Contrast-enhanced endoscopic ultrasound (CE-EUS) is a tool used to enhance the endoscopic ultrasound evaluation of lymph nodes, solid pancreatic lesions, pancreatic cystic neoplasms, pancreatitis, gallbladder lesions, gastrointestinal wall lesions, and small liver lesions. This article discusses general principles of CE-EUS, indications for CE-EUS, and the relative value of CE-EUS compared to conventional EUS.

INTRODUCTION

CE-EUS is a noninvasive diagnostic technique that allows endoscopists to better visualize certain lesions and more accurately distinguish between benign and malignant masses. Some studies have shown that CE-EUS has advantages over conventional EUS and other imaging modalities. The addition of contrast to EUS has not been widely adopted in the USA, but it has been utilized more frequently in recent years, allowing for more widely available data to assess its ability to expand the diagnostic capabilities of EUS. CE-EUS has potential utility in many clinical scenarios; studies have described its use in the evaluation of lymph nodes, solid pancreatic lesions, pancreatic cystic neoplasms, pancreatitis, gallbladder lesions, gastrointestinal wall lesions, and small liver lesions.

General Principles of Ultrasound and Contrast

CE-EUS is an advanced endoscopic technique that combines high-resolution ultrasound of internal organs with the administration of intravenous contrast agents. Unlike the iodinated contrast used in CT imaging, microbubbles of air or gases make up the contrast medium used in ultrasound. Microbubbles of air allow for enhancement on ultrasound due to the change in resistance at the tissue-fluid-gas interfaces. This contrast is distributed intravascularly, which improves identification and enhancement of blood vessels and microcirculation. (Figure 1.) EUS contrast agents are different from CT or MR contrast agents in that the contrast does not leave the intravascular space. The size and distribution of the microbubbles improve visualization of tumor microcirculation. This is useful to endoscopists as
the unique vascularization behaviors exhibited by inflammatory lesions, necrosis, and malignancy are distinguishable by CE-EUS. The duration of enhancement after a bolus injection of contrast varies among contrast agents, but is typically two to ten minutes.

CE-EUS procedures do not require radiation. Beyond this, another potential advantage of CE-EUS over CT and MRI include improved real-time imaging of fine vascular structures and visualization of microflow patterns within lesions, allowing endoscopists to more accurately distinguish between inflammatory lesions and malignant ones. Critically, CE-EUS can also be performed without obtaining screening bloodwork or concern for poor renal function.

This review provides endoscopists with the basic knowledge regarding the clinical applications of and indications for CE-EUS as well as the advantages and disadvantages of CE-EUS.

### Applications of CE-EUS

CE-EUS may be utilized as a diagnostic tool in examining lymph nodes, cystic pancreatic lesions, solid pancreatic masses, acute and chronic pancreatitis, sequelae of pancreatitis, gallbladder lesions, subepithelial lesions, and small liver lesions. CE-EUS is particularly useful in distinguishing cystic and neoplastic lesions from other pathologies.

#### Lymph nodes

Accurate and timely diagnosis of the presence of malignant adenopathy is important as it affects subsequent management and patient outcomes. EUS is often used to evaluate mediastinal, abdominal, and pelvic lymph nodes. Based on size, shape, borders, architecture, echogenicity, vascular pattern, and distance of lymph nodes from the neoplasia, clinicians can make some assessment as to whether the lymph node is of malignant or benign etiology. Patients with malignant adenopathy have lymph nodes that are rounder, darker, larger, closer to the primary tumor, and more homogeneous than those of patients without malignant adenopathy. The presence of at least one lymph node of one cm or greater within one cm of the tumor and with a morphology score, calculated based on the sum of roundness, homogeneity, and echogenicity, of 14 or greater had a positive predictive value for malignant adenopathy of 81%.

