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REVIEW

Morphological and dynamic evaluation of complex cystic focal liver lesions by contrast-enhanced ultrasound: current state of the art

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Abstract

Complex cystic and cystic-like focal liver lesions (FLLs) encompass a spectrum of disorders ranging from non-neoplastic conditions to benign and malignant tumors. In this prospective, the possibility of non-invasive differentiation of these lesions is extremely important, because the clinical implications and therapeutic strategies vary considerably. Because of its advantageous cost/benefit ratio, widespread availability and easy execution, ultrasound (US) is the first-line imaging modality in most countries for the initial liver survey and represents the imaging technique that usually detects a complex liver cyst. However, US showed poor efficacy in the differential diagnosis of complex cystic FLLs. Thus, for years, computed tomography (CT) and magnetic resonance (MR) imaging have been used for further assessment of these lesions. Recently, the development of low mechanical index real-time contrast-enhanced ultrasound (CEUS) technique performed with the second generation of US contrast agents has led to an accurate depiction of macrovasculature and microvasculature. The technique yields information about contrast enhancement of the liver and FLLs almost as CT and MRI do, but in real time and without the use of ionizing radiation. To date, there is only a small amount of evidence about the role of CEUS in the less common setting of complex liver cysts. The aim of this review is to offer an up-to-date overview on the state of the art of CEUS in the study of the most common complex cystic focal liver lesions. To our knowledge, there are no literature comprehensive reviews on this topic.

Keywords Contrast-enhanced ultrasound (CEUS) · Cystic liver lesions · Complex cystic liver lesions · Ultrasound microbubbles · Ultrasound contrast agent

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Introduction

Complex cystic focal liver lesions (FLLs) are fluid-containing hepatic lesions with one or more of the following complex features: wall thickening or irregularity, internal septation, nodularity, calcifications, and hemorrhagic or proteinaceous contents (Fig. 1) [1, 2]. These lesions encompass a broad spectrum of disorders ranging from non-neoplastic conditions to benign and malignant tumors (Table 1) [3]. Consequently, the radiologist must carefully assess imaging features, not only location, size, and unifocal or multifocal nature of cysts, but also cyst complexity and other associated findings [4, 5].

Because of its advantageous cost/benefit ratio, widespread availability and easy execution, ultrasound (US) is the first-line imaging modality in most countries for the initial liver survey and represents the imaging technique that usually detects a complex liver cyst [6, 7]. However, also when supplemented with Doppler techniques [8], US showed poor efficacy in the differential diagnosis of complex cystic FLLs [9]. Cystic lesions, e.g., hemorrhagic, may have a solid appearance, simulating malignant lesions [9]. At the same time, lesions with cystic appearance can turn out to be solid after contrast agents' injection, especially when they appear markedly hypoechogenic or are located in a steatotic background [10, 11].

Doppler techniques are complementary to conventional US, because they yield information about the presence of internal blood flow to confirm the solid nature of a lesion with a cystic appearance [12], regardless of the pattern and degree of vascularity [13–15]. However, according to Bartolotta et al. [16], Doppler signal is not easily identified. Also in our personal experience [9], intralesional signal was not identified in 88% of lesions (44 of 50 cystic and cystic-like FLLs), thus confirming the poor diagnostic performance of color (CD) and power Doppler (PD) techniques.

For years, computed tomography (CT) and magnetic resonance (MR) imaging have been used for further assessment of these lesions. Recently, the development of low mechanical index real-time contrast-enhanced ultrasound (CEUS) technique performed with the second generation of US contrast agents has led to the accurate depiction of macrovasculature and microvasculature [17–19]. The technique yields information about contrast enhancement of the liver and FLLs almost as CT [20, 21] and MRI [22, 23] do, but in real time and without the use of ionizing radiation.

