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● *Review*

THE ASIAN FEDERATION OF SOCIETIES FOR ULTRASOUND IN MEDICINE AND BIOLOGY (AFSUMB) GUIDELINES FOR CONTRAST-ENHANCED ENDOSCOPIC ULTRASOUND

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Abstract—The Asian Federation of Societies for Ultrasound in Medicine and Biology aimed to provide information on techniques and indications for contrast-enhanced harmonic endoscopic ultrasound (CH-EUS), and to create statements including the level of recommendation. These statements are based on current scientific evidence reviewed by a Consensus Panel of 15 internationally renowned experts. The reliability of clinical questions was measured by agreement rates after voting. Six statements were made on techniques, including suitable contrast agents for CH-EUS, differences between contrast agents, setting of mechanical index, dual imaging and duration and phases for observation. Thirteen statements were made on indications, including pancreatic solid masses, pancreatic cancer staging, pancreatic cystic lesions and mural nodules, detection of subtle pancreatic lesions, gallbladder sludge and polyps, hepatic lesions, lymph nodes, subepithelial lesions, visceral vascular diseases, guidance of fine needle aspiration and evaluation for local therapy. These international expert consensus guidelines will assist endosonographers in conducting CH-EUS according to evidence-based information. (E-mail: kitano@wakayama-med.ac.jp) **© 2021 The Author(s). Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).**

Key Words: **Endoscopic ultrasound, Contrast-enhanced harmonic endoscopic ultrasound, Guidelines, Techniques, Indications.**

INTRODUCTION

Endoscopic ultrasound (EUS) is a special ultrasound technique in which the tip of the digestive endoscope is equipped with a high-frequency ultrasound transducer, making it distinct from extracorporeal ultrasound. For the diagnosis of intra-abdominal diseases, the spatial resolution of EUS is superior to that of other imaging modalities such as transabdominal ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). However, the differential diagnosis of solid lesions is difficult with conventional EUS because

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most solid lesions are depicted as hypo-echoic masses. Ultrasound contrast agents have a good safety profile in all patients; indeed, severe adverse events are exceedingly rare (Moriyasu and Itoh 2009; Miyamoto et al. 2014; Tang et al. 2017; Chou et al. 2019; Hu et al. 2019). Therefore, evaluation of vascularity using the recently developed technique of contrast-enhanced harmonic EUS (CH-EUS) may improve the characterization of intra-abdominal lesions. In fact, CH-EUS is increasingly being used in the diagnosis of intra-abdominal lesions, and its utility has been extensively reported. However, indications and standardization of methods and settings for CH-EUS remain to be determined. The Asian Federation of Societies for Ultrasound in Medicine and Biology (AFSUMB) aimed to provide internationally applicable information based on current scientific evidence reviewed by a panel of internationally renowned experts on the aforementioned topics, to allow further utilization and research in the field of CH-EUS possibly throughout Asia and the rest of the world.

METHODS

The AFSUMB invited 15 international experts from Asia and Europe to form a Consensus Panel. Key topics on current issues and the optimal utilization of CH-EUS were assigned to the Consensus Panel members. The first step in developing the present guidelines was to define clinical questions (CQs) for techniques and indications of CH-EUS. A literature review of papers relevant to contrast-enhanced EUS was performed by the Consensus Panel. All Consensus Panel members raised as many CQs as possible, which were then consolidated to a smaller number. A draft of all CQs was then approved by all panel members. The second step was to evaluate the quality of clinical evidence and the risk−benefit balance for the CQs by performing a systematic review. For each clinical question, several statements were made and revised through discussion among all Consensus Panel members. Multiple iterations were required for each domain until complete agreement was obtained. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the level of evidence per statement (see http://www.uptodate.com/home/gradingtutorial). The third step was to create the statements, including the level of recommendation. The strength of the recommendation was graded as "strong" if it was very certain that benefits outweighed risks and burdens or "weak" if the risks and burdens appeared to be finely balanced. The fourth step was to establish agreement on each statement among the members. To gauge the level of objective support from the international expert panel, voting was performed by the members on their level of agreement with the recommendations using a 9-point Likert scale and their GRADE score, which was then used to calculate Cronbach's α reliability coefficient (http://hdl.handle.net/1805/344). Voting was performed *via* a Web-based system to avoid the influence of other committee members' opinions. The people who voted ≥ 7 or more on the 9-point Likert scale were counted, and this number was divided by the total number who voted to estimate the agreement. The agreement results were classified as strong (>80% of votes were ≥ 7), conditional (>65% of votes were ≥ 7) or weak (<65 % of votes were ≥ 7).

RESULTS

CQ 1: Which ultrasound contrast agents are suitable for CH-EUS?

Statement 1.1. SonoVue (Lumason), Sonazoid or Definity should be used as an ultrasound contrast agent to perform CH-EUS.

Quality of evidence: low. Recommendation: strong. Agreement: strong ($\alpha = 1.00$).

Statement 1.2. There is no clear difference in diagnostic ability between the three contrast agents for CH-EUS.

Quality of evidence: low. Recommendation: weak. Agreement: weak ($\alpha = 0.600$).

