Review Article

Do we need contrast agents for EUS?

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ABSTRACT

We recently introduced a series of articles that dealt with controversies in EUS. In Part I, the authors discussed which clinical information is necessary prior to EUS and whether other imaging modalities are required before embarking on EUS examinations. Part II focuses on technical details and controversies about the use of EUS in special situations. In this article, important practical issues regarding the application of contrast-enhanced EUS in various clinical settings are raised and controversially discussed from different points of view.

Key words: contrast agents, contrast enhacement, pancreas, guidelines

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INTRODUCTION AND REVIEW OF THE LITERATURE

The development of microbubble-based contrast agents together with technological advances and refinement in ultrasound technology has led to improved imaging of fine vascular structures and visualization of microflow patterns within target lesions. As a result, a fascinating and entirely new field in real-time ultrasound scanning was born. The principle of contrast-enhanced ultrasound imaging is to selectively depict signals arising from microbubbles of ultrasound contrast agents (UCAs) that resonate nonlinearly when exposed to ultrasonic beams. Under such conditions, background tissue signals are automatically subtracted, and only signals from the contrast agents are enhanced. UCAs remain within the intravascular compartment since the microbubbles do not exit blood vessels.[1-3] The mechanical index (MI) represents the ratio between the peak negative pressure amplitude and the square of the frequency and is related to an oscillation of the microbubbles.[4] Two ultrasound modalities are currently used for contrast-enhanced ultrasound scanning and differ in terms of using either high mechanical index (HMI) or low mechanical index (LMI). The former (HMI) modality uses color and/or power Doppler enhancement to depict vascular structures following contrast injection (contrast-enhanced Doppler EUS). The latter technique is based on the application of a specific contrast harmonic imaging software that depicts the macro- and microvasculature of scanned organs or lesions without the artifacts encountered with Doppler modes (contrast-enhanced EUS [CE-EUS]).[5-9] The terminology of contrast-enhanced EUS *vs.* contrast harmonic EUS has been widely discussed.[1,10-12]

Lesions of interest should be reported and documented in terms of their specific contrast enhancement by looking separately into the arterial phase and the venous phase over time. Thereby, the temporal behavior of signals can be assessed and compared with those signals arising from the surrounding tissues (non-, hypo-, iso- or hyperenhancement) and with its contrast distribution (*i.e.*, being homogenous or heterogeneous). Besides qualitative descriptions, the intensity of depicted contrast signals can be quantified by the calculation of time–intensity curves both during the wash-in and wash-out phases.[10,13] Several parameters can be calculated for further reviews such as peak enhancement, rise time, wash-in and wash-out rate, area under the curve, and others.[7]

Clinical applications include differential diagnosis of focal pancreatic masses and evaluation of acute and chronic pancreatitis, particularly complications associated with pancreatitis, assessment of cystic lesions, characterization of intraductal biliary/pancreatic filling defects, gallbladder lesions, subepithelial lesions (SEL), lymph node assessment, and others.[2,3,10,14,15] Differentiating mucous plugs from small neoplastic nodules in cystic pancreatic lesions represents a unique feature and advantage of this contrast-enhanced modality over other imaging techniques such as computed tomography (CT).

Three contrast agents such as "SonoVue/Lumason" (Bracco Imaging, Milan, Italy), "Definity" (Lantheus Medical Imaging, N Billerica, USA), and "Sonazoid" (Daiichi-Sankyo, Tokyo, Japan; GE Healthcare, Milwaukee, USA) are currently available. "Sonovue" contains microbubbles composed of sulfur hexafluoride gas enclosed in a lipid shell. After intravenous injection, the arterial phase occurs within 15–30 s before a venous phase starts approximately 30–45 s after injection. In contrast, another agent called "Sonazoid" (Daiichi-Sankyo, Tokyo, Japan) comprises perfluorobutane in a lipid shell and is taken up by Kupffer cells, thereby conferring a longer imaging duration than "Sonovue." However, "Sonazoid" is currently not available in Europe apart from Norway and Denmark.[4,10,11]

