

# The role of contrast-enhanced endoscopic ultrasound in pancreatic adenocarcinoma

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## ABSTRACT

Contrast-enhanced endoscopic ultrasound (CE-EUS) allows characterization, differentiation, and staging of focal pancreatic masses. The method has a high sensitivity and specificity for the diagnosis of pancreatic adenocarcinoma which is visualized as hypo-enhanced as compared to the rest of the parenchyma while chronic pancreatitis and neuroendocrine tumors are generally either iso-enhanced or hyper-enhanced. The development of contrast-enhanced low mechanical index harmonic imaging techniques used in real time during endoscopic ultrasound (EUS) allowed perfusion imaging and the quantification of intensity of the contrast signal through time-intensity curve analysis. Thus, contrast harmonic imaging-EUS has been used to differentiate pancreatic adenocarcinoma based on lower values of the peak enhancement. Future applications of CE-EUS in pancreatic adenocarcinoma include not only use of targeted contrast agents for early detection, tridimensional and fusion techniques for enhanced staging and resectability assessment but also novel applications of perfusion imaging for monitoring ablative therapy, improved local detection through EUS-guided sampling of portal vein flow or enhanced drug delivery through sonoporation and ultrasound-induced release of the drugs locally.

**Key words:** Contrast harmonic imaging, endoscopic ultrasound, pancreatic adenocarcinoma

## INTRODUCTION

Contrast-enhanced endoscopic ultrasound (CE-EUS) is a new method which allows enhanced characterization, differential diagnosis, and accurate staging of focal pancreatic masses.<sup>[1-5]</sup> The method has a high sensitivity and specificity for the diagnosis of pancreatic adenocarcinoma, with pooled values of 0.89 and 0.84 in a recent meta-analysis that included both transabdominal ultrasound and endoscopic

ultrasound (EUS) approaches.<sup>[6]</sup> Thus, masses visualized as hypovascular, hypo-enhanced as compared to the rest of the pancreatic parenchyma can be correctly classified as pancreatic adenocarcinomas, even in the case of false negative EUS-guided fine-needle aspiration (EUS-FNA).<sup>[7]</sup> CE-EUS enhances the grayscale images and allows targeting of aspiration procedures while it

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also has an incremental effect on diagnostic accuracy when used in conjunction with EUS-FNA.<sup>[8,9]</sup>

A large amount of data currently supports the use of contrast-enhancement as a standard of care for ultrasound pancreatic examinations.<sup>[10]</sup> Both high and low mechanical index (MI) techniques of contrast-enhancement have been used, and the results have been analyzed in a recent meta-analysis that indicated a pooled sensitivity of 94% and pooled specificity of 89% for the diagnosis of pancreatic adenocarcinoma.<sup>[11]</sup> Quantitative analysis by means of time-intensity curves (TICs) has also highlighted the importance of the peak enhancement (maximum intensity), which helps to differentiate between chronic pancreatitis and pancreatic adenocarcinoma.<sup>[12,13]</sup> Moreover, there are correlations in between TIC analysis parameters and histopathological variables, such as microvascular density (MVD) detected by CD34 staining.<sup>[14]</sup> Thus, although most of the pancreatic adenocarcinomas (88.4%) are hypo-enhanced as compared to the pancreatic parenchyma, the peak enhancement (maximum intensity) seems to correlate with MVD and can be further used as a surrogate marker of blood perfusion.

## EXAMINATION TECHNIQUE

The technique for CE-EUS has been described in detail in other articles, and in principle, it is similar to transabdominal CEUS<sup>[1]</sup> as stressed in the EFSUMB guidelines and recommendations on the use of contrast in nonliver applications.<sup>[15]</sup> Briefly, a second-generation microbubble ultrasound contrast agent (UCA) is injected peripherally; due to the small size (2–10  $\mu\text{m}$ ), they reach the entire vascular system, effectively enhancing the backscattered ultrasound signals.<sup>[2]</sup> High MI examinations were used initially, with contrast used as an effective signal enhancer for either color Doppler or power Doppler.<sup>[16]</sup> Similar to transabdominal applications, low MI examinations based on the second harmonic imaging algorithms were slowly developed and became commercially available to support contrast harmonic imaging (CHI) in real time during EUS.<sup>[17,18]</sup>

One of the advantages of CHI-EUS examinations based on low MI algorithms is the absence of motion and blooming artifacts as the contrast induces a specific signal and is restricted to the vascular system (blood pool UCAs).<sup>[2]</sup> Moreover, the intensity

of the contrast signal can be quantified by calculation of time-related intensity values of the wash-in and wash-out phases, with fitting of the values based on mathematical models.<sup>[19]</sup> Thus, a series of parameters can be estimated based on TIC analysis, such as peak enhancement (maximum intensity), rise time, wash-in and wash-out rate, and area under the curve.<sup>[20,21]</sup> Both techniques (low and high MI) can easily be combined in the same examination using a sequential approach based on the long persistence of the enhancing effect of microbubbles [Figure 1a and b].

