Romanian National Guidelines on Contrast Enhanced Ultrasound in clinical practice

Ioan Sporea[1], Radu Badea[2], Ciprian Brisc[3], Simona Ioanițescu[4], Tudor Moga[1], Alina Popescu[1], Adrian Săftoiu[5], Larisa Săndulescu[5], Zeno Spârchez[6], Roxana Șirli[1]

[1]Department of Gastroenterology and Hepatology, „Victor Babeș" University of Medicine and Pharmacy Timișoara, [2]Department of Ultrasound, 3rd Medical Clinic, „Octavian Fodor" Institute of Gastroenterology and Hepatology, „Iuliu Hațieganu" University of Medicine and Pharmacy Cluj Napoca, [3]Department of Gastroenterology, University of Oradea, [4]Department of Internal Medicine, Fundeni Clinical Institute & "Carol Davila" University of Medicine and Pharmacy Bucharest, [5]Department of Gastroenterology, Research Center of Gastroenterology and Hepatology Craiova, University of Medicine and Pharmacy Craiova, [6]3rd Medical Deparment, „Octavian Fodor" Institute of Gastroenterology and Hepatology, „Iuliu Hațieganu" University of Medicine and Pharmacy Cluj Napoca, Romania

Abstract

Contrast-enhanced ultrasound (CEUS) allows a real-time assessment of the vascular pattern of different types of lesions, as it has no renal or liver toxicity, it lacks radiation exposure and it is also cheaper than other imaging methods, having a diagnostic capability that matches contrast-enhanced CT or MRI. In Romania CEUS is used more and more, especially by clinicians, and since some centres have extensive experience in this domain, we felt the need to disseminate our expertise in order to implement this method in as many centres as possible. These Guidelines present the clinical applications of CEUS in the liver, spleen, pancreas, kidney, testis, bowel, intra-cavitary and endoscopic ultrasound, as well as other applications.

Keywords: Contrast Enhanced Ultrasound; guidelines; clinical applications

Introduction

Following the introduction of ultrasound contrast agents (UCA), the ultrasonography method has gained a diagnostic capability that matches contrast-enhanced CT or MRI (CECT or CEMRI) [1-3]. A true benefit is seen in patients with contraindications for CECT or CEMRI, such as renal failure or claustrophobia. Contrast-enhanced ultrasound (CEUS) has many advantages: it allows a real-time assessment of the vascular pattern, in different vascular phases [4]; it has no renal or liver toxicity; it lacks radiation exposure; it is also cheaper than other imaging methods and does not need additional specialized personnel, aside from the operator. The limi-

tations of CEUS are those of conventional ultrasound (US). In order to obtain the best results, CEUS must always be corroborated with clinical data and with the standard US examination [5].

Second generation UCA consist of microbubbles approximately the same size as the red blood cells, filled with an inert gas and stabilized by a shell with a short half-life. The UCA used in Europe is SonoVue® (Bracco, Italy), that contains sulphur hexafluoride with a phospholipid shell [6]. To perform CEUS dedicated software is needed, able to perform low mechanical index (MI) examination, during which microbubbles will show a nonlinear response, as opposed to the linear one of the surrounding tissues, whilst under high MI bubbles will burst. CEUS should be performed by an experienced operator, at least level II according to the European Federation of Societies in Ultrasound and Medicine (EFSUMB) classification [7].

An informed consent must be obtained before performing CEUS, even if CEUS is a safe method with very

few side effects [8]. There are limited data regarding the use of CEUS in pregnancy and breastfeeding.

Intravenous access on the left antecubital vein, by at least a 20-gauge cannula, is preferred. The injection of UCA (1 – 2.4 ml/examination for liver CEUS) is followed by a 10 ml saline flush. A timing counter on the ultrasound machine should be available to monitor the vascular phases described for the liver: arterial phase – starting 10 seconds after the contrast bolus, lasting 30 seconds; portal phase: 30-120 seconds following the contrast bolus; and the late phase, starting 120 seconds following the contrast bolus, lasting until the total disappearance of the bubbles [5]. Only two phases, arterial phase – starting 10-15 seconds from contrast bolus; and venous phase – starting 30 seconds following contrast bolus, are described for other organs, for e.g. spleen, pancreas, gastrointestinal (GI) tract wall, etc. The enhancement patterns of structures evaluated by CEUS are described as hyper-, iso-, hypo-, or non-enhancing as compared with the surrounding tissues.

In Romania CEUS is used more and more, especially by clinicians, and since some centres have extensive experience in this domain, we felt the need to disseminate our expertise in order to implement this accurate, non-toxic, inexpensive method in as many centres as possible. These Guidelines present the clinical applications of CEUS in the liver, spleen, pancreas, kidney, testis, bowel, intra-cavitary and endoscopic ultrasound, as well as other applications.