One study showed that no single morphologic feature of the lymph node independently predicted malignant invasion. If all four features of malignant involvement (size greater than one cm, hypoechoic, distinct margins, and round shape) were present in the same lymph node, the accuracy for predicting malignant invasion was 80%; however, all four features were only present in 25% of malignant lymph nodes, allowing for confident differentiation between malignant and benign etiology in about 25% of cases. Accuracy of diagnosis is improved when EUS is complimented by fine needle aspiration (FNA) or fine needle biopsy (FNB).

While EUS is useful in the evaluation of adenopathy, it is difficult to diagnose lymph node metastasis with EUS images alone. Kanamori et al. evaluated benign and malignant mediastinal and abdominal lymph nodes with CE-EUS based on blood flow patterns. In the retrospective portion of the study, EUS revealed lymph nodes (22 benign, 24 malignant) in the mediastinum or abdominal cavity in 46 patients. The sensitivity, specificity, and accuracy rate for detecting malignancy based on the morphologic classification in this particular study were 88.2%, 77.3%, and 82.1%, respectively. In all 24 patients with malignant adenopathy, an

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enhancement defect was observed on CE-EUS. During the prospective portion of the study, authors evaluated the enhancement effects and diagnostic capabilities of CE-EUS in the same 46 patients; the sensitivity, specificity, and accuracy rate of CE-EUS were 100%, 81.8%, and 92.0%, respectively. Authors concluded that CE-EUS is a useful diagnostic tool in differentiating benign and malignant adenopathy.

Other investigations failed to recommend CE-EUS as a diagnostic tool for lymphadenopathy. Lisotti et al. conducted a meta-analysis to examine the diagnostic accuracy of CE-EUS in distinguishing between benign and malignant lymphadenopathy and ultimately concluded that CE-EUS had inadequate sensitivity. However, the investigators did find that contrast harmonic-EUS (CH-EUS) may be useful for diagnostic purposes based on sensitivity and specificity. Harmonic ultrasonic imaging is a novel method that produces images based on non-linear (a term to describe the response of a system to the applied echo-signal) acoustic effects of ultrasound interactions with tissues or microbubble contrast agents.

**Pancreas**

**Pancreatitis**

The specificity of differentiation between malignant and benign lesions of the pancreas in patients with chronic pancreatitis is variable with a wide range reported (33%-75%), but studies have shown that perfusion characteristics of microvessels as seen on CE-EUS may provide clinicians with a more useful method to differentiate between pancreatic carcinoma and chronic pancreatitis. In one study, investigators compared conventional EUS to CE-EUS in evaluating possible pancreatic carcinoma in 86 patients with pancreatitis. With conventional EUS, study investigators reported a sensitivity and specificity of 73.2% and 83.3%, respectively, for pancreatic carcinoma. With CE-EUS, sensitivity and specificity improved to 91.1% (in 51 of 56 patients with malignant pancreatic lesion) and 93.3% (in 28 of 30 patients with chronic inflammatory pancreatic disease), respectively. While pancreatic carcinoma appears as a hypo-enhanced lesion, mass-forming chronic pancreatitis (as well as autoimmune pancreatitis) present as hyper-enhanced pseudotumors. The investigators concluded that CE-EUS does improve differentiation between pancreatic carcinoma and chronic pancreatitis in comparison to conventional EUS.

CE-EUS has been shown to be an effective imaging method to differentiate between pancreatic carcinoma and autoimmune pancreatitis, which is recognized to be a difficult distinction to make. In a study by Hocke et al., with the exception of one patient (who showed a normal vascularization pattern), all lesions caused by autoimmune pancreatitis showed hypervascularization while lesions caused by pancreatic cancer showed hypovascularization. (Figure 2.) While only case studies exist, CE-EUS may also allow clinicians to depict and interpret vascular complications associated with pancreatitis more accurately. CH-EUS may even be beneficial in evaluating the therapeutic response to steroids in the treatment of immunoglobulin G4-negative focal autoimmune pancreatitis.