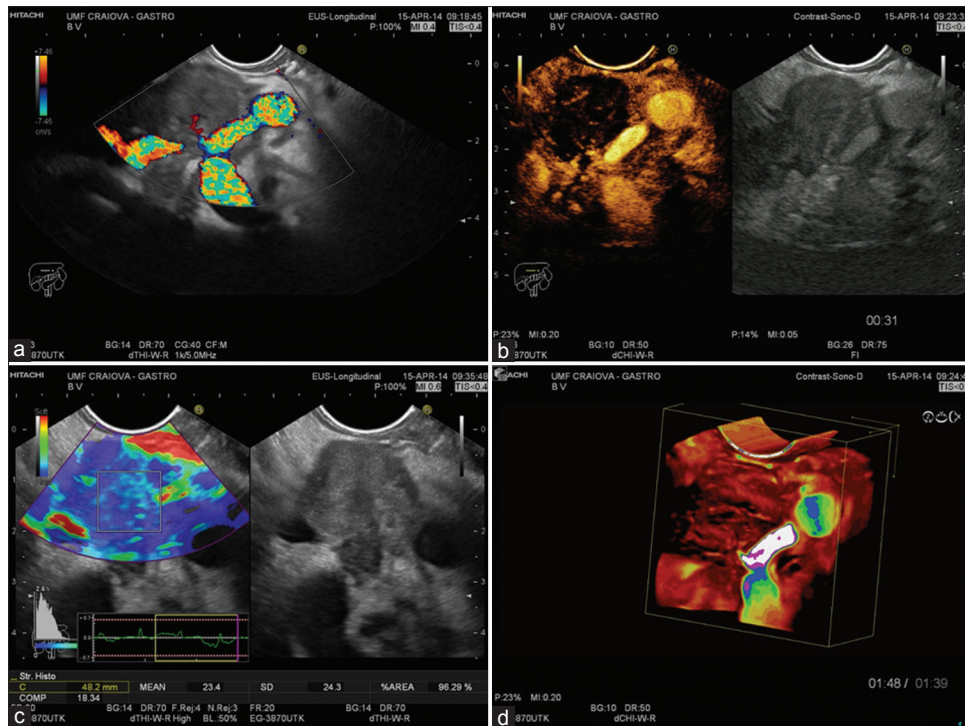
## CLINICAL APPLICATIONS

The value of contrast enhancement for the differential diagnosis between pancreatic cancer and chronic pancreatitis has been analyzed in a recent meta-analysis that combined the results of both transabdominal and EUS papers.<sup>[6]</sup> For the primary objective of the meta-analysis, the pooled sensitivity and specificity for the diagnosis of ductal adenocarcinoma based on the hypovascular, hypo-enhanced appearance were 89% and 84%, respectively. The secondary objective was to distinguish neoplastic and nonneoplastic lesions, where the sensitivity and specificity were 95% and 72%.

Looking specifically at EUS, a recent meta-analysis indicated that both high and low MI techniques are useful for the differential diagnosis of pancreatic adenocarcinoma, yielding a pooled sensitivity of 94% and a pooled specificity of 89%. The area under the receiver operating characteristic curve (AUROC) was 0.9732.<sup>[11]</sup> Exclusion of the earlier studies leads to a sensitivity and specificity of 93% and 93%, respectively, with an AUROC of 0.9745.

Our data retrieved from a multicenter trial of quantitative CHI-EUS showed that TIC analysis is helpful for the differential diagnosis of pancreatic adenocarcinoma.<sup>[12]</sup> Thus, the peak enhancement and the area under the curve have significantly lower values as compared to the surrounding normal parenchyma. Contrast-enhanced-guided FNA can be further performed not only to target hypo-enhanced, hypovascular areas but also to avoid necrotic and unenhanced avascular areas.<sup>[9]</sup>

The most important clinical application for CE-EUS is for the patients with negative EUS-FNA procedures. Thus, contrast-enhanced power Doppler imaging EUS