Focal pancreatic masses

Several studies and meta-analyses have shown that CE-EUS can differentiate the nature of solid pancreatic lesions, particularly pancreatic ductal adenocarcinoma (PDAC) that is typically hypoenhanced. In this regard, PDAC differs from other solid lesions such as neuroendocrine tumors (NETs), pancreatic metastases, or pseudotumoral (*i.e.*, mass forming) focal chronic pancreatitis,[16-19] since the latter three conditions typically present as iso- or hyperenhanced lesions at CE-EUS. A meta-analysis on CE-EUS studies that used both high and low MI techniques reported that CE-EUS had a sensitivity and specificity for the detection of PDAC of 94% and 89%, respectively.[16] Another meta-analysis of both the techniques including 18 eligible studies with 1668 patients showed a pooled sensitivity of 93% and a specificity of 88% of CE-EUS with an area under the receiver operating characteristic curve of 97%.[18] Contrast harmonic imaging allows the real-time depiction of microvessels and parenchymal perfusion without Doppler-related artifacts. A recently published meta-analysis focusing on the diagnostic

ability of CE-EUS to diagnose PDAC revealed pooled estimates of sensitivity and specificity of 93% and 80%, respectively.[19] A large multicenter trial that included 167 consecutive patients indicated that peak enhancement, wash-in area under the curve, wash-in rate, and the wash-in perfusion index significantly differed between patients with chronic pancreatitis and PDAC.[9] Furthermore, using a model of artificial neural networks for the parameters listed above, the authors found an increased sensitivity (94%), specificity (94%), positive predictive value (97%), and negative predictive value (90%) for CE-EUS in this setting. For tumors <20 mm in size, CE-EUS has been reported to be more accurate than contrast-enhanced multidetector CT (MDCT) imaging due to its higher spatial resolution.[20] In a Japanese study, the sensitivity of CE-EUS was 91.2%, while the corresponding sensitivity of contrast-enhanced MDCT imaging was only 70.6%.[21,22] Another Japanese study confirmed these data and showed superiority of CE-EUS in diagnosing early pancreatic cancer (≤20 mm) compared to MDCT and magnetic resonance imaging (MRI).[22] The clinical accuracy of CE-EUS for the diagnosis of PDAC *versus* non-PDAC lesions in pancreatic solid lesions <15 mm has been confirmed in a recent multicenter trial including 219 patients, indicating an overall 89% accuracy of CE-EUS.[20] Recently, time–intensity curve analysis has also been used with a high diagnostic accuracy of 91% to characterize focal pancreatic lesions.[23]

CE-EUS may distinctly impact subsequent clinical decision-making, particularly when applied in combination with EUS elastography, which is predominantly applied and helpful in cases with focal pancreatic masses and negative results of EUS-guided tissue acquisition (EUS-TA). Results from one prospective study involving 50 consecutive patients with negative EUS-TA suggest that sequential use of elastography and CE-EUS might form the basis for an effective imaging algorithm to be used in the diagnostic workup of focal pancreatic masses.[24] Contrast-enhanced EUS can be used for targeting EUS-fine-needle aspiration (FNA), which increases accuracy from 78% (based on core histology) to 87% (based on CE-EUS).[25] In a small study of 51 patients, CE-EUS-guided biopsy was shown to increase the accuracy of FNA from 78% to 87%, though this increase was not significant.[25] Similarly, CE-EUS may reduce the number of FNA passes needed to reach a diagnosis as compared to conventional EUS-FNA. These data are still limited due to a small number of patients.[26]

