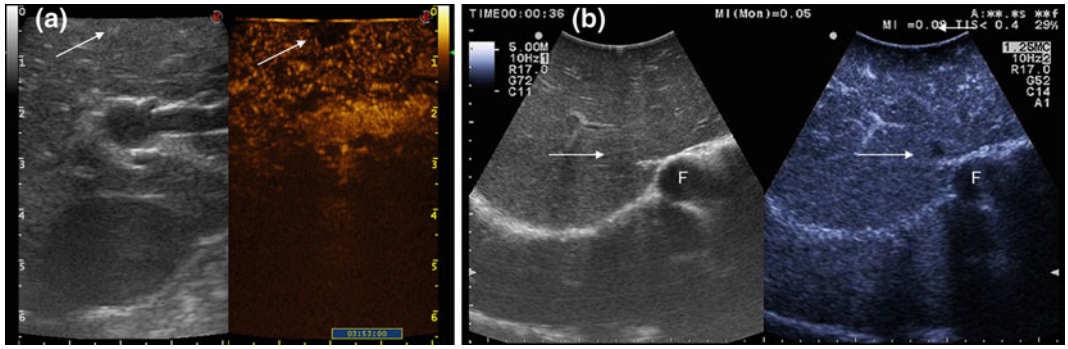

Fig. 5.9 **a** CEIOUS makes lesions visible (*arrow on the right*) that otherwise are not visible in B-mode (*arrow on the left*); **b** combination of finger palpation (*F*) and CEIOUS further facilitates the detection of small lesions (*arrow on the right*) otherwise invisible by IOUS (*arrow on the left*)

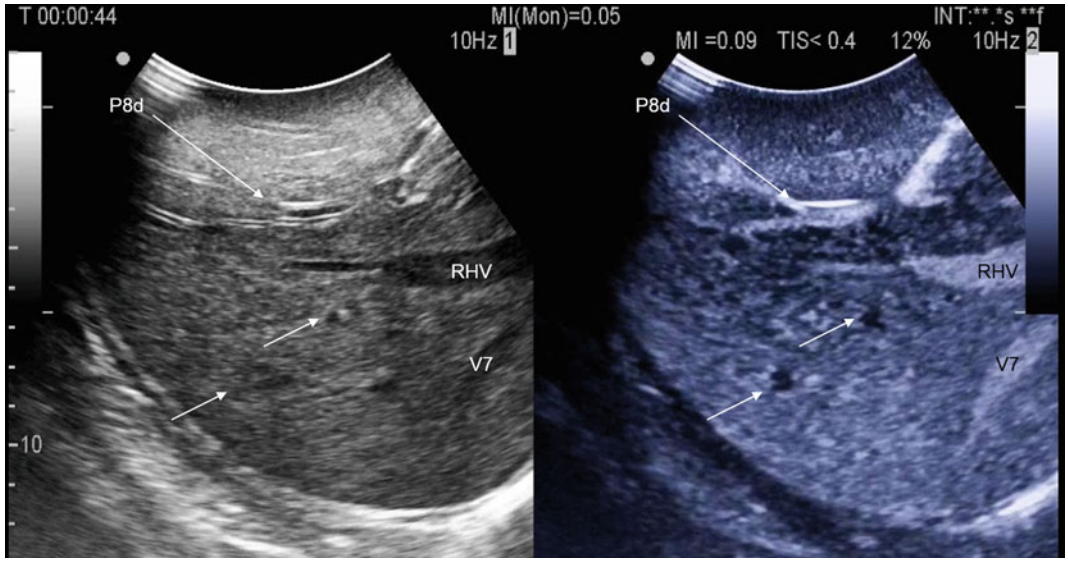

Fig. 5.10 In the case of multiple tiny isoechoic lesions in B-mode (*arrows on the left*), CEIOUS allows their detection (*arrows on the right*); portal branch feeding subsegment 8 dorsal (*P8d*); right hepatic vein (*RHV*); hepatic vein draining segment 7 (*V7*)

respect, CEIOUS seems to be able to play a role in limiting their significance in terms of risk of missed lesions aiding in the detection of otherwise undetectable small CLM (Fig. 5.9a, b). This is particularly the case for patients with multiple lesions (Fig. 5.10). However, a condition where the application of CEIOUS is useless is evidence of bright liver in IOUS, which correlates with the effects of intracellular fat amount and distribution [15], and accounts for 10 % of our patients [11]. In these cases, the visibility of CLM, which is generally hypoechoic, is enhanced by the brightness of the surrounding liver parenchyma mimicking the effect of contrast enhancement (Fig. 5.11). As a confirmation, we never detected new CLM by CEIOUS in those patients with bright liver in IOUS.

