Techniques of image enhancement in EUS (with videos)

Pietro Fusaroli, MD, Adrian Saftoiu, MD, Maria Grazia Mancino, MD, Giancarlo Caletti, MD, Mohamad A. Eloubeidi, MD, MHS, FASGE

Bologna, Italy

Since its introduction to clinical practice in the 1980s, EUS has been progressively used to stage and diagnose pancreaticobiliary and GI benign and malignant disorders. Comparison studies have shown that EUS is more accurate than transabdominal US, CT, and magnetic resonance imaging in the detection and staging of GI and extraluminal lesions.[1-3] In addition, EUS-guided FNA (EUS-FNA) is a well-established technique allowing for tissue sampling whenever indicated.[4] However, EUS presents a few limitations. First, it is very operator dependent. Second, it requires high levels of training and a high yearly volume of examinations to maintain adequate diagnostic skills.[5] Third, biliary stents and chronic pancreatitis act as confounding factors limiting EUS accuracy in pancreaticobiliary exploration.[6,7] The same limitations may hamper EUS-FNA accuracy, too.[8-11]

To limit EUS shortcomings, researchers have used several techniques of image enhancement. These imaging techniques will hopefully make EUS less operator dependent, predict the histologic nature of the lesions before EUS-FNA, and allow more reliable assessment of malignant infiltration. The purpose of this review is to describe the methodology of the available techniques and to put them in the appropriate clinical context.

RESEARCH METHODS

All articles pertinent to the techniques of image enhancement in EUS ever published were retrieved by using a PubMed search. The main search terms were elastography, contrast harmonic enhancement, ultrasound contrast agents, tissue harmonic, power Doppler, color Doppler, 3D imaging, electronic scanning, endoscopic ultrasonography, endoscopic ultrasound, EUS, and endosonography. All of the references of the retrieved articles were scrutinized to identify any additional articles that might have been missed by the PubMed search. In addition, the authors reported their own experiences both in technical and clinical aspects correlated with the techniques under review.

Abbreviations: 3-D, 3-dimensional; CHE-EUS, contrast harmonic–enhanced EUS; ER-ES, electronic radial echoendoscope; EUS-FNA, EUS-guided FNA; UCA, US contrast agent.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

See CME section; p. 634.

0016-5107/$36.00
doi:10.1016/j.gie.2011.03.1246

ELECTRONIC EUS

The electronic echoendoscopes represented the first attempt to enhance the image quality in EUS, compared with mechanical ones. Initial experiences with an electronic radial echoendoscope (ER-ES) in humans were reported by Anderson and Scheiman,[12] who evaluated the performance of a prototype ER-ES compared with a mechanical sector scanning echoendoscope. Although ER-ES was not inferior to the mechanical echoendoscope, a significant advantage was the ability to use it with the same processor of the linear echoendoscope, overcoming the need for multiple US processors. Subsequently, Niwa et al[13] showed a superiority of the images acquired by the ER-ES when compared with those acquired by the mechanical radial echoendoscope in the investigation of both cystic and solid diseases of the pancreas.

A prospective, randomized study[14] compared electronic versus mechanical scanning, evaluating both image quality and performance variables like time needed to obtain a definitive visualization of defined structure. One advantage of the ER-ES turned out to be the significantly quicker identification of the common bile duct both by the experienced endosonographers and by the trainees, irrespective of the use of Doppler.

BASIC TECHNIQUES OF IMAGE ENHANCEMENT

Color Doppler EUS

Color Doppler EUS is a powerful and simple method for detecting blood vessels and can be of great advantage in difficult cases. After the first seminal studies with mechanical echoendoscopes in the field of portal hypertension from Caletti et al,[15,16] several investigators have addressed the utility of color Doppler EUS in this setting.

Sato et al[17] first evaluated the direction of blood flow in perforating veins (communicating vessels between esophageal varices and paraesophageal veins) by using color

Doppler EUS with an ER-ES. Subsequently, they reported that an ER-ES was superior to the linear echoendoscope in detecting two additional parameters (palisade veins and pulsatile waves) deemed useful in choosing esophageal varices treatment.[18] Additionally, they demonstrated that color Doppler EUS could predict a high risk of hemorrhage from gastric varices by evaluating blood flow velocity and wall thickness at the level of submucosal gastric varices.[19]

Probably the most important finding in this field is the importance of the analysis of the blood flow of variceal feeders from the portal venous system for therapeutic purposes. It has recently been shown that the frequency of detection of perforating veins and the inflowing type of perforating veins by using color Doppler EUS was significantly associated with variceal recurrence after sclerotherapy.[20]

Power Doppler EUS

Săftoiu et al[21] first showed that power Doppler EUS provided useful information for the differential diagnosis between pancreatic cancer and pseudotumoral inflammatory masses, even without the enhancement produced by US contrast agents (UCAs). In detail, the accuracy of the absence of power Doppler signals inside the mass in diagnosing pancreatic cancer was 88%, with a negative predictive value of 83%, which was comparable with the accuracy and negative predictive value of EUS-FNA of 93% and 81%, respectively.