Liver

CEUS should be performed after conventional and Doppler US examinations. The clinical and biological background of the patient should be known, since co-morbidity with liver cirrhosis influences the diagnostic approach. CEUS is used to evaluate focal liver lesions (FLL), to monitor oncologic patients, to follow-up treatment results, to guide core biopsy in hepatic tumors and others. The main indications for liver CEUS are to characterize FLL in the next scenarios: a) an incidental FLL detected by US; b) a newly detected lesion on a cirrhotic liver; c) FLL inconclusive after either CECT or CEMRI; d) follow-up of inconclusive lesions; e) guidance of FLL biopsy; f) follow-up of previously treated FLLs in order to evaluate the therapeutic response or disease progression [5,9].

CEUS has proved to be a very good method for FLL characterization. In a meta-analysis of Friedrich-Rust that included 7231 FLLs, CEUS had a general sensitivity of 93% and 90% specificity for differentiating benign vs. malignant lesions. There were no significant differences

between CEUS and CECT/CEMRI regarding specificity (88% vs. 83%, p=0.11) and sensitivity (95% vs. 89%, p=0.033) [10]. Other published studies showed that CEUS has a sensitivity higher than 90% for diagnosing malignancy [2,11-13].

In another meta-analysis, CEUS was compared with CECT and CEMRI for FLL characterization and had a pooled sensitivity of 88% (the highest among the three), and a pooled specificity of 81% [3].

The same good results were found in a Romanian multicenter study: when only cases categorized as conclusive for benign/malignant differentiation were taken into consideration, CEUS had 95.7% sensitivity, 96.4% specificity, 98% positive predictive value, 92.6% negative predictive value, and 96% accuracy [13].

Hemangiomas are the most common benign liver tumors [14]. On US, their typical aspect is hyperechoic homogeneous round lesions with distinct margins [15]. The typical CEUS pattern of hemangiomas is globular enhancement in the periphery in the arterial phase, with progressive centripetal fill-in. During the late phase, the centripetal fill-in appears complete in 40–50% of cases, with a persistent hyper- or isoechogenicity [5].

CEUS is a highly accurate method for characterization of liver hemangiomas (accuracy >94%) [12,16-17], with sensitivities ranging from 62.5% in the DEGUM multicenter study [18] to 90.4% in a Romanian multicenter study [16], with a calculated pooled sensitivity of 86% in the Friedrich-Rust meta-analysis [10]. The specificity can be as high as 99% [17].

Focal Nodular Hyperplasia (FNH) is the second most common benign FLL. It is a regenerative mass of variable size, resulting from a vascular abnormality – an abnormal feeding artery that generates a hyperplastic response from the hepatocytes [19]. There is no specific grey-scale appearance in FNH. It can be hypoechoic, isoechoic, or slightly hyperechoic, with a central scar appearing as hyperechoic [20]. Colour Doppler enables visualisation of the feeding artery and the „spoke-wheel" vascular pattern. On CEUS, in the arterial phase, a rapid (or very rapid) fill-in from the centre outwards (70%) or with an eccentric vascular supply (30%) can be seen. During the portal and late phases, FNHs remain hyper-enhancing or become isoenhancing, sometimes with the visualisation of a central hypoechoic scar [5]. CEUS is an accurate method to characterise FNH with 95.5% general accuracy in the DEGUM study [18], and 98.5% in the Romanian multicenter study [21]. In the STIC study, CEUS had 82.5% sensitivity and 94.3% specificity for the diagnosis of FNH [22], while in the DEGUM study they were 57.1% and 99.3%, respectively [18]. The calculated pooled sensitivity for FNH was 88% in the Frie-

drich-Rust meta-analysis [10] and the specificity can go as high as 100% [12,23].

Adenoma is a rare benign liver tumor, more frequent in young women and in people using steroid containing drugs [24]. In conventional US, adenomas can be hyperechoic, hypoechoic, isoechoic, or inhomogeneous [25]. On CEUS, adenoma usually shows homogeneous arterial hyperenhancement, initially at the periphery with a very rapid centripetal filling, the opposite to that seen in FNH. In the early portal venous phase, it usually becomes isoechoic or, more rarely, remains slightly hyperechoic. Sometimes, wash-out occurs in the late phase, thus being false positive for malignancy [5].

Imaging diagnosis of adenoma is difficult, regardless of the method used, and often guided biopsy is needed for a definite diagnosis. Nevertheless, in the DEGUM study CEUS correctly diagnosed 57.9% of the adenomas [2].

Focal fatty liver alterations. On conventional US, they appear as hyperechoic areas in a normal liver (focal steatosis) or as hypoechoic areas in a fatty, hyperechoic liver (focal sparing), without mass effect and usually irregular delineation. Their pathogenesis is probably linked to arterio-portal and venous abnormalities [26]. On CEUS, they are isoenhancing as compared to the surrounding liver in all vascular phases [5]. In a Chinese study the reported sensitivity of CEUS in the diagnosis of focal fatty alterations was 88% and its overall accuracy was 96% [27]. In a Polish study, CEUS had 95.8% sensitivity, 100% specificity and 99.6% accuracy to diagnose focal fatty liver infiltrations, while for focal fatty sparing the sensitivity was 91.2%, the specificity 100%, with 99.4% accuracy [28]. In the Romanian multicentre study, CEUS had 96.6% sensitivity, 86.7% specificity and 87.3% accuracy to diagnose focal fatty alterations [13].