To date, CEUS has proven to be extremely useful in the evaluation of both solid liver lesions and complex renal cysts [24–26]. Also, CEUS in non-hepatic applications has been widely documented [27]. However, there is little experience about the role of CEUS in the less common setting of complex liver cysts. Lin et al. [1] compared the diagnostic performance in a retrospective analysis of complex cystic focal lesions using CEUS and Sonovue®. In this study, CEUS was found to be extremely accurate in discriminating complex liver cysts as benign or malignant, with a sensitivity and

Table 1 Differential diagnoses of the most common complex cystic FLLs

Complex cysts
Non-neoplastic complex cysts
Complicated infectious and hemorrhagic cyst
Abscess
Pyogenic
Amebic
Fungal
Hydatid cysts (echinococcosis)
Hematoma
Biloma
Intrahepatic pseudocyst
Neoplastic complex cysts
Biliary cystadenoma or cystadenocarcinoma
Cavernous hemangioma
Cystic metastases
Hepatocellular carcinoma (HCC)
Embryonal sarcoma

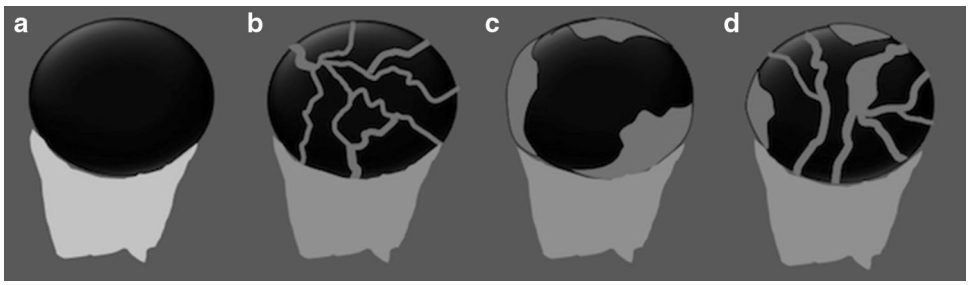

Fig. 1 US appearance of complex cystic FLLs. **a** Simple cysts are defined as well circumscribed, round or ovoid, anechoic lesions which increased through transmission of ultrasound waves. **b** Complex multilocular cystic FLL with hairline thin and a few thick intracystic septa. **c** Complex cystic FLL with mural nodules. **d** Complex cystic FLL with irregular, thick septa and septal and mural nodules

specificity that was variable, from 87 to 93% and from 88 to 98%, respectively, depending on the operator's experience. Our group, in a prospective study [28], provided an analysis of the CEUS findings and diagnostic impact of microbubble injection in the assessment of complex cystic FLLs unclassified at US. Specifically, complete non-enhancement throughout three phases or sustained enhancement in portal–sinusoidal phase was observed in most benign complex cystic FLLs, except one (of three) cystadenoma and two (of four) abscesses. On the other hand, all malignant complex cystic FLLs had a hypo-enhanced appearance during the portal–sinusoidal phase. Overall, CEUS correctly identified all malignancies, although it misclassified half of the abscesses and it did not distinguish cystadenoma from biliary cystadenocarcinoma. In another study, our group [9] assessed the diagnostic performance and confidence of CEUS versus US in the characterization of atypical cystic and cystic-like lesions, to determine that the use of CEUS can reduce the need for further diagnostic work up in these patients. Diagnostic performance improved after review of CEUS examinations by both readers of the study (Az = 0.781 vs 0.972 and Az = 0.734 vs 0.957 for conventional US versus CEUS). In terms of differential diagnosis, the occurrence of correctly characterized lesions increased after CEUS for both readers (reader 1, 62% to 98%; reader 2, 56% to 96%). Ultimately, our data indicated the usefulness of CEUS in the evaluation of patients with these lesions, especially in countries where US is regarded as the first-choice modality for liver surveys.

The aim of this review is to offer an up-to-date overview on the state of the art of CEUS in the study of most common complex cystic focal liver lesions. To our knowledge, there are not in literature comprehensive reviews about this topic.

Non-neoplastic complex cysts

Complicated infectious and hemorrhagic cysts

Akiyama et al. [29] described a single case of hemorrhagic cyst evaluated as avascular using first-generation contrast agent (Levovist®) and power Doppler. Naganuma et al. [30] presented a case of a hepatic cyst with intracystic bleeding in which CEUS with Levovist® showed that an amount of contrast media oozed from the cyst wall into the cavity. This phenomenon continued for 10 min after intravenous injection, suggesting that CEUS was able to detect intracystic slow bleeding, which was confirmed by US-guided drainage of the lesion. In the study of Lin et al. [1], performed using Sonovue®, complete non-enhancement throughout three phases was observed in all cysts with intracystic hemorrhage. Also in our studies [9, 28], hemorrhagic cysts were easily distinguishable from other cystic and cystic-like lesions on CEUS, which demonstrated the avascularization of intracystic structures with solid US appearance mimicking malignancy, corresponding to clots and fibrin strands (Fig. 2a, b).