**Pancreatic solid tumors**

CE-EUS has been shown to be a useful diagnostic method in identifying pancreatic masses. Specifically, CE-EUS has been shown to be effective in differentiating small solid pancreatic tumors. Dietrich et al. prospectively evaluated the role of contrast-enhanced endoscopic Doppler ultrasound (CE-EDUS) in the characterization
and differentiation of solid pancreatic tumors. Investigators compared the vascular pattern of the pancreatic lesions during the arterial phase with the vascularity of the residual pancreatic parenchyma in 93 patients with undetermined, solitary, predominantly solid, lesions ≤40 mm, and a definite histologically proven diagnosis. In 57 of 62 patients with adenocarcinoma, hypovascularity of the tumor was noted using CE-EDUS while all other pancreatic lesions (20 neuroendocrine tumors, ten serous microcystic adenomas, and one teratoma) revealed an isovascular or hypervascular pattern. Investigators concluded that the hypovascularity of pancreatic tumors using CE-EUS indicates malignancy with 92% sensitivity and 100% specificity.

Cystic lesions of the pancreas
Some cystic pancreatic lesions carry an elevated risk of malignancy, including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). Differentiating mural nodules from mucous clots or even simple intracystic debris in IPMNs is useful as mural nodules within a cyst and main duct involvement suggest an increased potential for underlying malignancy; however, this can be difficult to assess with conventional EUS which has high sensitivity, but poor specificity. Yamashita et al. and Harima et al. have shown that specificity is greater with the addition of contrast. CE-EUS with utilization of Doppler and/or harmonic modes can raise the specificity even more. CE-EUS shows no vascularity in mural clots, but does show vascularity in mural nodules. CE-EUS is useful in evaluating the malignant potential of IPMNs. Most pancreatic cancers appear as solid lesions with hypoenhancement on CE-EUS. While CE-EUS has similar sensitivity to that of conventional EUS in identifying mural nodules, the specificity of CE-EUS for the evaluation of these mural nodules is nearly double that seen with conventional EUS, likely due to the improved analysis of vascularity patterns. Kamata et al. reported that endoscopists identified mural nodules more accurately through CE-EUS as compared to conventional EUS, providing sensitivity and specificity values of 97% and 75%, respectively, for CE-EUS and 97% and 40%, respectively, for conventional EUS.

Biliary tract
Studies have demonstrated that CE-EUS is useful in differentiating infiltrating and exophytic carcinoma of the gallbladder from benign gallbladder pathologies including chronic cholecystitis and cholesterol polyps, the latter two of which show an intact three-layer structure on imaging. Adenosquamous carcinoma, cholesterol polyps and chronic cholecystitis do not enhance with
EUS upon administration of EUS contrast agents, while most adenocarcinomas of the gallbladder do. CE-EUS can also distinguish neoplasia of the gallbladder from sludge (which does not enhance). Typically, carcinomas of the gallbladder show hyperenhancement during the arterial phase and hypoenhancement during the venous phase. CE-EUS allows for visualization of the depth of invasion in the gallbladder wall which can differentiate T1b from T1a lesions. CE-EUS may also be useful in assessing complications of acute cholecystitis; perforation may be suspected if there is no enhancement of the gallbladder wall.

Differentiating between cholesterol polyps and adenomas is of particular importance; while cholesterol polyps are benign and do not require resection, adenomas may transform into malignant lesions. In one study, the sensitivity and specificity of CH-EUS in making this distinction was low: 75% and 67%, respectively. However, to increase the diagnostic accuracy of CH-EUS in this scenario, the study investigators applied a quantitative perfusion analysis and only assessed the malignant potential of gallbladder polyps larger than ten mm given that gallbladder polyps less than ten mm are typically managed through observation. When accounting for perfusion defects and considering the presence of irregular vessels as predictors of malignancy, the sensitivity and specificity of CH-EUS in diagnosing malignant polyps were 94% and 93%, respectively.

The sensitivity, specificity, and accuracy of CE-EUS in the diagnosis of carcinoma of the gallbladder has been reported as high as 90%, 98%, and 96%, respectively. In a study using CE-EUS to diagnose carcinoma of the gallbladder, investigators assessed gallbladder wall thickening, noting a sensitivity, specificity, and accuracy of 90%, 98%, and 94%, respectively. In another study using CE-EUS to diagnose carcinoma of the gallbladder, investigators used irregular intratumoral vessels and heterogeneous perfusion defects as outcome parameters, and demonstrated high sensitivity and specificity, 93% and 91%, respectively.