Liver abscess. The US appearance varies, usually as a hypoechoic mass with irregular thick walls, internal septa and sometimes gas inside [29]. Clinical information is certainly important. CEUS criteria for the diagnosis of liver abscesses are: marginal rim enhancement in the arterial phase, with enhancement of the septa due to inflammation ("honeycomb" appearance), with no enhancement in the anechoic, liquid areas. Later, during the venous phase, hypoenhancement of the wall and septa can be seen [5]. CEUS is helpful to delineate avascular areas inside the abscess, in order to guide percutaneous drainage [30-32]. In some cases, direct intracavitary injection of UCA allows the assessment of a correct positioning of the needle or catheter, and detects possible communication between cavities in complex abscesses [33,34]. In the Romanian multicentre study, CEUS had 76.9% sensitivity, 88.9% specificity and 86.9% accuracy to diagnose liver abscesses [13].

Metastases. Their typical US appearance is of a "target" lesion, but they can also be hyperechoic, hypoechoic or isoechoic. Most liver metastases are hypoenhancing during the arterial phase on CEUS, sometimes with a rim enhancement [5,35,36]. Hypervascular metastases show arterial hypenhancement, with quick "wash-out" in the portal phase [5,37,38]. Reported sensitivities and specificities for CEUS for the diagnosis of liver metastases range from 80% to 95% [9,39,40]. Characteristic for the majority of liver metastases is early and progressive "wash-out", started at the end of the arterial phase [5]. In the Romanian multicentre study, CEUS demonstrated 87.1% sensitivity, 82.9 % specificity and 83.7% accuracy in diagnosing liver metastases [13]. In the Friedrich-Rust meta-analysis, the overall sensitivity was 91% [10]. CEUS has similar performances in detecting liver metastasis as CT and MRI [39,41].

Hepatocellular carcinoma (HCC) is a primary malignant hepatic tumor that usually occurs in high-risk patients (chronic liver disease with severe fibrosis or cirrhosis). US is considered to be the imaging method for screening in order to detect early HCC [42]. Due to its development process, from regenerative nodule to dysplastic nodule with HCC foci, to well or poorly differentiated HCC, it may present variations in the enhancing pattern at CEUS [5,43,44]. Often HCCs are hyperenhanced in the arterial phase, with an irregular or a chaotic pattern [45] that is influenced by the lesion's size [46] with mild, late, or very late "wash-out". The timing of "wash-out" is correlated with the differentiation of the tumor, therefore CEUS examination of the HCC should take a least four-five minutes [47-49]. Specific algorithms have been developed, such as CEUS LI-RADS [https://www.acr.org/Quality-Safety/Resources/LIRADS/CEUS-LIRADS], in order to standardize the reporting system and the diagnostic decision in HCC. It is important to keep in mind that a new lesion on a cirrhotic liver, hyperenhancing in the arterial phase on CEUS, is probably HCC [50,51]. In the DEGUM study, CEUS managed a correct diagnosis of HCC in 84.9% of the cases [18], while in the Romanian multicentre study the accuracy was 90.2% [13].

In a meta-analysis which evaluated the sensitivity and positive predictive value (PPV) of CEUS, CECT and CEMRI for the detection of HCC, CEUS had 84.4% sensitivity, CT 76.3% and MRI 85.6%. The PPV was 89.3% for CEUS, 85.8% for CT and 94.2% for MRI [52]. In the STIC study, CEUS for HCC diagnosis had 69.8% sensitivity and 94.7% specificity [22]. In the meta-analysis of Friedrich-Rust, the overall sensitivity for the diagnosis of HCC was 88% [10].

Intrahepatic cholangiocellular carcinoma (ICC) is a malignant tumor derived from the intrahepatic bile ducts,