Abscesses

Several literature reports indicated that US contrast agents' injection allows to better define the abscess, its borders and internal structure, so as to distinguish colliquative necrosis areas from the still solid ones (Fig. 3a, b) [31, 32]. In fact, while the regions with colliquative necrosis are totally avascular, the other ones show contrast enhancement, recognizable both in the peripheral portion as rim-like pattern and inside in correspondence of the septa, which can loculate totally or partially the abscess [33]. The non-colliquative areas, which show contrast enhancement during the arterial phase, can exhibit a variable degree of wash-out resulting hypo-perfused during the portal–sinusoidal phases. In these cases, the differentiation from colliquative metastases is not simple, considering that metastatic lesions, especially from colorectal carcinoma, can also undergo an abscessualization [28]. The presence of discrete arteries along the abscess margins and within the multiple septa can also be observed [9]. Furthermore, even if not typical for the abscesses, a frequent CEUS finding is the hyperemia of the surrounding perilesional parenchyma, which shows a transient hyper-perfusion during the arterial phase, followed by a more or less rapid passage to iso-perfusion during the portal–sinusoidal phase (transient hepatic echogenicity difference, THED) [9]. In the study of Liu et al. [31], according to EFSUMB [33], rim-like enhancement and no central enhancement patterns were detected in 94% of the abscesses, while enhanced septa were detected in 69%. However, despite the EFSUMB document proposing the hyper- or iso-enhancement pattern during the portal phase as a typical CEUS finding of hepatic abscess [33], Liu et al. [31] documented that over 50% of the lesions showed wash out during the portal phase. Also in our series [28], arterial septal or nodular enhancement with wash out in portal–sinusoidal phase were observed in two (of four) abscesses, whereas sustained enhancement in all phases (i.e., no washout) was observed in the remaining two ones. Thus, CEUS was not able to correctly classify abscesses that exhibited the ''hyperperfusion-to-hypoperfusion pattern'' typical of malignant lesions.

Hydatid cysts

A correct diagnosis is of clinical relevance since biopsy of these lesions is not recommended. CEUS finding in cystic echinococcosis is simple, although not specific: constant avascularization, including the septa among the daughter cysts, independently from the developmental stage of