NETs represent up to approximately 10% of focal pancreatic solid masses.[27,28] The sensitivity of EUS for diagnosis and preoperative localization of pancreatic NETs is approximately 95%, which is higher than data from MDCT (81%). In addition, its performance is far better than the results of transcutaneous ultrasound (45%).[29] Furthermore, meta-analytic data have proven that EUS is the preferable imaging technique for the detection of pancreatic NETs.[30,31] Some case series have reported improved detection rates for NETs using CE-EUS. These studies showed iso-/hyperenhancement in the majority of NET cases in the early arterial phase,[32,33] suggesting that NETs can be discriminated from PDAC by their hypervascularization at the capillary level. The typical features of small NETs (<15 mm) can be easily visualized by EUS. Hypoechogenicity in B-mode and hyperenhancement during CE-EUS are the typical characteristics in >95% of small pancreatic NETs.[34,35] CE-EUS may also predict NET aggressiveness, as tumors with heterogeneous enhancement have fewer vessels and more fibrosis which are the features associated with more aggressive tumors.[36,37] As a result of the reported advantages above, CE-EUS is the imaging modality of choice to discriminate pancreatic NETs from PDAC at the first clinical assessment, particularly in the case of small tumors.

Acute and chronic pancreatitis

Acute pancreatitis can be classified as mild, moderate, or severe (necrotizing). The presence of pancreatic and peripancreatic necrosis and/or fluid collections is of utmost importance in determining further clinical course and prognosis. Chronic pancreatitis is frequently accompanied by complications such as chronic pain syndrome, fluid collections (pseudocysts), vascular complications (pseudoaneurysms, splenic vein thrombosis, etc.), and duodenal obstruction.[38] The role of EUS for therapeutic purposes in this setting (*i.e.*, local therapy of pancreatic cysts and fluid collections such as walled off pancreatic necrosis (WOPN)) has been reviewed elsewhere.[39]

As outlined previously, CE-EUS can be successfully used for evaluation and diagnostic workup of focal pancreatic masses.[40,41] Both mass-forming chronic pancreatitis and autoimmune pancreatitis present as hyperenhanced pseudotumors as opposed to the hypoenhanced lesions associated with pancreatic

adenocarcinoma.[42,43] Contrast enhancement can also be used to assess therapeutic response in the treatment of autoimmune pancreatitis.[44] Finally, the addition of contrast agents to EUS may aid the interpretation of vascular complications, even though the literature on this topic is limited to a few case series.[45]

Pancreatic cystic lesions

CE-EUS may aid the clinician in the evaluation of pancreatic pseudocysts and cystic neoplasms.[46,47] Based on a study that included 76 patients with pancreatic cystic lesions, assessment of cyst walls and septae was greatly improved using contrast enhancement. In this study, serous and mucinous cysts were frequently hyperenhanced, while pseudocysts were hypoenhanced in up to 90% of cases.[48] CE-EUS was also significantly more accurate than the standard EUS in diagnosing malignant cysts (84% *vs.* 64%).[49] A recent prospective study also showed superior accuracy of CE-EUS for the differentiation of malignant *vs.* benign cystic pancreatic lesions compared to MDCT and MRI.[50]

Differentiation of solid components within the cyst lumen is facilitated by CE-EUS since mucus clots and debris are typically nonenhancing, whereas hyperenhanced solid structures within cysts or at its margins may indicate solid neoplastic tissue that may harbor border-line lesions or malignancy. In particular, CE-EUS differentiates mural nodules from mucous clots with 100% sensitivity and 80% specificity[51] and can be used for risk assessment of intraductal papillary mucinous neoplasms (IPMN) of the pancreas.[52] In this setting, CE-EUS can guide FNA/FNB with a biopsy that is directed toward enhancing solid components in the cyst under constant visualization.

Based on these considerations, it is plausible that CE-EUS is very helpful for the assessment of pancreatic cystic lesions and should be applied to determine whether there are distinguishing characteristics of cystic neoplasms such as IPMN and mucinous cystic lesions, cystic PDAC, and/or cystic NETs, as compared to benign lesions (such as pseudocysts, dysontogenetic cysts, or serous cystic lesions).