usually occurring in non cirrhotic liver, and much more rarely in cirrhosis (only 1-2% on the newly diagnosed nodules) [53-55]. ICC appears on standard US as a poorly delineated tumor that has a hypoechoic-heterogeneous aspect [56,57]. The imaging diagnosis of ICC is difficult, no matter the technique used (CECT, CEMRI, or CEUS), since it can be misdiagnosed as HCC, especially in cirrhosis [53]. On CEUS, the most common aspect of ICC is of a rim-like hyperenhancing lesion in the arterial phase, with early "wash-out" in the portal phase [58-60], as opposed to CECT, where late "wash-out" does not occur, due to the accumulation of the CT contrast agent in the fibrous stroma [61,62]. On the other hand, HCC appears as homogenous, hyperenhanced in the arterial phase, with "wash-out" or isoenhancing pattern in the late phase [63]. In a Spanish study, a similar vascular pattern of ICC and HCC was observed in half cases [64]. However, several studies support the use of CEUS for diagnosing ICC. In the study of Chen et al CEUS showed the same accuracy as CECT [65]. In a subanalysis of the DEGUM study, CEUS managed a correct diagnosis for ICC in 95.2% of cases [66]. According to a Chinese study, most ICCs (87.9%) show "wash-out" in the first 60 seconds, and all of them 3 minutes after the contrast bolus [67] and, based on these criteria, CEUS had 78.8% sensitivity, 88% specificity and 84.3% accuracy for diagnosing ICC [68]. In the Romanian multicentre study, CEUS had 60% sensitivity, 85.1% specificity and 83.9% accuracy for diagnosing ICC [13].

> **Recommendations:**
> a. *Liver CEUS is very accurate in the differentiation between benign and malignant FLLs;*
> b. *CEUS has a high accuracy for the diagnosis of hemangiomas, FNHs, focal fatty alterations and liver metastasis. For adenomas, HCCs or ICCs diagnosis is more difficult.*

Spleen

The spleen is involved in many clinical conditions and the use of CEUS considerably increases the diagnostic confidence in comparison with conventional US [69].

Focal splenic lesions (FSLs). CEUS is able to reveal underlying splenic lesions and differentiate between infarcted areas, abscesses and splenic tumour infiltrations mimicking infarction [70,71]. Hyperechoic FSLs incidentally detected on US are in most cases benign. CEUS improves the differentiation between benign and malignant FSLs especially for isoechoic or hypoechoic incidental lesions, unclear on conventional US [72]. Benign FSLs typically appear as nonenhancing in all phases (cystic lesions, infarcted areas) or show rapid enhancement followed by persistent late-phase enhancement (solid lesions). Malignant FSLs usually show early diffuse or peripheral enhancement, followed by "wash-out" in the late phase, with progressive hypo-enhancement [70,72,73]. In some cases the behaviour of malignant and benign lesions overlap, and benign lesions as haemangiomas, hamartomas, or other uncommon splenic abnormalities show some degree of "wash-out", mimicking a malignant pattern [70,74]. In such cases the analysis of the patient's medical history and complementary investigations are necessary. Splenic metastases are very rare and appear in the late stages of a known malignancy [75]. Some splenic metastases are hyperechoic on conventional US and can have a complex pattern on CEUS, but the clinical context is clear and the diagnosis is already set.

Splenic infarction. CEUS is useful for better delineation of splenic infarction when it is suspected clinically or on conventional US. The infarcted areas are completely non-enhancing on CEUS and usually more extensive than the inhomogeneous areas seen on conventional US. Commonly they have typical "wedge-shaped" appearance, but there are situations when they can mimic FSLs [76-78]. The complete lack of enhancement on CEUS confirms the diagnosis [78,79]. Splenic infarction has a high tendency to spontaneous healing [80] and CEUS can be successfully used for follow-up until complete resorption.

Accessory spleens or splenosis. The ectopic splenic tissue has the same behaviour on CEUS as the normal spleen and can be differentiated from other abdominal lesions due to its particular long-lasting late enhancement [81-85].

Malignant lesions. CEUS is useful for the detection of malignant FSLs in oncologic patients, when CECT and/or CEMRI and/or PET are contraindicated or inconclusive. Studies showed 90% sensitivity and 100% specificity as compared to CECT with respect to lesion detection in lymphoma patients [86] and increased the detection rate of metastases by 38% as compared to splenic conventional US [75]. In monitoring response to chemotherapy, the positive results are seen earlier on CEUS compared to PET-CT [70].

> **Recommendations:**
> a. *CEUS is very useful in the characterization of splenic parenchymal inhomogeneity and for accurate delineation of splenic infarction.*
> b. *CEUS improves the detection of splenic malignant lesions in oncologic patients.*
> c. *CEUS improves the differentiation between benign and malignant FSLs. Clinical context should always be considered in overlapping imaging situations.*

Pancreas

CEUS of the pancreas is performed by scanning the area on interest in the arterial and late phases [70]. In the arterial phase, the pancreas shows a homogeneous intense enhancement due to its rich vascularity, followed by a rapid loss of UCA, at 2 minutes the pancreas appearing as hypoenhancing as compared to the nearby liver [87].

CEUS can be used to characterize focal pancreatic lesions, either solid or cystic, and for the assessment of pancreatic vascularity.