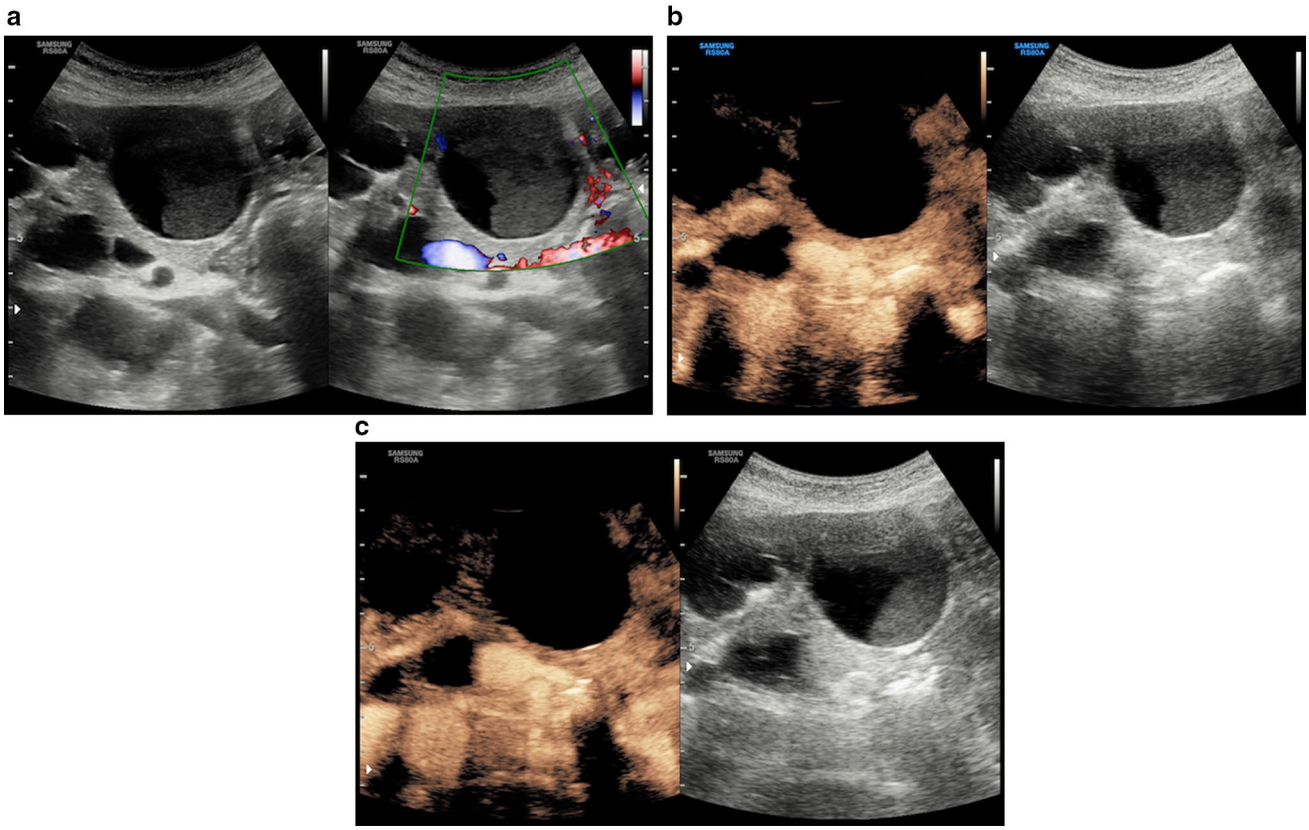

Fig. 2 CEUS diagnosis of a hemorrhagic cyst in a 40-year-old woman. **a** Split-screen mode with US image on the left side and bidirectional PD image on the right. US reveals a cystic lesion containing an echogenic internal component, which shows no flow signals on Doppler imaging. **b**, **c** Split-screen mode with fundamental US image on the right side and CEUS image on the left. CEUS images obtained at 45 s and 100 s from contrast injection reveals the homogeneous non-enhancement of the lesion. Diagnostic confirmation was obtained with MRI, which confirmed that the intracystic component was a blood clot caused by the hemorrhage