Tissue harmonic EUS

Tissue harmonic imaging is an important derivative technique of the harmonic imaging method, which was developed to increase the efficiency of visualization by using UCAs. Tissue harmonic imaging was first used for transabdominal US; subsequently, its availability in electronic processors has allowed its use in EUS, too.

Ishikawa et al[22] published the first study comparing tissue harmonic imaging to fundamental imaging in evaluating pancreatic lesions. For cystic and solid lesions, tissue harmonic imaging was significantly clearer than fundamental harmonic imaging (ie, standard EUS imaging) for visualizing boundary and septum and nodules (Fig. 1). In particular, the microcystic features of serous cystadenomas were clearly delineated only by tissue harmonic imaging.

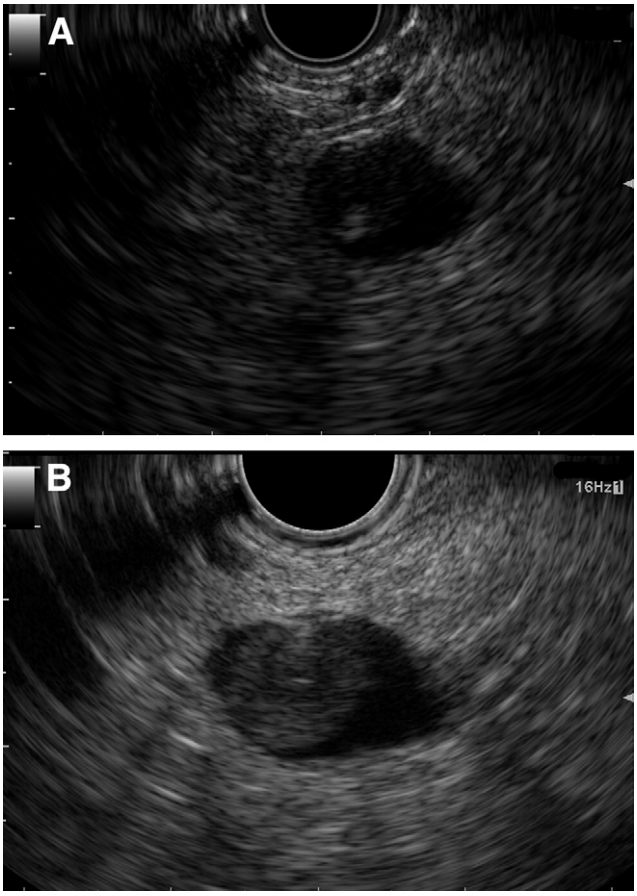

Figure 1. Linear echoendoscope imaging of a pancreatic cyst with internal vegetation in a patient with intraductal papillary mucinous neoplasm. **A,** Standard endoscopic ultrasound imaging. **B,** Tissue harmonic imaging allows better appreciation of the internal vegetation and of the boundaries between the cyst and the surrounding parenchyma.

EUS elastography

Description of the technique. EUS elastography is an imaging technique that displays differences in hardness between tissues, thus estimating elasticity distribution in normal and pathological areas. The images are obtained in real time, being overimposed as a transparent color overlay on the usual EUS gray-scale images.[23,24] The probe generates US waves, inducing slight compression and decompression of tissues under examination. The backscattered US signals are analyzed by the built-in software to estimate the axial strain. For an optimal spatial resolution, the software incorporates 3-dimensional (3-D) techniques.[25] By measuring the tissue strain induced by compression, it is possible to estimate the mechanical properties of tissues, which may be useful in diagnosing and differentiating benign and malignant tumors.