Solid focal pancreatic lesions. Pancreatic ductal adenocarcinoma is usually hypoenhancing in the early phase as compared to the adjacent pancreatic tissue [88-91]. CEUS also allows a better delineation of the tumor and the assessment of vascular invasion [88,92,93]. By contrast, *neuroendocrine tumors* have an intense enhancement in the arterial phase [37,38]. For both types of lesions, CEUS is useful for detecting liver metastases in the late phase ("wash-out" of liver lesions). Several studies proved the utility of CEUS for the characterization of pancreatic tumors [94-98]. The accuracy for the diagnosis of solid pancreatic lesions varies from 91.7% to 93.8% [94,95,97]. In a recent meta-analysis that included 23 CEUS studies, the pooled estimate sensitivity for the diagnosis of ductal adenocarcinoma was 89%, with average specificity of 84% [99].

Cystic focal pancreatic lesions. CEUS is useful for the differential diagnosis between pseudocysts, which are completely nonenhancing during CEUS, as opposed to cystic tumors, where the cystic wall, as well as the septa and protrusions will enhance after the contrast bolus [88,94,100-103].

Acute pancreatitis (AP). CEUS can be used in acute pancreatitis (when the pancreas is well seen on conventional US) and UCA reveals necrotic areas as nonenhancing ones. Several studies confirmed the value of CEUS for detecting pancreatic necrosis and for predicting the severity of AP, with sensitivity ranging from 82% to 90.3% and specificity from 89% to 98.8% [95,104,105].

Recommendations:
a. *CEUS is useful for the differential diagnosis between ductal adenocarcinoma vs. neuroendocrine tumors.*
b. *CEUS can be used for differentiating pseudocysts from cystic pancreatic tumors.*
c. *CEUS is useful for the diagnosis of pancreatic necrosis in acute pancreatitis.*

Kidney

Kidney CEUS is a safe diagnostic method (especially in patients with renal dysfunction) and cancels the risk of nephrotoxicity due to CT contrast agents [106,107].

Differentiation of renal tumors from pseudotumours. CEUS is considered highly effective for this indication [70,108]. The enhancement pattern of pseudotumours mirrors that of the surrounding parenchyma in all phases. Any other enhancing pattern should be considered suspicious for malignancy [107,109,110].

Complex renal cysts. Cysts can present as equivocal, complex, or hyperdense and require differentiation of malignant from benign. The Bosniak classification system modified for CEUS evaluates the cystic lesions in terms of quantity, thickness and enhancement of walls and septa [111]. Benign lesions typically show no enhancement; this reliably confirms benignity with a 100% PPV [112]. CEUS can identify more septa, characterize them as thicker and pick up solid components within cystic lesions at least as accurately as CT [106,107,109,112]. CEUS can demonstrate slow and low flow within lesions and allows their characterization as solid [113].

Indeterminate renal lesions. The differentiation between renal cell carcinomas (RCCs) and various benign entities, such as angiomyolipomas or oncocytomas is difficult [113], therefore CEUS alone is not recommended for the purpose of characterising solid lesions [109]. The typical enhancement pattern of solid RCCs includes a rapid "wash-in" phase, with a hyper-enhanced appearance at peak enhancement, followed by "wash-out" [107,109,110].

Perfusion deficit assessment. CEUS is an effective and reproducible method for detecting *acute renal infarction*, with accuracy comparable to CT. On CEUS it appears as a "wedge-shaped" area of nonperfusion; *cortical necrosis* appearance is similar, but with preserved hilar vascularity [70,107,108].

Renal infection. Renal abscesses demonstrate central non-enhancement in all phases. CEUS is as good as CT for diagnosing uncomplicated pyelonephritis, demonstrating *focal pyelonephritis* as a "wedge-shaped" or round region of hypoenhancement, best seen in the late parenchymal phase [107,114,115].

Targeted renal ablation (RFA and cryotherapy) guidance and follow-up. CEUS is recommended when performing US-guided RFA, as it can improve lesion localisation. On follow-up CEUS, the residual tumour appears as nodular or a „crescent like" lesion, with similar enhancement characteristics as on the preablation imaging [107].

Transplant kidneys. CEUS may assess vascular dynamics to predict graft success or failure: if the allograft does not enhance or lacks cortical or regional enhancement, this may indicate an inflow or outflow problem [109]. CEUS can also improve the vessels' conspicuity, as it is not angle dependent like Doppler US [106,107].

Recommendations:
a. *CEUS can discriminate between cystic and solid kidney lesions.*
b. *CEUS is very accurate in the diagnosis of acute vascular disturbances.*
c. *Kidney abscesses can be accurately diagnosed by CEUS.*

Testis diseases

Inflammations and abscesses. Orchitis and orchi-epididymitis are acute diseases, showing testicular pain and swelling [116]. US reveals hypoechoic lesions, hyperemic on Doppler examination [117,118]. In *abscesses*, CEUS reveals a lesion with intense, peripheral contrast uptake, with a nonenhancing center [119].

Acute vascular diseases. The typical US alteration in *acute testicular torsion* is hypoechogenicity of the testicle and a lack of vascular signal on Doppler, which may still be present if the torsion is incomplete. CEUS may reveal a different uptake of the UCA within the affected testicle as compared with the healthy one [120,121]. *Segmental infarction* is usually hypoechoic or with mixed echogenicity, well defined, feather or round shaped, with decreased or absent vascularity, raising differential diagnosis issues with a hypovascular tumor [122]. CEUS shows lack of contrast enhancement within the lesion [117,122].