CEIOUS may also be employed to aid in detecting CLM positively treated after chemotherapy, although, in this sense results are still inconclusive [16, 17]. Actually, tiny shrunk CLM, sometimes appearing as linear defects, may not be visible by CEIOUS, while being evident upon careful IOUS with high-frequency probes (Fig. 5.12).

Scars may not become evident at palpation of tiny CLM and may generate artifacts which mask them in IOUS, while being detectable in CEIOUS (Fig. 5.13).

Care should be taken in the case of patients with CLM in a liver bearing cystic lesions. In fact, these latter appear similar to CLM during the delayed phases of contrast enhancement: however, the cysts should have been already mapped into the liver upon basic exploration (see Chap. 4), and the CLMs known prior to surgery should have been already differentiated from the cysts themselves. Therefore, any new "black hole" detected in the liver in different locations from those where cysts were eventually detected should be considered as suspicious for malignancy. This example further stresses the usefulness of keeping a side-by-side modality of exploration having the possibility of

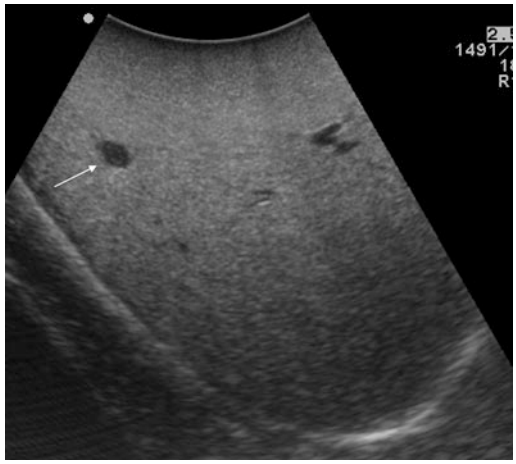

Fig. 5.11 Identifying a lesion, even if small (*arrow*), is satisfactory per se if the lesion is hypoechoic and the liver appears as a "bright liver"

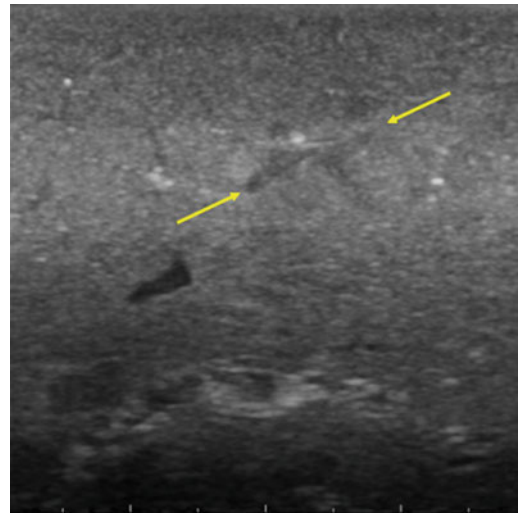

Fig. 5.13 Lesions almost disappeared after chemotherapy and are only bearly visible in IOUS (*arrows*): the detection of these lesions is facilitated by having available in the operating room the images obtained prior to chemotherapy, which would show the baseline of the disease presentation

simultaneously visualizing both the IOUS and CEIOUS images, allowing to recognize both CLM and cysts.

5.3 Resection Guidance

The echogenicity may affect detection power [1]. This reduces the operator's ability to depict the tumor burden and can make it more difficult to judge the relationship between a tumor and an adjacent vessel. As also further elaborated in Chaps. 7 and 8, this impacts both surgical strategy and resection guidance. Thus, CEIOUS, which allows improved visualization of tumor margins even of main lesions, supports a superior definition of tumor-vessel relationships. CEIOUS facilitates outlining the resection area and determining the dissection plane, resulting in easier resection guidance (Fig. 5.14a–d). Our experience has shown this to be the case in 1/5 of patients with CLM [11].

The precise correlation between palpatory and IOUS findings can be checked by exploring the liver in positioning the probe on the opposite side of the lesion while the latter is palpated with the left hand (see Chap. 2): this maneuver can be repeated during contrast enhancement (Fig. 5.15).