Real-time EUS elastography can be performed with normal radial (Pentax EG 3670 URK; Hamburg, Germany) or linear (Pentax 3870 UTK) EUS transducers, based on the addition of special software that can interpret the deformation distribution (Hitachi Medical Systems, Europe Holding Ag, Zug, Switzerland). Until now, elastography was not available with Olympus echoendoscopes. Similar to color Doppler examinations, EUS elastography can be performed by using a two-panel image, with the conventional gray-scale B-mode EUS image on the right and the elastography image on the left (Fig. 2). A region of interest for the elastography calculations is manually selected and should include the targeted lesion as well as the surrounding soft tissues. For

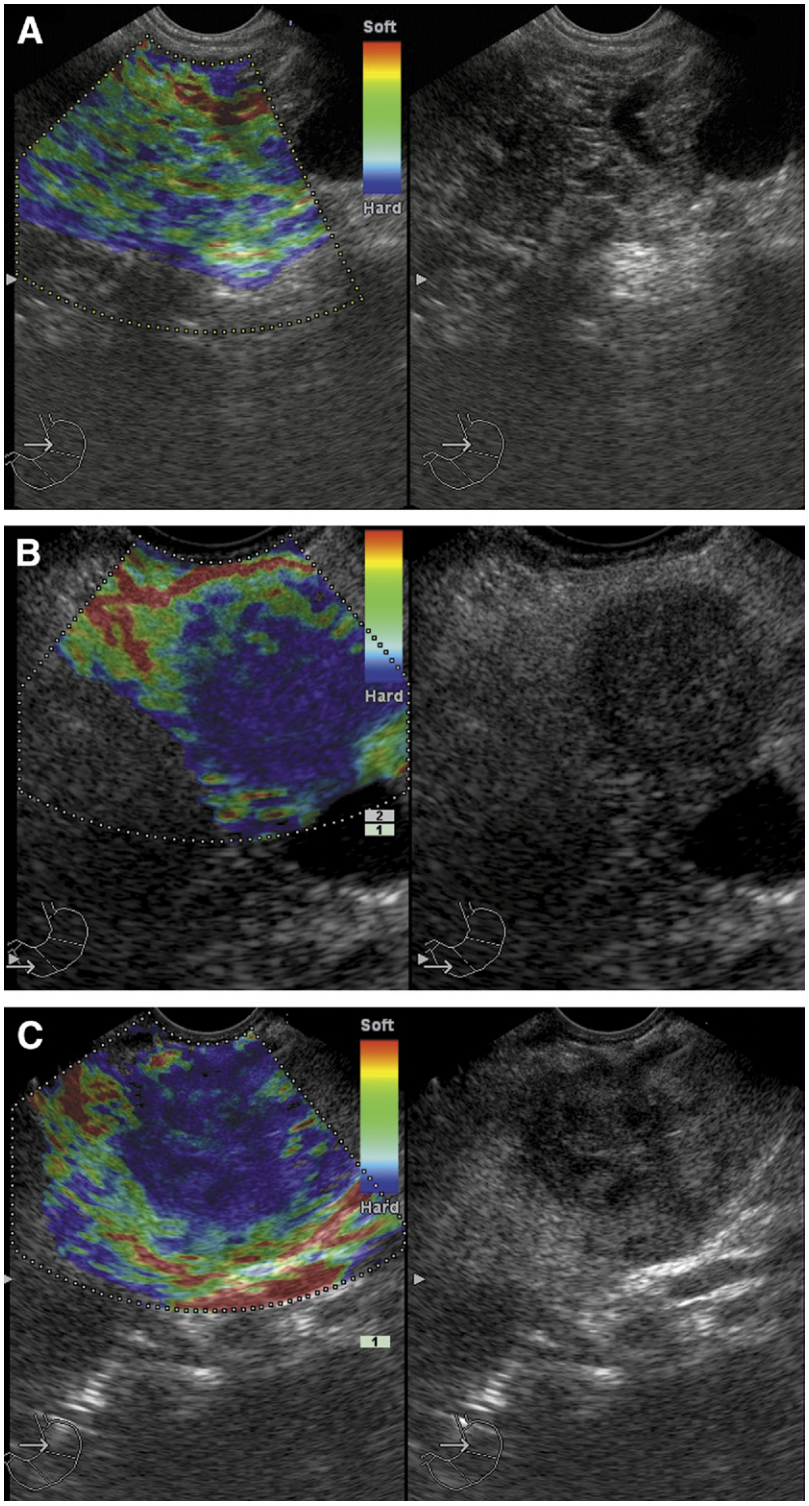

Figure 2. EUS elastography images depicting suggestive aspects of chronic pancreatitis (**A**), pancreatic adenocarcinoma (**B**), and a pancreatic neuroendocrine tumor (**C**). Elastography region of interest is user-defined and shows the relative strain of the tissues, according to a color scale, with values from 0 to 255.