**Figure 1.** (a) Contrast-enhanced color Doppler imaging endoscopic ultrasound using a high mechanical index (0.4) showing hypoechoic pancreatic tumor mass which was completely encasing the celiac trunk at the bifurcation, with encasement also of the splenic and hepatic arteries. (b) Contrast-enhanced endoscopic ultrasound using a specific contrast harmonic imaging mode with a low mechanical index (0.2) showing the same hypoechoic appearance, with scarce vessels inside the tumor as compared to the surrounding pancreatic parenchyma and structures. The mass was completely encasing the celiac trunk at the bifurcation, with encasement also of the splenic and hepatic arteries. (c) Real-time elastography endoscopic ultrasound showing a hard tumor with low values of the strain histogram analysis indicating a low-strain mass, highly suspicious of a pancreatic adenocarcinoma, even in the presence of negative or inconclusive endoscopic ultrasound fine-needle aspiration. (d) Tridimensional reconstruction of contrast-enhanced endoscopic ultrasound performed with low mechanical index in a contrast harmonic imaging specific mode, showing the relationship between the tumor and the celiac trunk at its bifurcation

combined with real-time sonoelastography has a high positive predictive value for the diagnosis of pancreatic adenocarcinoma, of over 95%, even for the patients with negative or inconclusive EUS-FNA and a strong suspicion of pancreatic adenocarcinoma [Figure 1c]. Furthermore, low MI examinations with CHI modules have a similar positive predictive value (over 95%) while the sequential usage of real-time elastography followed by CHI-EUS leads to a very high specificity (reaching 100%) in the setting of negative EUS-FNA and could consequently be used for the differential diagnosis of focal pancreatic masses.<sup>[22]</sup>

Improved staging can be achieved through a better depiction of the surrounding vasculature based on low MI contrast-enhanced harmonic EUS examinations.<sup>[23]</sup> Contrast enhancement leads to significantly improved tumor (T) staging as compared to EUS only, with an accuracy of 92% as compared to 69%.<sup>[24]</sup> Moreover, the vessels' outlines are better depicted when using CHI-EUS, thus yielding important information for the definition of resectability as well.

## PERSPECTIVES

So far, CHI-EUS has been used for the differential diagnosis of focal pancreatic masses, but applications designed to improve the accuracy of early diagnosis and screening of high-risk cancer would be desirable.<sup>[23]</sup> Preclinical usage of targeted UCAs has been described to improve detection of early cancer, based on usage of VEGFR2-targeted microbubble contrast agents, showing increased signal intensity in smaller tumors as compared to control tissues.<sup>[25]</sup> Nevertheless, these preliminary data need to be translated to human patients as pancreatic adenocarcinoma behaves in most of the cases (over 90%) as a hypovascular tumor due to the intense desmoplastic reaction. These hypoxic areas could be tentatively reduced through vascular normalization (i.e., an increase in vascularized area, as well as oxygen and nutrient delivery), with a subsequent reduction of factors promoting cancer stem cells and drug resistance.<sup>[26]</sup> These tumor microvascular changes can easily be monitored longitudinally in real time by CHI-EUS, leading to a better follow-up of the patients

during therapy. Furthermore, usage of CE-EUS for early detection and identification of precursors such as pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, and mucinous cystic neoplasms might improve the current methodology of pancreatic cancer screening.

Enhanced staging and evaluation of resectability are desirable in locally advanced and borderline resectable pancreatic adenocarcinoma as computed tomography (CT), magnetic resonance (MR), and/or EUS still have significant room for improvement.<sup>[27]</sup> Progress in tridimensional ultrasound could enhance staging of pancreatic cancer [Figure 1d],<sup>[28]</sup> especially in the setting of real-time four-dimensional technologies and/or fusion imaging with PET-CT/MR.<sup>[29,30]</sup>

Assessment of perfusion based on CHI-EUS is helpful to predict efficacy of chemotherapy in pancreatic cancer as the presence of vessels indicates a better progression-free survival and overall survival.<sup>[31]</sup> Contrast-enhanced EUS can also be used in the assessment of the results of ablative therapy, either by ethanol ablation or by radiofrequency ablation.<sup>[32]</sup> Evaluation of tumor perfusion and vascularity pre- and post-ablation therapy is especially useful in the case of hypervascular tumors, for the evaluation of lack of enhanced (perfused) areas after successful treatment. EUS-guided sampling of the portal vein flow has been actually proposed to detect circulating tumor cells, with the aim of better selecting patients for chemotherapy or local resections.<sup>[33]</sup> Local delivery of cytotoxic or even magnetic nanoparticles, based on EUS-guided portal vein injections, has also been envisaged in advanced pancreatic adenocarcinoma with liver metastases.<sup>[34]</sup>