Subepithelial Lesions (SEL)

Endoscopists can visualize the microvasculature of SELs in greater detail through CE-EUS. Gastrointestinal stromal tumors (GIST) often demonstrate arterial hyperenhancement and central necrosis, which is typically not displayed in other subepithelial lesions, so CE-EUS may be helpful in distinguishing GISTs from benign SEL. The sensitivity and specificity for the hyperenhancement of GISTs ranges from 85% to 100% and from 79% to 100%, respectively. In predicting likelihood of high-grade GISTs specifically, investigators have assessed for the presence of irregular intratumoral vessels, citing a much broader range for sensitivity and specificity - from 54% to 100% and from 63% to 100%, respectively.

Liver

When evaluating patients with liver disease, CE-EUS may help to diagnose small liver lesions and be useful for targeting tissue sampling, but in general, the utility of CE-EUS in these scenarios is limited as EUS is unable to visualize the entire liver, with portions of the right lobe being very hard to clearly identify. Despite this limitation, CE-EUS still offers advantages in examination of the liver during the late phase of contrast-enhancement; this makes it particularly useful during biopsies requiring direct guidance of the needle when lesions are poorly visualized with conventional gray-scale ultrasound. Despite the need for more research, it is thought that adding contrast to EUS, allowing for improved visualization of the microvasculature and tumor architecture, does help endoscopists to better differentiate between malignant and benign lesions in the liver.

Oh et al. conducted a study comparing the use of CE-EUS and traditional EUS in the diagnosis of hepatic masses in 30 patients. The authors found that 73.3% of hepatic masses were visible by traditional EUS. With CE-EUS, 93.3% of hepatic masses were visible and able to be distinguished from the surrounding liver parenchyma. Authors concluded that the addition of contrast improved diagnostic accuracy. In another study, Minaga et al. demonstrated that there is an additive role of CE-EUS (to traditional EUS or multidetector CT scan) in the identification of metastasis of pancreatic adenocarcinoma to the liver. They found that CE-EUS was associated with a significantly higher detection rate of left-lobe metastasis; the diagnostic (continued on page 40)
accuracy of CE-EUS was 98.5% compared to 91.1% for traditional EUS and 90.5% for CT scans. Additionally, tissue obtained via CE-EUS resulted in improved diagnostic accuracy, including for lesions less than one cm in diameter.

Overall Value Assessment and Conclusion
It is important to note that CE-EUS is to some extent dependent on the operator’s skill and experience. Ultimately, CE-EUS is a tool that facilitates decision making and offers additional and complementary information beyond what conventional EUS can provide - with minimal risk to the patient. The addition of contrast has the potential to help clinicians delineate benign from malignant pathology, guide therapeutic procedures, and better characterize vasculature.

Ultrasound contrast agents have an excellent safety profile, and the incidence of patients having a major adverse event in response to contrast is similar to that of MR contrast agents and lower than that of CT contrast agents. Additionally, CE-EUS can be performed on patients who have not had labs prior to the procedure since ultrasound contrast agents are not cardio-, hepato-, or nephro-toxic.

Future studies comparing the diagnostic capabilities and financial burden of traditional EUS and CE-EUS in specific clinical scenarios will help to better determine the role of this modality in clinical practice. From a time consideration, the procedure is only minimally extended with the addition of EUS contrast agents, although depending on the operator’s experience, the time (and accuracy) of his or her interpretation of the imaging study will vary.

The value of contrast agents in enhancing diagnostic accuracy in EUS in certain clinical scenarios is well-established. We conclude that CE-EUS is a low-risk, complementary imaging study in many clinical scenarios as described previously. While CE-EUS is not critical to performing EUS, given its safety profile and potential benefit, it should be considered if available.

References