Trauma. Hematoma (hematocele) – in early traumatic injury, the US appearance is echoic and, in time it becomes anechoic, with or without septa, with no Doppler signal and with no enhancement on CEUS [123-125]. *Testicular fracture* – CEUS detects the viable testicular tissue and its delimitation as well as the fracture line [125,126]. *Testicular rupture* – US is able to identify testicular rupture with 100% sensitivity and 65% specificity [127]. CEUS can identify intratesticular fluid collections, their extent and ruptures of the albuginea [128].

Tumors. CEUS is useful in the discrimination between cysts and parenchimal tumors (no enhancement in cystic lesions), but there is no specific pattern in relation to the tumor type.

Recommendations:
a. *CEUS is useful for evaluating testicular torsion and the complications of acute orchitis/epididymitis.*
b. *CEUS can be used in the assessment of testicular trauma, to identify the lesions' extent, possible hematomas and non-viable testicular tissue.*

Bowel

Inflammatory bowel diseases. In *Crohn's disease* (CD), CEUS enables discrimination between active and inactive disease, highlighting the enhancement pattern of the bowel wall microcirculation. In qualitative studies, active disease is characterized by hyperenhancement. In quantitative analysis, linear enhanced pattern in the entire intestinal wall indicates active disease, while enhancement in the submucosa indicates inactive disease [129,130]. CEUS enables the diagnosis of *CD complications* – discrimination between inflammatory and fibrotic intestinal strictures – by identifying hyperenhancement in inflammatory stenosis and hypoenhancement in fibrotic stenosis [129,131]. In the case of stenosis, combining CEUS with oral fluid enables the assessment of stenosis severity [129,132]. Also, CEUS is useful for the differential diagnosis between inflammatory pseudo-tumors (intense enhancement within the lesion and in the peripheral tissue) and abscesses (peripheral enhancement without enhancement within the lesion) [129,131,133]. CEUS can be used to monitor therapeutic response of inflammation and wall neovascularity in CD [130,133,134].

The usefulness and practical applicability of CEUS in *ulcerative colitis* (UC) is less defined so far. The main benefits of CEUS in UC is demonstrating the selectivity of parietal layer involvement [129], establishing the disease activity (hyper-enhancement in the thickened submucosal layer of the colon) [131,135] and monitoring the treatment response [134].

CEUS is also useful for the diagnosis of *acute bowel ischemia and necrosis* (irrespective of the cause), suggested by the lack of, or diminished enhancement of the bowel wall [131,136].

CEUS can be used in complicated *acute diverticulitis* to differentiate between phlegmonous and abscessed areas, or to guide percutaneous drainage of a peridiverticular collection [129,137,138].

Recommendations:
a. *In inflammatory bowel disease (especially Crohn's disease), CEUS is useful for establishing disease activity and for the assessment of complications;*
b. *In complicated acute diverticulitis, CEUS can be used to differentiate between the phlegmon and abscess and to guide percutaneous drainage.*

CEUS in trauma

CEUS can provide significant diagnostic aid in blunt abdominal trauma (BAT). Approach to a trauma patient implies a timely and appropriate choice of the imaging method, depending on the impact severity and cardiovascular status. Thus, a high-energy multitrauma case will call for a rapid baseline conventional US scan, through the well-established Focused Assessment with Sonography in Trauma (FAST) protocol [139], which is highly

sensitive for detecting free abdominal fluid. The second step is establishing the presence and extent of organ lesions. Although CECT is the gold-standard method for evaluating solid organ lesions, CEUS has proven to be superior in some trauma-related settings. This is the case of hypovascular areas with slow blood flow at the edge of lacerations, or in contusion areas, where blood flow is hindered by the presence of edema [140]. CEUS has a high sensitivity for detecting post-traumatic lesions of the liver, spleen and kidney, given the rich vascularity of these organs. Trauma-related organ lesions recognizable through CEUS are non-enhancing defects, as in haematoma and lacerations, and also vascular complications, such as active bleeding, arterial-venous fistulas or pseudoaneurysms [141]. Parenchymal enhancement and duration of each vascular phase is different, depending on the vascular particularity of each organ. Thus, CEUS examination should be performed in the following sequence: right kidney – left kidney – liver – spleen [142]. Main limitations of CEUS in the assessment of trauma patients reside in the examination time, lack of a complete abdominal survey and the poor ability to evaluate injuries of the urinary tract (because UCA are strictly intravascular) [142].

Recommendations:
a. CEUS has good diagnostic accuracy in identifying traumatic lesions of the liver, spleen and kidney.
b. The most suitable candidates for CEUS examination in trauma are hemodynamically stable patients, who have suffered a low-energy BAT, pediatric patients and fertile women (avoiding radiation).