Galbladder lesions

CE-EUS is useful for the differentiation between gallbladder lesions and sludge with a sensitivity, specificity, and accuracy that reaches 100%, 99%, and 99%, respectively. These numbers are higher than those observed with B-mode EUS imaging.[53] In addition, CE-EUS may yield additional information that aids in the diagnosis of gallbladder carcinoma with a sensitivity, specificity, and accuracy of up to 90%, 98%, and 96%, respectively.[53] CE-EUS criteria include thickened gallbladder wall, visualization of irregular vessels, and heterogeneous enhancement of wall structures.[53-55] Another study evaluating the ability of CE-EUS to diagnose malignant gallbladder wall thickening demonstrated a sensitivity, specificity, and accuracy of 90%, 98%, and 94%, respectively, with a relatively high interobserver agreement (k = 0.77).[56] Similar findings of irregular intratumoral vessels and heterogeneous perfusion defects were used as outcome parameters to increase the sensitivity and specificity for the diagnosis of malignant gallbladder polyps up to 93% and 91%, respectively.[55] In three studies, CE-EUS proved to be significantly more accurate than B-mode EUS for the diagnosis of gallbladder cancer.[53,54,56] CE-EUS has been used to support differential diagnosis of gallbladder adenomas from more benign lesions such as cholesterol polyps. However, the sensitivity and specificity of CE-EUS were quite low in this study.[57] CE-EUS has been also used in parasitosis.[58-60]

Subepithelial lesions

Although the number of clinical studies evaluating CE-EUS in the diagnosis of SEL is on the rise, direct comparison of data remains difficult due to differences in the use of echo-endoscopes, processors, contrast agents (Sonovue *vs.* Sonazoid), and MI. Nevertheless, a recent meta-analysis has shown that CE-EUS can be useful to discriminate benign SEL from gastrointestinal stromal tumour (GIST).[61,62] Hyperenhancement of SEL can be considered a typical feature favoring the diagnosis of a GIST with a sensitivity and specificity ranging from 85% to 100% and from 79% to 100%, respectively. In a study on 73 patients undergoing resection, the sensitivity and specificity of hyperenhancement were found to be 84.5% and 73.3%, respectively.[63] Another retrospective study showed hypervascularity together with a low long-to-short axis ratio to be independent predictors of a diagnosis of GIST.[64] While assessing the malignant potential of SEL, the presence of irregular intratumoral vessels has been suggested to be predictive of high-grade GISTs, with a sensitivity and specificity ranging from 54% to 100% and from 63% to 100%.[61-63,65,66] Furthermore, intensity-curve analysis may be of value in discriminating the malignancy risk of SELs.[67] In conclusion, the results of a few preliminary

studies suggest that CE-EUS can successfully visualize the microvascularization of SEL in great detail. This feature may improve the ability and clinical usefulness of EUS to differentiate SEL and predict the malignant potential of GIST. However, further prospective comparison studies are needed to establish more objective and reproducible criteria of the microvascularity of SELs.

Lymph nodes

Differentiating benign from malignant lymphadenopathy is crucial in the management and assessment of prognosis in patients with various tumors. Enlarged mediastinal or abdominal lymph nodes are often assessed using the standard EUS-based criteria such as size, shape, border, echogenicity, vascular pattern,[2,40,68-74] and distance from the primary tumor, but the accuracy of this approach is low.[75] The results of studies using CE-EUS to determine the nature of obscure lymphadenopathy are conflicting. In a recent meta-analysis of contrast-enhanced and CE-EUS assessment of lymphadenopathy that included four studies and 336 patients, the pooled calculated sensitivity and specificity were 82.1% (75.1%–87.7%) and 90.7% (85.9%–94.3%), respectively. Subgroup analysis including studies performing only CE-EUS revealed better results with a pooled sensitivity of 87.7% (77.0%–93.9%) and pooled specificity of 91.8% (84.5%–96.4%), rates that are similar to the diagnostic performance of EUS-FNA.[76]

Primary liver tumors and liver metastasis

It is well known that contrast-enhanced ultrasound (CEUS) is an accurate and cost-effective tool for characterizing focal hepatic lesions, and it sometimes outperforms CT and MRI in terms of diagnostic performance when dealing with small liver tumors.[77,78] In this perspective, EUS may have an important role when staging pancreatic cancer with very small liver metastasis, and it may also influence hepatocellular cancer staging.[79,80]

DO WE NEED CONTRAST AGENTS FOR EUS? THE ANSWER IS "YES"!