Supporting evidence and comments. Contrast-enhanced harmonic imaging with first-generation ultrasound contrast agents (UCAs) such as Levovist requires high acoustic power to oscillate or break the microbubbles. However, EUS is equipped with only a small transducer, and the transmission signals from the transducer are typically too low in this respect (Săftoiu et al. 2012). Second-generation UCAs are made to oscillate and/or break under a lower acoustic power and, therefore, are suitable for CH-EUS. There are three second-generation UCAs suitable for CH-EUS: SonoVue (Lumason, sulfur hexafluoride microbubbles; Bracco, Milan, Italy; available in Europe, China, India, Korea, Hong Kong, New Zealand, Singapore and Brazil); Definity (octafluoropropane microbubbles; Bristol-Myers Squibb Medical Imaging, New York, NY, USA; available in the United States, Canada and Australia); and Sonazoid (perfluorobutane microbubbles; GE Healthcare, Chicago, IL, USA; Daiichi Sankyo, Tokyo, Japan; available in Japan, South Korea, Taiwan and Norway). Although dynamic contrast effects seem to differ between the different contrast agents, there is little evidence available on comparison of the properties of the different UCAs (Baert and Sartor, 2005; Yamashita et al. 2019). However, direct comparisons may be difficult to perform because the second-generation UCAs may be used off-label in different regions of the world, with only one of them being available

in each country (Sanchez et al. 2009; Alvarez-Sánchez and Napoléon 2014).

CQ 2: How do we set the mechanical index for CH-EUS?

Statement 2.1. The mechanical index (MI) should be between 0.2 and 0.4. Within this range, the MI should be adjusted in accordance with the type of EUS (radial or linear), ultrasound machine, image processing technology and focal points. Quality of evidence: low. Recommendation: strong. Agreement: strong ($\alpha = 1.00$)

Supporting evidence and comments. The MI can be used to characterize the response of microbubbles to an applied acoustic wave (Leen, 2001; Lencioni et al. 2002; Averkiou et al. 2003; Kollmann 2007). The MI used in published reports ranges from 0.1 to 0.4 because it depends on various factors including EUS type (radial or linear EUS), ultrasound machine, image processing technology (phase-inversion harmonic imaging or amplitude modulation imaging) and focal points (Kitano et al. 2008a, 2008b; Fusaroli et al. 2010; Seicean et al. 2010; Matsubara et al. 2011; Romagnuolo et al. 2011; Imazu et al. 2012; Kitano et al. 2012; Gheonea et al. 2013; Gincul et al. 2014; Săftoiu et al. 2015; Yamashita et al. 2015b; Yamamoto et al. 2016; Chantarojanasiri et al. 2017; Iglesias-Garcia et al. 2017; Omoto et al. 2017; Kamata et al. 2018b; Leem et al. 2018).

CQ 3: Is dual imaging necessary for CH-EUS?

Statement 3.1. CH-EUS should be performed with dual imaging. Quality of evidence: low. Recommendation: strong. Agreement: strong ($\alpha = 0.934$)

Supporting evidence and comments. Dual imaging is necessary for color Doppler and elastography to confirm the location of the target. There are no reports comparing CH-EUS with dual imaging against CH-EUS without dual imaging. However, most published studies and review articles have reported the advantages of dual imaging (Kitano et al. 2008a, 2012; Fusaroli et al. 2010; Seicean et al. 2010; Gheonea et al. 2013; Alvarez-Sánchez and Napoléon 2014; Gincul et al. 2014; Park et al. 2014; Săftoiu et al. 2015; Yamashita et al. 2015b; Yamamoto et al. 2016; Chantarojanasiri et al. 2017; Iglesias-Garcia et al. 2017; Kitano and Yamashita 2017; Kamata et al. 2018b). The CH-EUS image is not suitable for routine imaging because it is obtained at low MI. Dual imaging is useful to first confirm the location of the target lesion, with it then being followed by CH-EUS, which should reveal an entirely black background before contrast administration.

CQ 4: How long should we observe CH-EUS?

Statement 4.1. CH-EUS should be observed for 120 s after injection of contrast agents. Quality of evidence: low. Recommendation: weak. Agreement: conditional ($\alpha = 0.667$).

Supporting evidence and comments. The observation times described in published reports vary considerably, ranging from 45−300 s (Kitano et al. 2008a, 2008b; Fusaroli et al. 2010; Seicean et al. 2010; Matsubara et al. 2011; Kitano et al. 2012; Park et al. 2014; Soares et al. 2015; Yamashita et al. 2015b; Yamamoto et al. 2016; Iglesias-Garcia et al. 2017; Cho et al. 2018; Kamata et al. 2018b; Leem et al. 2018), with the most often reported time being 120 s (Seicean et al. 2010; Yamamoto et al. 2016; Iglesias-Garcia et al. 2017; Leem et al. 2018). The duration of observation also depends on the target organ. In the pancreas, the signals from UCAs appear from 10 to 15 s after injection and peak at approximately 20 s (Kitano et al. 2017). The phases are identified as follows: arterial phase (early phase) at 10−30 s (concomitant with enhancement in the abdominal aorta, celiac trunk or superior mesenteric artery), and venous phase (late phase) at 30−120 s (enhancement in splenic vein, portal vein and superior mesenteric vein). In the liver and spleen, the observation times include the sinusoidal phase over 120 s and the late washout phase over 240 s (Seicean et al. 2010; Alvarez-Sánchez and Napoléon 2014). The most suitable duration of observation for accurate diagnosis could not be determined because there are no studies comparing different durations of observation.

CQ 5: Is it necessary to analyze CH-EUS images separately on early and late phases?

Statement 5.1. It is necessary to analyze CH-EUS images separately on early and late phases. Quality of evidence: low. Recommendation: weak. Agreement: strong ($\alpha = 0.867$).

Supporting evidence and comments. Among studies on CH-EUS in patients with pancreatobiliary, lymph node, epithelial or intra-abdominal lesions, seven studies reported the advantages of analyzing CH-EUS images separately in early and late phases (Fusaroli et al. 2010; Choi et al. 2013; Gheonea et al. 2013; Yamashita et al. 2015a; Kamata et al. 2017, 2018b; Cho et al. 2018). However, only a few reports have addressed the advantages of separately analyzing CH-EUS images in early and late phases to increase diagnostic yield. With respect to observation of the liver, CH-EUS with Sonazoid, which allows a long duration of

enhancement, can improve detection of small liver tumors with use of the late washout phase over 240 s (Minaga et al. 2021). Further studies are required to compare the early and late phases of CH-EUS in diagnosis.