Pediatric population

Use of CEUS in pediatric applications has obvious benefits compared to alternative imaging modalities (CECT). Children should be assessed using a friendly imaging method, without any ionizing radiation. Despite its advantages and performance, currently pediatric CEUS is principally used as an "off-label" application in Europe. In 2016, the Food and Drug Administration (FDA) has authorized the use of sulfur hexafluoride lipid type A microspheres (LUMASON™) in the United States of America, for both adult and pediatric liver applications [143]. In 2017, EFSUMB assessed the current status of CEUS applications in children [144].

The main indication of CEUS in pediatrics is the *characterization of FLL*. The enhancement patterns of FLL in children are similar to those seen in adults. The largest series of FLL evaluated with CEUS in children showed 98% specificity for the diagnosis of benign FLL,

based on the enhancement patterns and the absence of "wash-out" during portal venous phases [145,146].

In *trauma*, CEUS has shown to be a reliable tool in the diagnosis and follow-up of liver, spleen and renal injuries in pediatric patients [147, 148].

Contrast-enhanced voiding *urosonography* is a well-established application of pediatric CEUS. The method is highly sensitive in the detection and grading of vesico-ureteral reflux and, in many centres, it has replaced the traditional voiding cystourethrogram [149,150].

There are only few data available regarding the assessment of focal lesions of the spleen, kidney, lung, or renal transplants in children, so CEUS has limited application in these fields.

Recommendation:
CEUS is an effective "off label" investigation in children, especially for FLLs characterization, for identifying parenchymal injuries following BAT and for contrast-enhanced voiding urosonography.

Intracavitary applications

Intracavitary use of UCA (IC-CEUS) is an "off-label" extravascular application. It can be used either as UCA injection into physiological cavities, or as an injection into non-physiological cavities and fistulas [70,151,152]. The UCA dose used for IC-CEUS is 0.1–1 ml Sono-Vue diluted in 0.9% saline [70]. A higher dose of UCA (up to 1-2 ml) is required for high frequency US probes or to demonstrate a connection between two cavities, as well as the anatomy of fistulas [70,151].

Injection into physiological cavities
Peritoneo-pleural communication. In patients with hydrothorax and ascites, the intraperitoneal administration of 1.2-4.8 ml Sono-Vue demonstrates the passage of UCA into the pleural cavity [153].

Bile ducts. The intrabiliary administration improves visualization of drainage catheters and assesses the level and severity of obstruction, with comparable accuracy to percutaneous transhepatic colangiography [154,155].

Pyelocalycial system. With IC-CEUS, it is possible to confirm the correct insertion of the needle or catheter and locate the obstruction. Complications such as catheter dislodgement and urine leakage may be easily diagnosed [156].

Voiding US for vesicoureteral reflux (this topic is described in pediatrics).

Imaging of tubal patency – hystero-salpingo contrast-sonography is accurate in determining tubal patency and evaluating the uterine cavity, suggesting it could supplant hystero-salpingography as the first-line diagnostic test in an infertility workup [157,158].

Other intracavitary applications. The oral administration of UCA can reveal space-occupying gastric lesions such as tumoral masses or gastric balloons; gastroesophageal reflux or gastric empting troubles; cholecysto-duodenal fistulas; spontaneous perforations, constrictions of the gastric outlet tract; and patency of endoscopically inserted stents [70,151].

Contrast injection into non-physiological cavities and fistulas

Abscesses. Administration of UCA into the drainage catheters improves the assessment of location characteristics (correct position, mishandled or dislocated) and of complications of drained fluid collections [152,159]. The communication with the biliary tree is depicted with high sensitivity in both intrahepatic abscesses and perihepatic collections [160].

Fistulas. An accurate preoperative assessment of perianal fistula tract is mandatory to decrease postoperative complications and risk of recurrence [161,162]. The injection of UCA (hydrogen peroxide or SonoVue) into the fistula allows a better visualization of its track and of the internal opening [151]. The diagnostic sensitivity is higher as compared to normal US, in both simple (95-96%) and complex fistulas (92.3%) [162]. Rectovaginal fistulas can also be evaluated via a transvaginal approach [163], and vesicoenteral fistulas via a transabdominal approach [163,164].

Recommendations:
a. *IC-CEUS is a useful technique in optimizing biliary interventions, possibly avoiding the use of X rays in selected cases.*
b. *In percutaneous drainage, the use of IC-CEUS increases the efficacy, decreases the complications rate and may select additional therapy.*

Contrast harmonic imaging endoscopic ultrasound

Endoscopic ultrasound (EUS) is a high resolution technique that allows a detailed examination of the gastrointestinal tract (GI) wall and surrounding structures, including the pancreas. Contrast harmonic imaging EUS (CHI-EUS) uses a low mechanical index (MI) mode, in order to better characterise focal pancreatic masses, improve staging for pancreatico-biliary and GI tract cancers, and possibly guide therapeutic EUS interventions, including EUS-fine needle aspiration (EUS-FNA) [165,166].