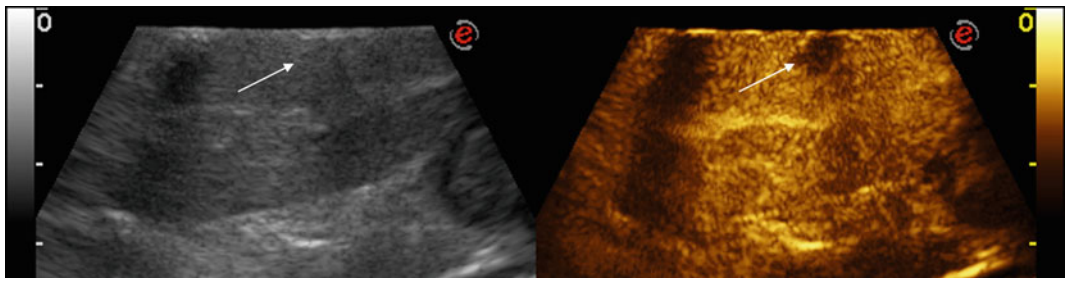

Fig. 5.12 Sometimes in a liver with an irregular surface, as, e.g., due to scars resulting from previous operations, shadowing echoes on the screen (*arrow on the left*) may mask lesions which do become evident in CEIOUS, however (*arrow on the right*)

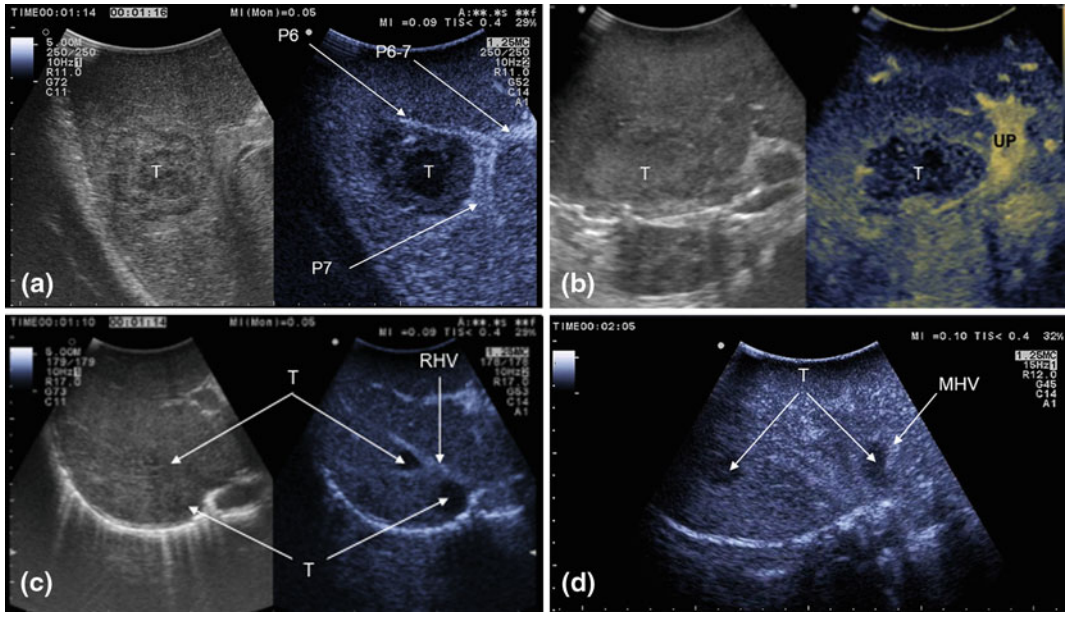

Fig. 5.14 **a** CEIOUS enhances lesion visibility may better defining the tumor–vessel relationship as for this CLM located between the portal branch to segment 6 (*P6*) and that of segment 7 (*P7*); **b** similarly, in this case, the relation of the lesion (*T*) with the umbilical portion is well disclosed by CEIOUS (*right*), compared to the B-mode image (*left)*; **c** in this case the two lesions (*T*) are not well visible by IOUS, and consequently also their tumor–vessel relationship remains undisclosed (*left*), although they are evident in CEIOUS (*right*); **d** in this CEIOUS image of two lesions (*T*), one remains in contact with the middle hepatic vein (*MHV*); right hepatic vein (*RHV*)

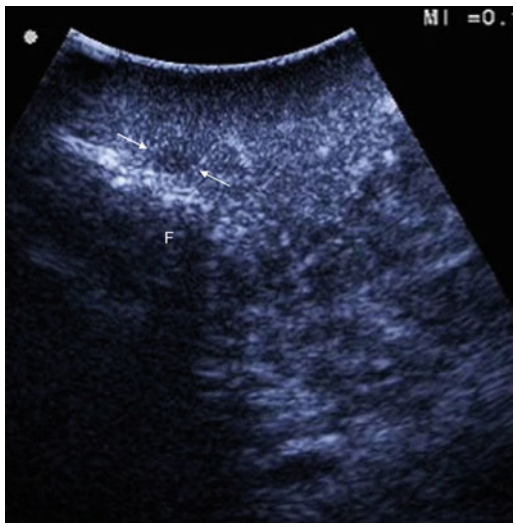

Fig. 5.15 Palpation (*F*) and CEIOUS may help in precisely locating tiny lesions (*arrows*)

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