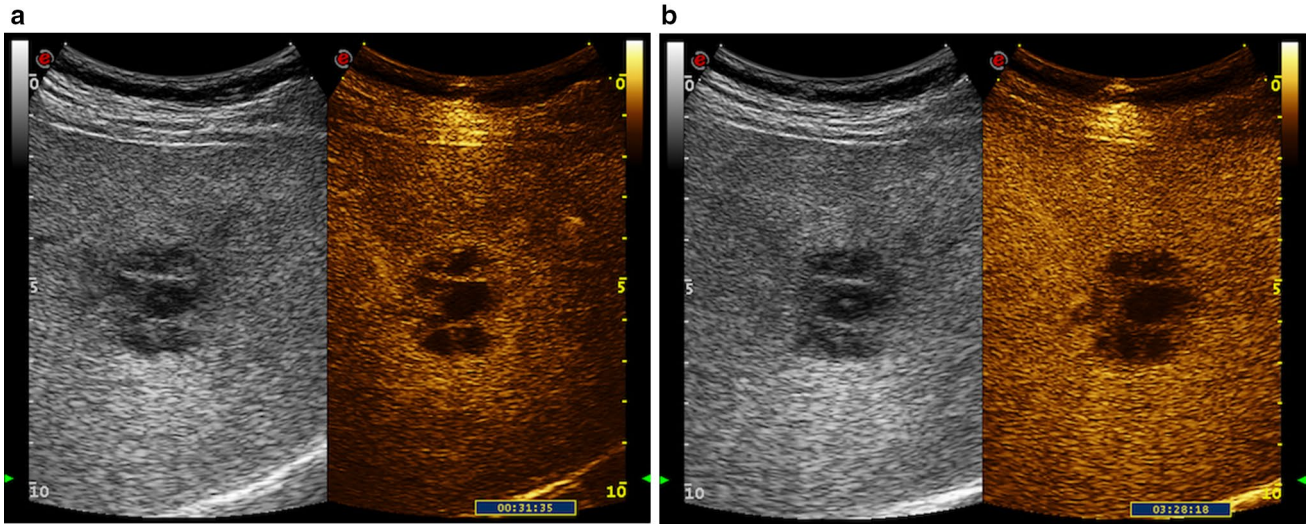

Fig. 3 CEUS diagnosis of a pyogenic abscess after a recent Whipple pancreatoduodenectomy in a 76-year-old man. **a**, **b** Split-screen mode with US image on the left side and CEUS image on the right. Gray-scale US shows a non-specific multiseptated cystic lesion. CEUS obtained 31 and 208 s after contrast injection allows to better define the abscess, its borders and internal structure. A thin enhancing rim and some enhancing regular internal septa in a honeycomb-like reticolar pattern are clearly depicted. Diagnostic confirmation was obtained by sonographic follow-up

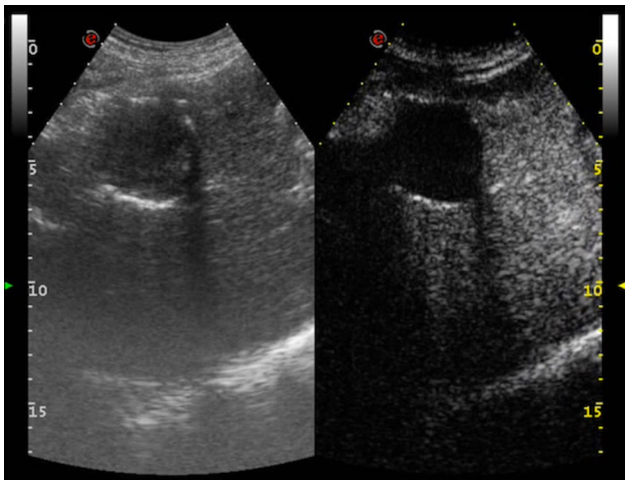

Fig. 4 CEUS diagnosis of echinococcosis in a 16-year-old girl. Split-screen mode with US image on the left side and CEUS image on the right. Gray-scale US shows a cyst containing fine echoes (''snow flake sign''), representing free-floating protoscoleces. CEUS depicts the lesion as avascular in the portal venous phase, as well as throughout the remaining vascular phases (not shown). Diagnostic confirmation was obtained with the microscopic examination of cyst fluid obtained from US-guided aspiration by observing protoscolices and free hooklets

hydatidosis (Fig. 4) [34, 35]. Specifically, the contrast agent does not circulate inside the echinococcal cyst. In fact, the larval part of the cyst (endocyst) does not any contrast enhancement, unlike the parenchyma of the organs in which the cyst is localized such as, e.g., in the liver, lung, and spleen. Therefore, the vascularization is limited to the pericyst, which consists of tissue of the parasitized organ, compressed by the growth of the larval portion [34]. According to Bartolotta [16], in our series, CEUS correctly depicted all hydatid cysts by showing their internal avascularity and, thus, the absence of proliferating intralesional vital tissue [9, 28].

Neoplastic complex cysts

Cystic hemangioma

On CEUS, cystic hemangioma shows, like its solid counterpart, a peripheral globular enhancement in the arterial phase followed by a progressive but incomplete centripetal filling because of the presence of thrombotic or hyalinized regions [36–38]. The recognition of this enhancement pattern allows an almost definitive diagnosis, since it is not detected in malignant lesions [39, 40]. However, it should be noted that an overlap may occur between globular and rim-like patterns, which could be a source of potential interpretative pitfalls, since many adjacent globules can give the erroneous idea of a continuous rim enhancement, even if irregular (Fig. 5a, b) [28].