CQ 6: Is CH-EUS recommended for characterization of pancreatic solid masses?

Statement 6.1. Use of CH-EUS is recommended for characterization of pancreatic solid masses. Quality of evidence: high. Recommendation: strong. Agreement: strong ($\alpha = 1.00$).

Supporting evidence and comments. The roles of fundamental B-mode EUS and EUS-guided fine-needle aspiration (EUS-FNA) and EUS-guided fine-needle biopsy in the detection and diagnosis of solid pancreatic masses are well established. However, there remain specific situations in which characterization with tissue acquisition is still indeterminate. Published data (retrospective and prospective studies, randomly allocated control trials, meta-analysis) have consistently confirmed the validity and usefulness of CH-EUS in this respect. The literature search revealed 3 systematic reviews or meta-analyses (D'Onofrio et al. 2014; Fusaroli et al. 2016c; Yamashita et al. 2019), 36 studies that focused on characterization of solid masses using contrast EUS alone (Hirooka et al. 1998; Becker et al. 2001; Hocke et al. 2006, 2007; Sakamoto et al. 2008; Dietrich et al. 2005, 2008; Napoleon et al. 2010; Kitano et al. 2008a, 2012; Săftoiu et al. 2010; Fusaroli et al. 2010; Seicean et al. 2010; Ang et al. 2011; Matsubara et al. 2011; Imazu et al. 2012; Gheonea et al. 2013; Lee et al. 2013; Gincul et al. 2014; Park et al. 2014; Uekitani et al. 2016; Omoto et al. 2017; Cho et al. 2018; Leem et al. 2018; Ishikawa et al. 2018), and 4 studies that combined both CH-EUS and EUS elastography to characterize pancreatic solid masses (Figueiredo et al. 2012; Hocke et al., 2012; Săftoiu et al. 2015; Chantarojanasiri et al. 2017).

In a meta-analysis, D'Onofrio et al. (2014) examined both contrast-enhanced US "CE-US" and contrast-enhanced EUS "CE-EUS", and reported a sensitivity of 89% (85%−92%) and specificity of 84% (77%−89%) for the diagnosis of pancreatic adenocarcinoma. In an earlier meta-analysis, Gong et al. (2012) analyzed CE-EUS for the diagnosis of adenocarcinoma and reported a pooled sensitivity and specificity of 94% (91%−95%) and 89% (85%−92%), respectively, higher than those of D'Onofrio et al. More recently, Yamashita et al. (2019) focused on CH-EUS only and revealed pooled estimates of sensitivity and specificity of 93% (91%−95%) and 80% (75%−85%), respectively. The characterization of pancreatic solid masses is generally based on a qualitative assessment of the degree of enhancement, with hypo-enhancement/heterogeneous enhancement corresponding to pancreatic adenocarcinoma; iso-enhancement corresponding to inflammatory mass; and hyperenhancement corresponding to neuroendocrine tumor (Kitano et al. 2008a). In the context of neuroendocrine tumors, heterogeneous enhancement and hypo-enhancement were predictive of malignancy (Ishikawa et al. 2010; Palazzo et al., 2018).

CQ 7: Is CH-EUS recommended for pancreatic cancer staging?

Statement 7.1. Use of CH-EUS is recommended for pancreatic cancer staging in selected patients with suspected major vessel involvement. Quality of evidence: low. Recommendation: weak. Agreement: conditional ($\alpha = 0.667$).

Supporting evidence and comments. Moderate-grade evidence revealed that CT and MRI have reliable accuracy for diagnosis of vascular involvement in pancreatic cancer (Treadwell et al. 2016). EUS could provide additional information compared with CT and MRI (Yang et al. 2014), although there is no report comparing CH-EUS with other imaging methods for staging of pancreatic cancer. Two prospective studies (Imazu et al. 2010; Seicean et al. 2010) on the utility of CH-EUS for pancreatic cancer T-staging have been reported, as has one study (Miyata et al. 2016) on N staging. Imazu et al. (2010) found that T-staging using CH-EUS was significantly better than that using EUS alone, with overall accuracies of 92.4% and 69.2%, respectively ($p < 0.05$). For the detection of portal vein involvement, CH-EUS had higher accuracy than EUS alone (100% vs. 84.6%), although the difference was not significant. Seicean et al. (2010) reported that CH-EUS using SonoVue (Lumason) provided better visualization of major vessel invasion in 20 patients with pancreatic cancer, including non-surgical cases. However, CH-EUS was not found to be superior to EUS alone for T-staging. Miyata et al. (2016) reported that CH-EUS was useful for distinguishing malignant from benign lymph nodes, but found no significant difference in the accuracy of N-staging between EUS-FNA and CH-EUS in 51 patients with pancreaticobiliary malignancies, including 29 who had pancreatic cancer (88% vs. 90%).

Potential limitations of these three studies (Imazu et al. 2010; Seicean et al. 2010; Miyata et al. 2016) include a small sample size and lack of normal controls. Moreover, two of the studies (Imazu et al. 2010; Miyata et al. 2016) included both pancreatic and biliary malignancies. However, the two studies (Imazu et al. 2010; Seicean et al. 2010) evaluating T-staging revealed that CH-EUS could depict the tissues between the pancreatic tumor and major vessels

more clearly, suggesting that the use of sonographic contrast medium with EUS may improve the accuracy of T-staging for pancreatic cancer. Because of low-quality evidence, further studies evaluating the role of CH-EUS for pancreatic cancer staging are required.

CQ 8: Is CH-EUS recommended for characterization of pancreatic cystic lesions?