An interesting concept is that sonoporation (the use of ultrasound to enhance the permeability of cell plasma membranes) might increase local delivery of chemotherapy in pancreatic adenocarcinoma as it has been shown in preclinical studies based on an orthotopic xenograft mouse model of pancreatic cancer and sonoporation after gemcitabine administration.<sup>[35]</sup> Targeted therapy approaches can also use microbubble UCAs which can release drugs at the target site.<sup>[36]</sup> One such example is the regression of orthotopic pancreatic tumors after paclitaxel nanoemulsions combined with ultrasound induced release of the drug at tumor levels.<sup>[37]</sup> Translation of these preclinical data into clinical studies will clarify the potential usage of targeted ultrasound approaches.

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### Conflicts of interest

There are no conflicts of interest.

### REFERENCES

1. Saftoiu A, Dietrich CF, Vilmann P. Contrast-enhanced harmonic endoscopic ultrasound. *Endoscopy* 2012;44:612-7.
2. Reddy NK, Ioncica AM, Saftoiu A, et al. Contrast-enhanced endoscopic ultrasonography. *World J Gastroenterol* 2011;17:42-8.
3. Kwek BE, Ang TL, Seo DW, et al. Contrast-enhanced harmonic endoscopic ultrasonography of solid pancreatic lesions. *Endosc Ultrasonol* 2013;2:142-7.
4. Alvarez-Sánchez MV, Napoléon B. Contrast-enhanced harmonic endoscopic ultrasound imaging: Basic principles, present situation and future perspectives. *World J Gastroenterol* 2014;20:15549-63.
5. Kitano M, Kamata K, Imai H, et al. Contrast-enhanced harmonic endoscopic ultrasonography for pancreatobiliary diseases. *Dig Endosc* 2015;27 Suppl 1:60-7.
6. D'Onofrio M, Biagioli E, Gerardi C, et al. Diagnostic performance of contrast-enhanced ultrasound (CEUS) and contrast-enhanced endoscopic ultrasound (ECEUS) for the differentiation of pancreatic lesions: A systematic review and meta-analysis. *Ultraschall Med* 2014;35:515-21.
7. Gincul R, Palazzo M, Pujol B, et al. Contrast-harmonic endoscopic ultrasound for the diagnosis of pancreatic adenocarcinoma: A prospective multicenter trial. *Endoscopy* 2014;46:373-9.
8. Fusaroli P, Spada A, Mancino MG, et al. Contrast harmonic echo-endoscopic ultrasound improves accuracy in diagnosis of solid pancreatic masses. *Clin Gastroenterol Hepatol* 2010;8:629-34.e1-2.
9. Seicean A, Badea R, Moldovan-Pop A, et al. Harmonic contrast-enhanced endoscopic ultrasonography for the guidance of fine-needle aspiration in solid pancreatic masses. *Ultraschall Med* 2015. [Epub ahead of print].
10. D'Onofrio M, Canestrini S, De Robertis R, et al. CEUS of the pancreas: Still research or the standard of care. *Eur J Radiol* 2015;84:1644-9.
11. Gong TT, Hu DM, Zhu Q. Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: A meta-analysis. *Gastrointest Endosc* 2012;76:301-9.
12. Saftoiu A, Vilmann P, Dietrich CF, et al. Quantitative contrast-enhanced harmonic EUS in differential diagnosis of focal pancreatic masses (with videos). *Gastrointest Endosc* 2015;82:59-69.
13. Gheonea DI, Streba CT, Ciurea T, et al. Quantitative low mechanical index contrast-enhanced endoscopic ultrasound for the differential diagnosis of chronic pseudotumoral pancreatitis and pancreatic cancer. *BMC Gastroenterol* 2013;13:2.
14. Wang Y, Yan K, Fan Z, et al. Contrast-enhanced ultrasonography of pancreatic carcinoma: Correlation with pathologic findings. *Ultrasound Med Biol* 2016;42:891-8.
15. Piscaglia F, Nolsøe C, Dietrich CF, et al. The EFSUMB guidelines and recommendations on the clinical practice of contrast enhanced ultrasound (CEUS): Update 2011 on non-hepatic applications. *Ultraschall Med* 2012;33:33-59.
16. Saftoiu A, Popescu C, Cazacu S, et al. Power Doppler endoscopic ultrasonography for the differential diagnosis between pancreatic cancer and pseudotumoral chronic pancreatitis. *J Ultrasound Med* 2006;25:363-72.
17. Dietrich CF, Ignee A, Frey H. Contrast-enhanced endoscopic ultrasound with low mechanical index: A new technique. *Z Gastroenterol* 2005;43:1219-23.