Routine use of CE-EUS should be encouraged as it offers complementary information over grayscale and elastographic imaging results.[81,82] The procedure is safe and carries a negligible risk of adverse events to patients. As UCAs are not excreted through the kidneys, they can be safely administered to patients with renal insufficiency.[10] Furthermore, no tests are necessary prior to CE-EUS examination, and UCAs do not appear to adversely affect thyroid function. The rate of anaphylactic reactions is less than that for iodinated computer tomography (CT) agents and similar to that of gadolinium-based contrast agents used for MRI.[15,83,84] Serious anaphylactic reactions were observed only in 1/10,000 patients.[85] The technique is minimally invasive and offers complementary information to B-mode EUS that can be used for characterization, differential diagnosis, and/or staging. CE-EUS provides information on both the macro- and microvasculature of the lesions, as well as, the relationship with the surrounding vessels, which are better depicted after contrast enhancement.

CE-EUS is recommended by the latest EFSUMB guidelines for the differential diagnosis of solid pancreatic lesions, clinical staging of pancreatic adenocarcinoma, characterization of pancreatic cystic neoplasms, gallbladder lesions, lymph nodes, and gastrointestinal wall lesions and assessment of visceral vascular diseases.[10] Moreover, CE-EUS seems to be superior to state-of-the-art MDCT for the differential diagnosis of PDAC and chronic pancreatitis.[42,86] The technique is also useful for the characterization of NETs as hyperenhanced masses compared to hypoenhanced PDAC. Moreover, decreased microvascular density (*i.e.*, characterized as heterogeneous enhancement in the early arterial phase) could represent a sign of enhanced malignancy.[36]

CE-EUS-targeted FNA can be used to increase the accuracy of diagnosis in focal pancreatic masses, although it has to be validated by larger multicenter trials.[25] Contrast enhancement is clearly useful for evaluating intracystic mural nodules and for differentiating between pseudocysts and cystic neoplasms, as well as between benign and malignant cysts, although it cannot differentiate serous from mucinous lesions.[48]

DO WE NEED CONTRAST AGENTS FOR EUS – IS THERE ANY CLEAR "NO"?

Performing CE-EUS may extend examination time. However, the total contrast examination lasts only few minutes once the learning curve has been overcome. There are still remaining problems with quantification of CE-EUS (time–intensity curve analysis) with different studies indicating various parameters that

may be useful to differentiate PDAC. These include peak enhancement, intensity at 60 s, time to peak, wash-in area under the curve, wash-in rate, and wash-in perfusion index.[9,87] Hence, further research is warranted to elucidate the clinical role of these parameters.

Costs of UCAs are similar to contrast agents used for CT but less expensive than MR contrast agents; however, the utility of contrast agents in cross-sectional imaging is fully established. CE-EUS is not required for every case in routine clinical practice; for instance, the diagnostic performance of EUS FNA/FNB in pancreatic masses is very high and a role for CE-EUS at index procedure is as yet unproven. There are no cost-effectiveness studies related to the utilization of CE-EUS as an additional technique to grayscale examinations, as supplementary costs are essentially solely related to equipment and consumables (SonoVue/Lumason). The only study regarding costs of CEUS for the characterization of focal liver lesions is a recent systematic review. This study showed that CEUS was a cost-effective replacement for contrast-enhanced MRI and even for contrast-enhanced CT, in particular clinical applications.[88]

CONCLUSIONS

CE-EUS has evolved as a useful clinical imaging tool that facilitates the diagnosis in many patients undergoing EUS. Tissue-based diagnosis still remains the "gold standard" of diagnosis against which any diagnostic modality must be measured. The range of clinical applications of CE-EUS is wide and includes characterization and differential diagnosis of solid pancreatic masses, cystic pancreatic lesions, evaluation of acute and chronic pancreatitis (plus sequelae), metastatic lesions, subepithelial lesions, unspecified tumors, vascular involvement, and a growing number of other clinical scenarios. Expertise should be pursued and achieved by all EUS practitioners to apply the full potential of this valuable modality to all patients in the aforementioned clinical settings. Further technical refinements and novel substances are likely to improve its diagnostic potential in the near future.

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There are no conflicts of interest.

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