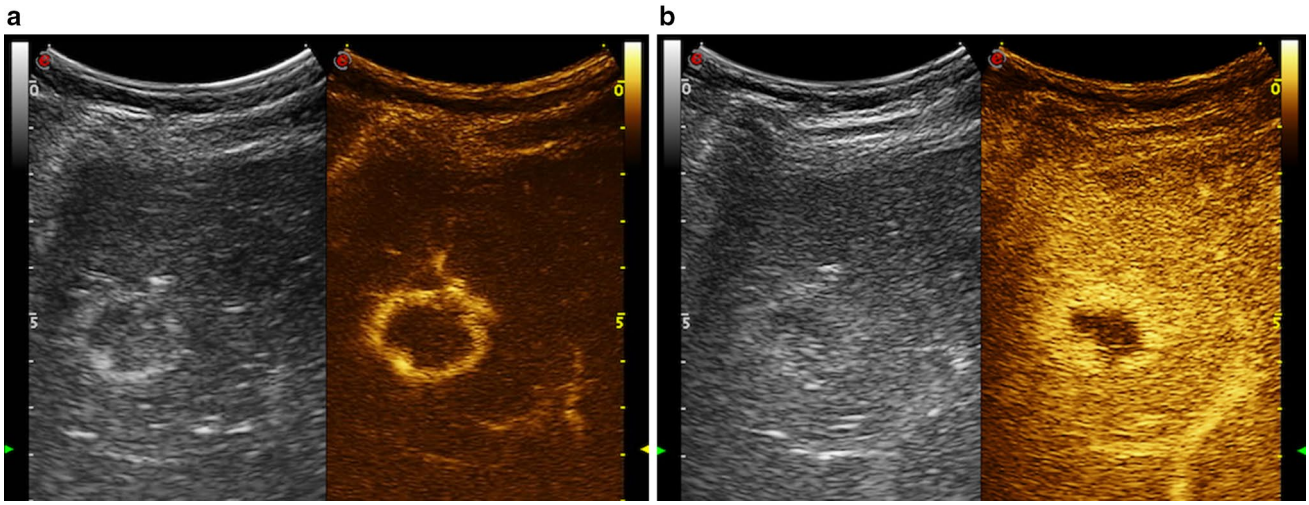

Fig. 5 CEUS diagnosis of thrombosed hemangioma incidentally detected during abdominal US examination in a 51-year-old man. **a**, **b** Split-screen mode gray-scale US images of left liver lobe (left) show an heterogeneous hypoechoic lesion with internal echoes. CEUS images (right) show a peripheral rim of enhancement in arterial phase (25 s after contrast injection) (**a**) and a partial centripetal fill in in portal and sinusoidal phases (106 s after contrast injection) (**b**). It should be noted that an overlap may occur between globular and rim-like patterns, which could be a source of potential interpretative pitfalls, since many adjacent globules can give the erroneous idea of a continuous rim enhancement, as in our case. Diagnostic confirmation was obtained at pathologic examination of specimens obtained from US-guided percutaneous biopsy

Biliary cystadenoma and biliary cystadenocarcinoma

Since the application of CEUS in the clinical practice, several reports have been documented about the use of US contrast agents for diagnosing cystadenomas and cystadenocarcinomas [41–44]. Hyper-enhancement of the cystic wall, internal septa and intracystic solid components in the arterial phase are typical features on CEUS. The enhancement generally washes out progressively, depicted as hypo-enhancement in the portal venous and sinusoidal phases [33]. In the study of Xu et al. [41], on CEUS there were no significant dynamic differences between cystadenoma and cystadenocarcinoma. The hyper- or iso-enhancement of the cystic wall, internal septa and solid components during the arterial phase was detected in all the cases of cystadenoma and cystadenocarcinoma and the hypo-enhancement during the portal–sinusoidal phase was detected in most cases, including the six cystadenomas reported in this study. In the study of Lin et al. [1], however, the absence of enhancement during all the phases or, on the contrary, the presence of a sustained enhancement pattern (persistent during the portal venous and sinusoidal phases) were the findings found in most of the benign lesions excepting biliary cystadenomas, which showed hypo-enhancement during the portal venous phase. In our series [28], CEUS did not distinguish biliary cystadenoma from cystadenocarcinoma. Specifically, one cystadenoma (of three) exhibited septal enhancement in the arterial phase with rapid wash out in the portal venous phase, mimicking a malignant lesion. According to Xu et al. [41] these data confirmed that there is no significant difference in enhancement features between cystadenomas and cystadenocarcinomas on CEUS evaluation. Therefore, the CEUS algorithm used to differentiate solid focal benign lesions from those malignant (hypo-enhancement during the portal and the sinusoidal phase suggestive of malignancy), would not seem to be usable, given the results, for cystic FLLs, or at least in the differential diagnosis between cystadenoma and cystadenocarcinoma [1]. Nevertheless, in our opinion [28], other conventional US findings, such as the presence or absence of mural or septal nodules and the presence of large (> 10 mm) intracystic nodules are helpful in suggesting the correct diagnosis.