Statement 8.1. CH-EUS has limited yield for the characterization and differential diagnosis of pancreatic cystic lesions. Quality of evidence: low. Recommendation: weak. Agreement: strong ($\alpha = 0.933$)

Supporting evidence and comments. Four retrospective studies have reported the usefulness of CH-EUS for characterization of pancreatic cystic lesions (PCLs). Hirooka et al. (1998) first reported the contrast enhancement characteristics of PCLs using Albunex. They noted that serous cystic neoplasms (3/3) and mucin-producing tumors (6/8) had contrast-enhancing lesions inside the cysts, but none were found inside pseudo-cysts (0/5). Three retrospective studies suggested that when using CH-EUS, identification of hyperenhanced nodular components inside PCLs is the most important characteristic for discriminating pseudocysts from cystic neoplasms (Hocke et al. 2014; Fusaroli et al. 2016d; Kamata et al. 2016). A prospective study revealed that CH-EUS had greater accuracy for identifying PCLs than CT, MRI and fundamental B-mode EUS (CE-EUS vs. CT: 92.3% vs. 76.9%; CE-EUS vs. MRI: 93.0% vs. 78.9%; CE-EUS vs. FB-EUS: 92.7% vs. 84.2%) (Zhong et al. 2019). However, CH-EUS has only a limited role in differentiating between serous and mucinous PCLs because it is difficult to differentiate tumor growth from wall and septae using vascular imaging with contrast agents (Hocke et al. 2014; Fusaroli et al. 2016d; Kamata et al. 2016). Diffusion MRI or positron emission tomography may compensate for this limitation (Pozzessere et al. 2016; Srinivasan et al. 2019). Morphological features other than enhancing mural nodules, including the presence of septations and delineation of ductal communication, should also be used for characterization of PCLs (Mohamed et al. 2018).

CQ 9: Is CH-EUS recommended for detection of mural nodules in pancreatic cystic neoplasms?

Statement 9.1. Use of CH-EUS is recommended for the identification of mural nodules in pancreatic cystic lesions. Quality of evidence: moderate. Recommendation: weak. Agreement: strong ($\alpha = 1.00$).

Supporting evidence and comments. One systematic review reported by Marchegiani et al. (2018) included 70 studies and 2297 resected intraductal papillary mucinous neoplasms (IPMNs), and the meta-analysis suggested that mural nodule (MN) size measured by CE-EUS has a considerable effect on predicting malignant IPMNs with a pooled standardized mean difference of 0.79. Four retrospective studies (Harima et al. 2015; Fujita et al. 2016; Fusaroli et al. 2016d; Kamata et al. 2016) found that the characteristics of MNs (*e.g.,* size, morphologic feature and enhanced pattern) correlated with the malignant potential of IPMNs. One prospective (Yamashita et al. 2013b) and two retrospective (Ohno et al. 2009; Yamamoto et al. 2016) studies reported that CH-EUS was useful for differentiating between mucous clots and neoplastic nodules. Ohno et al. (2009) reported that morphologic type (type III or IV) classified by CE-EUS findings correlated with the malignant potential of IPMNs. Yamamoto et al. (2016) reported on CH-EUS with time−intensity curve analysis for MNs, and suggested that malignant IPMNs exhibited significantly higher echo intensity change, echo intensity reduction rate and nodule/parenchyma contrast ratio. CH-EUS may help to distinguish neoplastic nodular lesions and mucous clot, and to estimate the malignant potential of IPMNs. Therefore, CH-EUS is recommended for detection of MNs in PCLs.

CQ 10: Is CH-EUS recommended for detection of subtle lesions in the pancreas?

Statement 10.1. Use of CH-EUS is recommended for detection of subtle pancreatic lesions when they are either small or difficult to detect. Quality of evidence: moderate. Recommendation: strong. Agreement: strong ($\alpha = 0.800$).

Supporting evidence and comments. The concept of subtle lesions in the pancreas tends to vary according to the experience of endosonographers and the presence of confounding factors, such as chronic pancreatitis and biliary stents. However, subtle lesions include both small lesions and lesions that are difficult to identify because poor echogenicity may be considered subtle. A prospective study from Japan identified 277 patients who underwent CH-EUS evaluation of the vascularity of pancreatic lesions. Among these patients, the sensitivity and specificity for small lesions ($\leq$20 mm) were 91% and 94%, respectively (Kitano et al. 2012). In this respect, CH-EUS was superior to multidetector CT for diagnosing ductal adenocarcinoma ($p = 0.034$). Interestingly, the authors determined very high inter-observer agreement ($K = 0.94$) between endosonographers, indicating good reproducibility of the analysis of the vascular patterns of pancreatic lesions.

A multicenter retrospective study looked at 219 patients with incidentally detected small pancreatic

lesions (≤15 mm). CH-EUS allowed differential diagnosis between ductal adenocarcinoma and all other types of lesions in 86% of cases. As a result, in approximately 40% of the patients with small solid pancreatic lesions, their pancreatic ductal adenocarcinoma was found at a potentially curable early stage. Furthermore, lesions other than adenocarcinomas did not require extensive surgery, thus sparing significant morbidity and mortality (Dietrich et al., 2016c).

One of the first descriptions of hyperenhancement of pancreatic neuroendocrine tumors dates back to 2002, when a small insulinoma of the head was enhanced by Levovist injection during EUS (Kasono et al. 2002). Evidence of a more scientific nature has accumulated over the years as numerous articles have described the high positive predictive value of CH-EUS for identifying small neuroendocrine tumors of the pancreas. A recent study from Germany reported 32 patients with histologically proven small neuroendocrine tumors (≤15 mm), including insulinoma, gastrinoma, glucagonoma and non-functional lesions. After contrast injection, 90% of the lesions exhibited hyperenhancement compared with the surrounding pancreatic parenchyma (Braden et al. 2017).