CHI-EUS can be used for the differential diagnosis of hypoenhancing pancreatic adenocarcinoma as opposed to other iso- or hyperenhancing solid pancreatic lesions (neuroendocrine tumors, pancreatic metastases, chronic pseudo-tumoral pancreatitis, etc.). It is useful for the differential diagnosis of benign and malignant pancreatic focal lesions, where the concomitant use of CHI-EUS and EUS-FNA has an additive value to increase the overall accuracy by decreasing false negative results of both techniques [167]. Two recent meta-analyses reported high sensitivity and specificity of CHI-EUS for the differential diagnosis of pancreatic adenocarcinoma [99,168].

Both qualitative and quantitative (time intensity curve analysis) CHI-EUS can be performed during pancreas examinations. Pancreatic ductal adenocarcinoma typically shows heterogeneous hypoenhancement, whilst other solid masses exhibit iso- or hyperenhancement [169]. Pancreatic neuroendocrine tumors typically show hyperenhancement followed by "wash-out", filling defects being predictive of malignancy [170]. CHI-EUS can be used complementary to EUS-FNA in order to increase the diagnostic yield and accuracy through the guidance of the needle during real-time CEUS [171].

Pseudotumoral chronic pancreatitis shows iso- or hyperenhancement [172]. Likewise, autoimmune pancreatitis shows hyper-enhancement during CHI-EUS and can be differentiated from pancreatic adenocarcinoma [173].

CHI-EUS has been used in cystic pancreatic lesions, due to the increased resolution and ability to image the wall, septa and mural nodules [174]. Thus, the differentiation between mural nodules as opposed to debris and intra-cystic mucus can be easily made [175]. Consequently, pancreatic pseudocysts can be differentiated from neoplastic cystic tumors (serous cystadenomas, mucinous cystic neoplasms and intrapapillary mucinous neoplasms). However, the differential diagnosis between serous cystadenoma and mucinous neoplastic lesions cannot be based on CHI-EUS only.

Other applications of CHI-EUS include the evaluation of malignant gallbladder polyps [176], as well as assessment of GI tract wall lesions, including malignant GIST lesions as compared to other benign submucosal tumors [177].

Recommendations:
a. *CHI-EUS is useful for the differentiation of focal pancreatic masses, especially hypoenhancing pancreatic adenocarcinoma as opposed to other iso- or hyperenhancing solid pancreatic lesions.*
b. *CHI-EUS is useful for the differential diagnosis of cystic pancreatic masses, due to the enhanced visualisation of the wall, septa and mural nodules, being able to differentiate pseudocysts and cystic neoplastic lesions.*

Other CEUS applications

Vascular applications. CEUS can accurately visualize and evaluate the micro-vascularization – through Dy-

namic Contrast Enhanced Ultrasound (DCE–US) – [70], and also the medium and large vessels [178]. CEUS can confidently be used to assess abdominal aortic aneurysm and its complications [179] and to characterize atherosclerotic plaques, especially in the carotid artery [180]. Arteriovenous fistulas can also be assessed by CEUS [181].

CEUS is able to evaluate the veins patency, to assess thrombus extension [181] and can differentiate between benign or malignant portal vein thrombosis [182, 183]. In liver transplantation, CEUS can depict the vascular patency, and also the ischemic areas or hemorrhage within the liver [5,184,185].

Lung applications. The lung has a dual vascularization consisting of pulmonary artery and systemic bronchial artery supply [186]. An arrival time in a consolidation area of less than 8-10 seconds ("early arterial enhancement") significates pulmonary arterial supply, while a delayed arrival time, over 10 seconds ("late arterial enhancement") indicates supply by the bronchial arteries [186,187]. In pneumonia there is early and intense arterial enhancement (<10 sec); "wash-out" is mild and late [186,188]. In embolic pulmonary infarcts, the CEUS enhancement is minimal or absent in 80% of cases [186,189]. In atelectasis, similar to pneumonia, the enhancement is early and intense (<10 s), followed by a plateau [186,190]. In pulmonary tumors, due to an arterial supply from the bronchial system, enhancement is usually late [186,187]. Unenhancing areas such as abscesses in pneumonia, or a hypoenhanced area representing a central tumor, in obstructive atelectasis can be easily detected by CEUS [186]. Using CEUS, either before or as a real time guiding tool during biopsy, it is possible to target a central lung tumor in an atelectatic mass, or to avoid necrosis in large lung and mediastinal lesions [191,192].

UCA can also play a role in delivering drugs or biological vectors [193].

Recommendations:

Other applications of UCA are: evaluation of microvascularization through Dynamic Contrast Enhanced Ultrasound, evaluation of abdominal aortic aneurysm and its complications, of venous thrombosis and of vessels patency and differential diagnosis in consolidation lung diseases.

Acknowledgements:

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