Cystic metastases

Typical CEUS features of cystic hepatic metastasis in the arterial phase are peripheral rim enhancement and hypoavascular internal necrotic regions (Fig. 6a–e) [45–49]. In our study [28], all complex cystic metastases exhibited hyper- or iso-enhancement of the cystic wall, internal septa and solid components in the arterial phase with slow or rapid wash out, resulting in a hypo-enhanced appearance during the portal–sinusoidal phase: practically, with the passing of seconds, the liver parenchyma surrounding the lesion enhanced, while the lesion progressively washed out, so the lesion–parenchymal contrast became more marked [47, 48]. In the studies of Lin et al. [1] as well as in ours [9, 28], the hypo-enhancement during the portal venous and sinusoidal phases was detectable in all complex cystic lesions with malignant nature, obviously including metastases. Therefore, in the appropriate clinical scenario (patient with extra-hepatic malignancy), any hypo-perfused lesion in the portal and sinusoidal phases must be considered metastatic until otherwise proven, regardless of its behavior in the arterial phase [28].

Cystic hepatocellular carcinoma (HCC)

HCC with heterogeneous internal architecture (mosaic patterned) may undergo varying degrees of spontaneous intratumoral necrosis or hemorrhage. The areas of necrosis or hemorrhage may be extensive, such that the HCC lesion could manifest as a cystic FLL [3]. On CEUS, enhancing components that microscopically correspond to viable tumor may demonstrate the classic solid HCC hemodynamics of arterial enhancement and portal–sinusoidal contrast material wash out by providing a reliable evidence of malignancy [50]. In the study of Lin et al. [1], including six cystic HCCs, all lesions exhibited irregularly peripheral hyper-enhancement with complete non-enhanced areas in the arterial phase. Two HCCs had also thick, coarse enhanced septa. During portal and sinusoidal phases, the hyper-enhanced areas in all the HCC lesions washed out and showed hypo-enhancement. In addiction, some authors [51] reported that in the arterial phase it is also possible to recognize, especially in the first few seconds from the microbubble injection, one or more afferent arteries, which detach from a branch of the hepatic artery and reach the periphery penetrating inside the lesion in correspondence to the solid portions. The peripheral parenchyma may show a transient hyper-perfusion during the arterial phase, followed by a more or less rapid transition to iso-perfusion during the portal–sinusoidal phase (THED) because of the suction effect caused by the tumor or obstruction of a portal vein branch [30].

Conclusions

The possibility of non-invasive differentiation of complex cystic lesions of the liver is extremely important, because the clinical implications and therapeutic strategies vary