Pancreatic metastases may appear as solid single or multiple small lesions. A study from Italy described pancreatic metastases originating from other organs. On CH-EUS, the majority of lesions (7/11) were hypo- or iso-enhanced; however, 4 of 11 lesions were hyperenhanced (renal cancer and lymphoma) (Fusaroli et al. 2014). Where the latter are concerned, the differential diagnosis from pancreatic neuroendocrine tumors is crucial. In this respect, EUS-guided tissue acquisition remains mandatory.

Intraoperative contrast-enhanced US also plays an important role in characterizing subtle lesions in the pancreas (Werner et al. 2020). Further studies comparing CH-EUS with intra-operative contrast-enhanced US are required to establish diagnostic strategies for subtle lesions in the pancreas.

CQ 11: Is CH-EUS recommended for characterization of lesions in the gallbladder?

Statement 11.1. CH-EUS may be useful for the differential diagnosis of biliary sludge from other perfused gallbladder lesions. Quality of evidence: low. Recommendation: weak: Agreement: strong ($\alpha = 1.00$).

Statement 11.2. CH-EUS may be used to differentiate between benign and malignant gallbladder polyps. Quality of evidence: low. Recommendation: weak. Agreement: conditional ($\alpha = 0.667$).

Supporting evidence and comments. Multimodality imaging is essential for characterization of lesions in the gallbladder (Ratanaprasatporn et al. 2018). EUS, high-resolution US and CT are comparable with respect to the differential diagnosis of gallbladder polypoid lesions (Jang et al. 2009). The use of CH-EUS improves the characterization and diagnostic accuracy of selected gallbladder lesions on EUS (Piscaglia et al. 2012; Sidhu et al. 2018a, 2018b). Gallbladder adenomas and cholesterol polyps are both round-shaped masses; however, adenomas are homogeneously enhanced, whereas cholesterol polyps are generally heterogeneously enhanced on CH-EUS (Park et al. 2013). The absence of enhancement in gallbladder sludge allows its differentiation from tumors, which in almost all cases exhibit enhancement on CH-EUS (Choi et al. 2013). On CH-EUS, benign gallbladder wall thickening exhibits isoenhancement with clear non-enhanced areas (represented as Rokitansky−Aschoff sinuses) in both arterial and venous phases (Imazu et al. 2014). Inhomogeneous enhancement patterns are suggestive of malignant gallbladder wall thickening (Imazu et al. 2014).

The differentiation between benign and malignant gallbladder lesions is often challenging, particularly when minor abnormalities are present. A heterogeneous enhancement pattern, the presence of perfusion defects and an irregular tumor vessel are features highly suggestive of gallbladder malignancy (Choi et al. 2013; Imazu et al. 2014; Sugimoto et al. 2016). Gallbladder wall destruction beneath a solid lesion and the infiltration of adjacent liver tissue are highly suggestive of invasive malignancy (Imazu et al. 2014). Because of low-quality evidence, further study to evaluate the role of CH-EUS for characterization of lesions in the gallbladder is required.

CQ 12: Is CH-EUS useful for characterization of hepatic lesions?

Statement 12.1. Use of CH-EUS is recommended for characterization and guidance of EUS-FNA only in liver lesions with unclear margins or in the case of previous negative EUS-FNA. Quality of evidence: low. Recommendation: weak. Agreement: strong ($\alpha = 1.00$).

Supporting evidence and comments. CT, MRI and contrast-enhanced ultrasound are useful for characterization of hepatic lesions (Hatanaka et al. 2010; Wildner et al. 2015; Lee et al. 2015). However, only one retrospective series has been published regarding CH-EUS. Oh et al. (2018) included 30 consecutive patients with liver tumors over a 7-y period and used linear array echo-endoscopes and second-generation UCAs. CH-EUS significantly improved lesion detection compared with fundamental B-mode (96.7% of cases vs. 73.3%, $p <$

0.01). CH-EUS was typical in 90% of cases of liver metastasis (non- or hypo-enhanced), 40% of hepatocellular carcinoma (hyperenhancement with delayed washout) and 50% of neuroendocrine carcinoma (early enhancement with early washout). EUS-FNA was performed after CH-EUS and had an adequacy of 93.3%. CH-EUS findings were compatible with malignancy in three of four lesions with false-negative EUS-FNA. Although this study seems to be in favor of CH-EUS, the ability of fundamental B-mode EUS to detect small lesions ≤5 mm missed by conventional imaging has been reported (Awad et al. 2002; Prasad et al. 2004; Fujii-Lau et al. 2015), and EUS-FNA can be immediately applied in such cases (Nguyen et al. 1999; Awad et al. 2002). In a prospective study (Hollerbach et al. 2003), fundamental B-mode EUS combined with EUS-FNA had very high performance, with 97% sample adequacy, 94% sensitivity and 100% specificity. No data are available on the detection of small metastases by CH-EUS, and criteria for their characterization must be confirmed.

CQ 13: Is CH-EUS recommended for differentiation of malignant from benign lymph nodes?

Statement 13.1. Routine use of CH-EUS is not recommended for differentiation of malignant and benign lymph nodes (BLNs) in addition to EUS-FNA. Quality of evidence: low. Recommendation: weak. Agreement: conditional ($\alpha = 0.734$).