18. Kitano M, Sakamoto H, Matsui U, *et al.* A novel perfusion imaging technique of the pancreas: Contrast-enhanced harmonic EUS (with video). *Gastrointest Endosc* 2008;67:141-50.
19. Greis C. Quantitative evaluation of microvascular blood flow by contrast-enhanced ultrasound (CEUS). *Clin Hemorheol Microcirc* 2011;49:137-49.
20. Tranquart F, Mercier L, Frinking P, *et al.* Perfusion quantification in contrast-enhanced ultrasound (CEUS) – Ready for research projects and routine clinical use. *Ultraschall Med* 2012;33 Suppl 1:S31-8.
21. Saftoiu A, Iordache SA, Gheonea DI, *et al.* Combined contrast-enhanced power Doppler and real-time sonoelastography performed during EUS, used in the differential diagnosis of focal pancreatic masses (with videos). *Gastrointest Endosc* 2010;72:739-47.
22. Iordache S, Costache MI, Popescu CF, *et al.* Clinical impact of EUS elastography followed by contrast-enhanced EUS in patients with focal pancreatic masses and negative EUS-guided FNA. *Med Ultrason* 2016;18:18-24.
23. Choi JH, Seo DW. The expanding role of contrast-enhanced endoscopic ultrasound in pancreatobiliary disease. *Gut Liver* 2015;9:707-13.
24. Imazu H, Uchiyama Y, Matsunaga K, *et al.* Contrast-enhanced harmonic EUS with novel ultrasonographic contrast (Sonazoid) in the preoperative T-staging for pancreatobiliary malignancies. *Scand J Gastroenterol* 2010;45:732-8.
25. Pysz MA, Machtaler SB, Seeley ES, *et al.* Vascular endothelial growth factor receptor type 2-targeted contrast-enhanced US of pancreatic cancer neovasculature in a genetically engineered mouse model: Potential for earlier detection. *Radiology* 2015;274:790-9.
26. Sasajima J, Mizukami Y, Sugiyama Y, *et al.* Transplanting normal vascular proangiogenic cells to tumor-bearing mice triggers vascular remodeling and reduces hypoxia in tumors. *Cancer Res* 2010;70:6283-92.
27. Pietryga JA, Morgan DE. Imaging preoperatively for pancreatic adenocarcinoma. *J Gastrointest Oncol* 2015;6:343-57.
28. Fritscher-Ravens A, Knoefel WT, Krause C, *et al.* Three-dimensional linear endoscopic ultrasound-feasibility of a novel technique applied for the detection of vessel involvement of pancreatic masses. *Am J Gastroenterol* 2005;100:1296-302.
29. Saftoiu A. State-of-the-art imaging techniques in endoscopic ultrasound. *World J Gastroenterol* 2011;17:691-6.
30. Gruionu LG, Saftoiu A, Gruionu G. A novel fusion imaging system for endoscopic ultrasound. *Endosc Ultrason* 2016;5:35-42.
31. Yamashita Y, Ueda K, Itonaga M, *et al.* Tumor vessel depiction with contrast-enhanced endoscopic ultrasonography predicts efficacy of chemotherapy in pancreatic cancer. *Pancreas* 2013;42:990-5.
32. Giday SA, Magno P, Gabrielson KL, *et al.* The utility of contrast-enhanced endoscopic ultrasound in monitoring ethanol-induced pancreatic tissue ablation: A pilot study in a porcine model. *Endoscopy* 2007;39:525-9.
33. Catenacci DV, Chapman CG, Xu P, *et al.* Acquisition of portal venous circulating tumor cells from patients with pancreatobiliary cancers by endoscopic ultrasound. *Gastroenterology* 2015;149:1794-803.e4.
34. Ungureanu BS, Mărgăritescu C, Pirici D, *et al.* Iron oxide nanoparticles biodistribution in an experimental pig model – A new approach for delivery and imaging. *Curr Health Sci J* 2015;41:333-8.
35. Kotopoulos S, Delalande A, Popa M, *et al.* Sonoporation-enhanced chemotherapy significantly reduces primary tumour burden in an orthotopic pancreatic cancer xenograft. *Mol Imaging Biol* 2014;16:53-62.
36. Postema M, Gilja OH. Contrast-enhanced and targeted ultrasound. *World J Gastroenterol* 2011;17:28-41.
37. Rapoport NY, Kennedy AM, Shea JE, *et al.* Controlled and targeted tumor chemotherapy by ultrasound-activated nanoemulsions/microbubbles. *J Control Release* 2009;138:268-76.