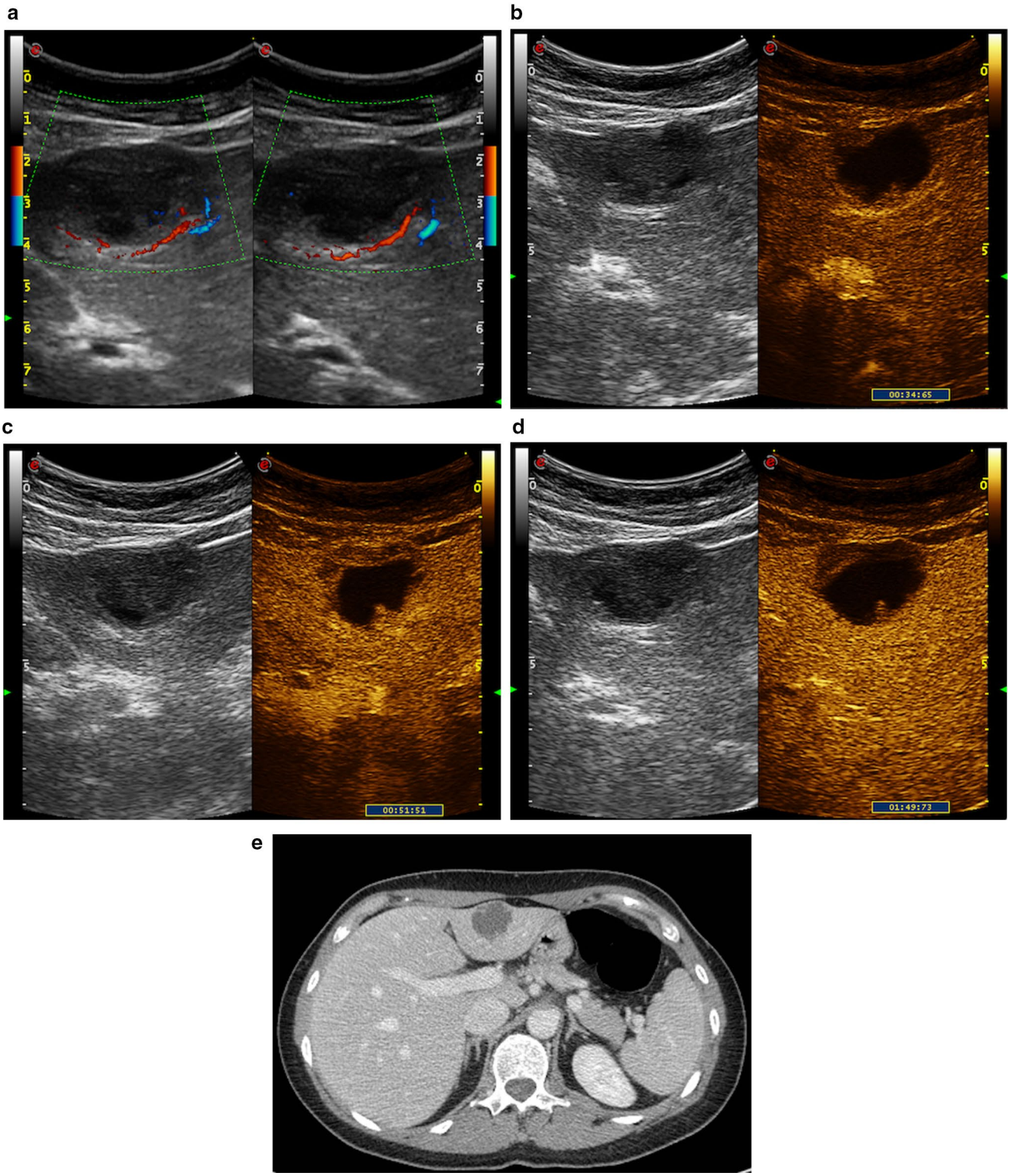

Fig. 6 CEUS diagnosis of a cystic metastasis in a 76-year-old woman with colorectal cancer. **a** Large cystic-like lesion with necrotic–colliquative center and some peripheral vascular signals on directional PD. **b** On CEUS, a thick rim enhancement is observed in the arterial phase (34 s from the injection). The non-enhanced area in the center represents necrosis. **c**, **d** In the portal venous phase (52 s from contrast injection), there is clearly a wash out of contrast in the metastasis (**c**), resulting in an hypo-enhanced appearance during the portal–sinusoidal phase: practically, with the passing of seconds, the liver parenchyma surrounding the lesion enhanced, while the lesion progressively washed out, so the lesion–parenchymal contrast became more marked (**d**). **e** CT confirmed the diagnosis of cystic metastasis in the left hepatic lobe

considerably. The development of low-acoustic power CEUS has made it possible to identify several imaging features of these lesions that, in association with history and clinical findings, may help to correctly characterize them. Literature data indicate the usefulness of CEUS in the evaluation of patients with these lesions. It has an added value in countries where US is regarded as the first-choice modality for liver surveys.

Compliance with ethical standards

Conflict of interest We confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere. Publication is approved by all authors and by the responsible authorities where the work was carried out. Each author has participated sufficiently in any submission to take public responsibility for its content. The authors have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all patients, and the study was approved by the ethics committee of the institution.

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