Supporting evidence and comments. In general, N-staging of pancreatic cancer is based on various imaging methods including CT, MRI and positron emission tompgraphy (PET) (Treadwell et al. 2016). To detect regional lymph node metastases of esophageal cancer, EUS is the most sensitive technique, whereas CT and PET are more specific (van Vliet et al. 2008). Although EUS has an advantage over the other imaging methods with respect to detection of small lymphadenopathy, conventional EUS is limited when it comes to differentiating malignant from benign lymphadenopathy. Five published studies have addressed the use of CH-EUS for differentiating malignant lymph nodes (MLNs) from BLNs (Kojima et al. 2003; Kanamori et al. 2006; Hocke et al. 2008; Xia et al. 2010; Miyata et al. 2016). None of the studies were randomly allocated controlled studies, and all included only a small number of patients. Two of the studies were from the same group (Xia et al. 2010; Miyata et al. 2016). The types of contrast used included Levovist, Sonazoid and SonoVue (Lumason). Four of the studies reported on the sensitivity, specificity and accuracy of CH-EUS in diagnosing MLNs, but only one reported the respective figures for BLNs. Final diagnosis of the lymph nodes was based on EUS-FNA, resected surgical specimens or the clinical course of the patient.

There was no agreement on the enhancement pattern that characterizes a malignant or benign lymph node. Four studies used the presence of a filling defect or heterogeneous enhancement to characterize a MLN, and homogeneous enhancement or non-enhancement to characterize a BLN. Using these criteria, the sensitivity, specificity and accuracy of CH-EUS for diagnosing an MLN were 83%−100%, 86.4%−100% and 88%−97% respectively. The corresponding values for diagnosing a BLN were 88.2%, 77.3% and 82.1%, respectively (reported in only one of the four studies). In the remaining study, an MLN was diagnosed by CH-EUS when there was "rarefication of the vascular pattern with areas without visible vessels," and a BLN was diagnosed when there was "a rich vessel appearance" (Hocke et al. 2008). The study only reported a sensitivity of 60% for MLNs and a specificity of 91% for BLNs. In studies with more than one reviewer of the CH-EUS images, there was excellent inter-observer agreement between the reviewers (κ coefficient = 0.81, $p < 0.01$; κ coefficient = 0.953, $p < 0.01$).

On the basis of the aforementioned results, the use of CH-EUS is associated with high sensitivity, specificity and accuracy for differentiating MLNs. However, whether similar performance could be obtained for BLNs is uncertain. Furthermore, whether the use of CH-EUS could provide additional value to EUS-FNA, particularly in patients whose EUS-FNA results are inconclusive, is also uncertain (Lisotti et al. 2019). Therefore, it is difficult to recommend the routine use of CH-EUS for differentiation of malignant from BLNs.

CQ 14: Is CH-EUS recommended for characterization of subepithelial lesions in the upper digestive tract?

Statement 14.1. Use of CH-EUS is recommended for characterization of subepithelial lesions in the upper digestive tract. Quality of evidence: low. Recommendation: weak. Agreement: strong ($\alpha = 0.867$).

Supporting evidence and comments. The numbers of patients in the studies reporting the usefulness of CH-EUS for characterization of subepithelial lesions in the upper digestive tract were small, and therefore, the confidence in the estimate of the effect is limited (Sakamoto et al. 2011; Kannengiesser et al. 2012; Yamashita et al. 2015a; Zhao et al. 2016; Kamata et al. 2017; Ignee et al. 2017; Tamura and Kitano, 2019; Tang et al. 2019). There were four reports on CH-EUS for the differential diagnosis between low-grade malignancy and high-grade malignancy gastrointestinal stromal tumors (GISTs) (Sakamoto et al. 2011;

Yamashita et al. 2015a; Park et al. 2016; Zhao et al. 2016). These studies reported sensitivity ranging from 53.8% to 100% and specificity ranging from 63% to 100% in the diagnosis of high-grade malignant GISTs (Sakamoto et al. 2011; Yamashita et al. 2015a; Park et al. 2016; Zhao et al. 2016). Three of the studies revealed that irregular (or intra-tumoral) vessels were a sign of high-grade malignancy GISTs (Sakamoto et al. 2011; Yamashita et al. 2015a; Zhao et al. 2016). One prospective study evaluated CH-EUS for the differential diagnosis between low-grade malignancy and high-grade malignancy GISTs in 29 patients, including 13 cases of low-grade malignancy and 16 cases of high-grade malignancy (Sakamoto et al. 2011). Irregular vessels were reported to be a sign of high-grade malignancy, with a sensitivity, specificity and accuracy of 100%, 63% and 83%, respectively (Sakamoto et al. 2011).

There were also five articles on CH-EUS for the differential diagnosis between GISTs and subepithelial lesions in the upper digestive tract (Kannengiesser et al. 2012; Ignee et al. 2017; Kamata et al. 2017). These articles reported that hyperenhancement was a sign of GISTs, with sensitivity for diagnosing GISTs ranging from 84.5% to 100% and specificity ranging from 73.3% to 100% (Kannengiesser et al. 2012; Ignee et al. 2017; Kamata et al. 2017; Pesenti et al. 2019; Cho et al. 2019). Lee et al. (2019) evaluated the feasibility of using CH-EUS with perfusion analysis software to distinguish subepithelial tumors and reported that peak enhancement, wash-in rate and wash-in perfusion index were significantly higher in GISTs than in leiomyomas (Lee et al. 2019). Because of low-quality evidence, further studies are required to evaluate the role of CH-EUS for characterization of subepithelial lesions in the upper digestive tract.

CQ 15: Is CH-EUS useful for evaluation of visceral vessels?

Statement 15.1. CH-EUS may be useful for evaluation of visceral vascular disease. Quality of evidence: low. Recommendation: weak. Agreement: weak ($\alpha = 0.600$).

Supporting evidence and comments. In general, angiography using CT, MRI and US is employed as a non-invasive diagnostic method of diagnosing visceral vascular diseases (Zaiem et al. 2018). Only one case series reported that CH-EUS accurately identified all 11 visceral vascular lesions (100% sensitivity), including superior mesenteric artery/celiac artery dissection and stenosis. EUS clearly visualized the true lumen and false lumen in all eight patients with superior mesenteric artery/celiac artery dissection, allowing correct diagnosis of dissection that abdominal CT imaging failed to depict in one patient (Paik et al. 2014). In the early days of contrast-enhanced EUS, Sato et al. (2004) reported that CE-EUS with a galactose-based contrast agent improved the visualization of flow in perforating veins in patients with recurrent esophageal varices after endoscopic therapy.

The limitations of these studies are small sample sizes and their retrospective nature, and there is currently insufficient evidence to recommend CH-EUS for the diagnosis of variable visceral vascular disease and esophageal varices. Therefore, it is difficult to recommend CH-EUS for evaluation of visceral vessels.

CQ 16: Is CH-EUS recommended for guidance of EUS-guided fine-needle aspiration?

Statement 16.1. Use of CH-EUS is recommended for guidance of EUS-FNA only in selected cases such as those with avascular areas or unclear margins. Quality of evidence: low. Recommendation: weak. Agreement: strong ($\alpha = 1.00$).

Supporting evidence and comments. There are two image enhancement techniques available for guidance of EUS-FNA: EUS-elastography and CH-EUS (Itonaga et al. 2020). However, no study has compared these two techniques in the context of tissue acquisition and diagnostic accuracy. With respect to using CH-EUS for guidance of EUS-FNA, two RCTs enrolled small numbers of patients (40 and 58) although their sample size estimations were not described. Kamata et al. (2018a) reported that sensitivity in the diagnosis of pancreatic adenocarcinomas was significantly higher for those with an avascular area (72.9%) than for those without an avascular area (94.3%), suggesting that EUS-FNA results are inadequate for pathologic diagnosis if an avascular area is detected within a pancreatic tumor on CH-EUS. Sugimoto et al. (2015) compared CH-EUS and EUS for tissue acquisition of pancreatic masses by EUS-FNA and concluded that avoiding avascular areas during CH-EUS improves tissue sampling. Hou et al. (2015) reported that the percentage of adequate biopsy specimens in a CH-EUS group (96.6%) was greater than the percentage in an EUS group (86.7%), although the increment was not statistically significant ($p = 0.054$). On the other hand, Seicean et al. (2017) reported that CH-EUS-FNA had an insignificant incremental effect on diagnostic accuracy compared with conventional EUS-FNA. Two studies reported that CH-EUS improves depiction of the rim in 2%–8% of pancreatic tumors, suggesting that CH-EUS may help identify the target of EUS-FNA in some subtle lesions (Fusaroli et al. 2010; Kitano et al. 2012).

Because of low-quality evidence, further studies are required to evaluate the role of CH-EUS for guidance of

EUS-guided fine needle aspiration by comparing it with conventional EUS and EUS elastography.

CQ 17: Is CH-EUS recommended for evaluation of the efficacy of local ablation therapy?

Statement 17.1. CH-EUS might be useful for evaluating the efficacy of local ablation therapy.

Quality of evidence: very low. Recommendation: weak. Agreement: conditional ($\alpha = 0.734$).

Supporting evidence and comments. EUS-guided local ablation has emerged as an alternative therapy for pancreatic tumors that are unsuitable for surgery (Dabizzi and Arcidiacono 2017). Contrast enhancement has the ability to delineate real-time tumor perfusion dynamics during EUS-guided local ablation. MRI and CT are regarded as a reliable reference imaging method after ablation therapy for hepatocellular carcinoma (Imai et al. 2017). CH-EUS may have an advantage over other imaging methods with respect to evaluating the efficacy of EUS-guided local ablation therapy for pancreatic tumors because CH-EUS can reproduce the images used to guide the local ablation therapy (Choi et al. 2020). However, only one study assessed CH-EUS for guidance and monitoring during endoscopic radiofrequency ablation (RFA). Choi et al. assessed the early treatment response after RFA and the targeting of residual viable tumors during additional ablation sessions. After the first RFA session, in 7 patients with treated tumors, CH-EUS revealed the disappearance of intra-tumoral enhancement, whereas 12 exhibited residual contrast enhancement and underwent additional RFA under real-time CH-EUS guidance (Choi et al. 2020). CH-EUS may be well accepted as a modality for assessing the efficacy of local ablation therapy if its usefulness is confirmed in further studies.

DISCUSSION

The AFSUMB guidelines for CH-EUS were formed using an evidence-based approach after discussion involving international experts from Asia and Europe. The AFSUMB invited European experts to ensure that the guidelines would be objective and evidence based, and the European experts contributed to these guidelines at all steps. The contributions of experts from different European and Asian countries minimized intrinsic biases toward different continents. These CH-EUS guidelines are the first to provide evidence levels and recommendations for key aspects of settings and techniques, along with indications for diagnosis of various diseases and therapy. Initially, 22 statements were created, with 19 of these being maintained in the final text and 3 being transferred to the Supplementary Data (online only). One of the removed statements regarding the safety of UCAs was described in the Introduction, because it is generally accepted. The other two were omitted from this text because one regarding multiple injections of UCAs was supported by very low evidence, and the other regarding peri-anal EUS was distinct from the other clinical statements on EUS within the upper gastrointestinal tract (Supplementary Data). Among the 19 statements, 3 had high or moderate quality of evidence (Tables 1 and 2). Several prospective and retrospective studies focusing on the role of CH-EUS for differentiating solid pancreatic lesions revealed its usefulness with high-quality evidence.

However, 16 statements were based on low- or very low-quality evidence because most reports relevant to these statements did not have high-quality evidence (Tables 1 and 2). Further large-scale prospective studies are required to establish the reliability of these statements. Weak agreement was obtained for 2 statements (Tables 1 and 2). It is difficult to obtain satisfactory agreement over the differences in diagnostic ability between the three UCAs because only one of the three second-generation UCAs is available in most countries, and there is no direct evidence evaluating the

Table 1. Recommendations for techniques stratified according to the levels of recommendation and agreement.

Statement		Quality of evidence	Recommendation	α score	Agreement
1.1	SonoVue (Lumason), Sonazoid, or Definity should be used to perform CH-EUS.	Low	Strong	*1.00*	Strong
2.1	The MI should be as low as 0.2−0.4. Within this range, the MI should be adjusted in accordance with the EUS type (radial or linear EUS) and focal points.	Low	Strong	*1.00*	Strong
3.1	CH-EUS should be performed with dual imaging.	Low	Strong	*0.934*	Strong
5.1	It is necessary to analyze CH-EUS images separately in early and late phases.	Low	Weak	*0.867*	Strong
4.1	CH-EUS should be observed for 120 s after injection of contrast agents.	Low	Weak	*0.667*	Conditional
1.2	There is no clear difference in diagnostic ability between the three contrast agents for CH-EUS.	Low	Weak	*0.600*	Weak

Table 2. Recommendations for indications stratified according to the levels of recommendation and agreement.

Statement		Quality of evidence	Recommendation	α score	Agreement
6.1	Use of CH-EUS is recommended for characterization of pancreatic solid masses.	High	Strong	*1.00*	Strong
10.1	Use of CH-EUS is recommended for detection of subtle pancreatic lesions when they are either small or difficult to detect.	Moderate	Strong	*0.800*	Strong
9.1	Use of CH-EUS is recommended for the identification of mural nodules in pancreatic cystic lesions.	Moderate	Weak	*1.00*	Strong
11.1	CH-EUS may be useful for the differential diagnosis of biliary sludge from other perfused gallbladder lesions.	Low	Weak	*1.00*	Strong
12.1	Use of CH-EUS is recommended for characterization and guidance of EUS-FNA only in liver lesions with unclear margins or in the case of previous negative EUS-FNA.	Low	Weak	*1.00*	Strong
16.1	Use of CH-EUS is recommended for guidance of endoscopic ultrasound-guided fine-needle aspiration only in selected cases such as those with avascular areas or unclear margins.	Low	Weak	*1.00*	Strong
9.1	CH-EUS has limited yield for the characterization and differential diagnosis of pancreatic cystic lesions.	Low	Weak	*0.933*	Strong
14.1	Use of CH-EUS is recommended for characterization of subepithelial lesions in the upper digestive tract.	Low	Weak	*0.867*	Strong
13.1	Routine use of CH-EUS is not recommended for differentiation of malignant and benign lymph nodes in addition to EUS-FNA.	Low	Weak	*0.734*	Conditional
17.1	CH-EUS might be useful for evaluating the efficacy of local ablation therapy.	Very low	Weak	*0.734*	Conditional
7.1	Use of CH-EUS is recommended for pancreatic cancer staging in selected patients with suspected major vessel involvement.	Low	Weak	*0.667*	Conditional
11.2	CH-EUS may be used to differentiate between benign and malignant gallbladder polyps.	Low	Weak	*0.667*	Conditional
15.1	CH-EUS may be useful for evaluation of visceral vascular disease.	Low	Weak	*0.600*	Weak

differences and similarities between the three second-generation UCAs; only case series reported the usefulness of CH-EUS for evaluation of visceral vascular disease. The statements with weak agreement should be curtailed or substantially modified unless new high-quality evidence emerges.

Most guidelines published for diagnosis of digestive diseases are organ or disease oriented, and include selection of various imaging techniques for a single organ or disease (Vege et al. 2015; Tanaka et al. 2017; Megibow et al., 2017; Expert Panel on Gastrointestinal Imaging, Kaur et al., 2017a, Qayyum et al., 2017b; European Study Group on Cystic Tumours of the Pancreas 2018). However, the World Federation for Ultrasound in Medicine and Biology (WFUMB) has published guidelines for the use of elastography techniques as well as contrast-enhanced ultrasound for various diseases (Ferraioli et al. 2015; Shiina et al. 2015; Barr et al. 2015, 2017; Dietrich et al. 2020). The AFSUMB has also published guidelines on the clinical practice of contrast-enhanced ultrasound using Sonazoid (Lee et al. 2020). The present AFSUMB guidelines are the first to focus on CH-EUS, including techniques and indications for various digestive diseases.

Analysis software has been developed in an attempt to provide some degree of quantitative assessment for CH-EUS (Seicean et al. 2010; Imazu et al. 2012; Săftoiu et al. 2015; Omoto et al. 2017; Takada et al. 2019; Buxbaum et al. 2020). Although limitations remain in quantitative analysis because of the subjectivity involved in determining a region of interest, combination of qualitative and quantitative analyses may improve the diagnostic ability of CH-EUS. In the future, development of ultrasound processing methods with higher frequency and resolution, as well as 3-D or 4-D imaging, may also improve the diagnostic ability of CH-EUS (Averkiou et al. 2020). A new ultrasound contrast agent that has an affinity to the kinase insert domain receptor (one of the key regulators of neoangiogenesis) was developed recently (Hackl et al. 2016; Willmann et al. 2017). Further studies are needed to apply ultrasound molecular imaging using BR55 to CH-EUS. However, when selecting imaging methods in the COVID-19 era, EUS should be considered, because it involves closer contact between medical personnel and patients than other imaging methods.

CONCLUSIONS

The main objectives of these guidelines are to reduce the variability of the methods and indications for CH-EUS and to provide information on the utility of CH-EUS. Consequently, an international consensus was obtained for some of the techniques and indications for CH-EUS although further clinical trials are needed to resolve issues not fully discussed in these guidelines because of a lack of reports with high-quality evidence.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2021.01.030.

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