visualization of an elasticity map inside the region of interest, different elasticity values are marked with different colors (on a scale of 0-255). Recent US systems provided the opportunity to calculate average hue histograms (over several compression cycles), that is, graphical representations of the colors (hues) distribution, describing hardness or elasticity of focal lesions. Consequently, the mean value of the histogram corresponds to the global hardness or

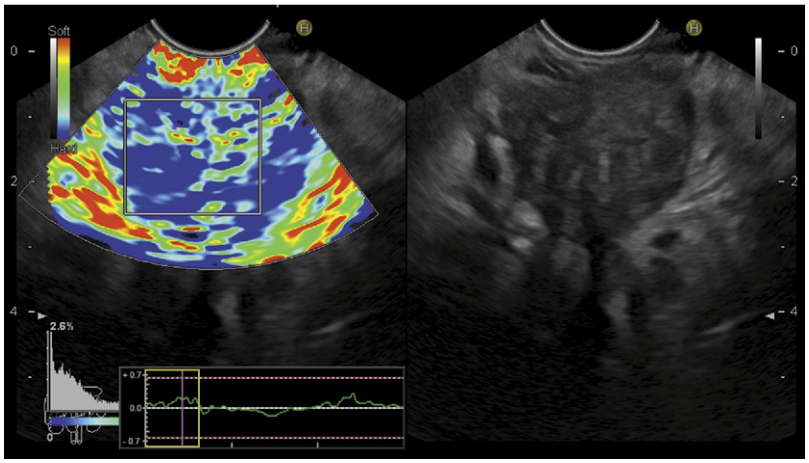

Figure 3. EUS elastography of a pancreatic adenocarcinoma, displayed by using the latest software, which shows the compression (displacement) of tissues induced by heart/respiratory movement as well as transducer compression. The software also has the possibility of averaging images over several frames and calculating mean hue histogram values, based on a scale from 0 to 255.

elasticity of the focal lesions, based on calculations inside a selected region of interest, which is smaller than the whole EUS elastography region of interest (Fig. 3; Video 1, available online at www.giejournal.org).

Analysis of the literature. EUS elastography was tested in an initial feasibility study, indicating that qualitative analysis of individual frames might be useful for the differential diagnosis of lymph nodes and focal pancreatic masses.[26] A subsequent multicenter study with similar methodology included 222 patients who underwent EUS examination for the evaluation of pancreatic masses (n = 121) or lymph nodes (n = 101).[27] EUS elastography was considered superior to conventional B-mode imaging, differentiating benign from malignant lymph nodes as well as pancreatic masses with excellent accuracy.

Several groups tested the value of EUS elastography for the differential diagnosis of lymph nodes. Qualitative pattern analysis yielded high sensitivity, specificity, and accuracy for the differential diagnosis of 91.7%, 94.4%, and 92.9%, respectively, with an area under the receiver operating characteristic curve of 0.95.[28] Another group used similar qualitative criteria and obtained excellent interobserver agreement (kappa = 0.84).[29] After the initial qualitative studies, it became evident that quantification of the color elastography information might be better in order to improve accuracy.[30,31] Quantification of relative elasticity values can be done easily by hue histogram analysis. This was demonstrated in a heterogeneous group of patients that included 78 cervical, mediastinal, or abdominal lymph nodes, through computer-enhanced dynamic analysis of EUS elastography movies. The sensitivity, specificity, and accuracy for the differential diagnosis of benign and malignant lymph nodes were 85.4%, 91.9%, and 88.5%, respectively.

EUS elastography of the pancreas was evaluated in an initial feasibility study that included normal patients, patients with chronic pancreatitis, and patients with pancreatic cancer.[32] Although the videos were considered reproducible and complementary to gray-scale movies, the authors could not precisely differentiate chronic pancreatitis and pancreatic cancer, based on qualitative evaluation of EUS elastography movies. However, another group used 4 elastographic patterns and two blinded investigators to differentiate normal pancreas and focal pancreatic masses.[33] Based on qualitative pattern analysis, the sensitivity, specificity, and overall accuracy for the diagnosis of malignancy were 100%, 85.5%, and 94.0%, respectively, with concordant results between two blinded observers (kappa = 0.77). A recent study from the same group was based on calculation of the strain ratio included in the software of the US system and showed high values of sensitivity, specificity, and overall accuracy of 100%, 92.9%, and 97.7%, respectively, with an area under the receiver operating characteristic curve of 0.98.[34] However, the selection of the reference tissue surrounding the pancreas can induce a high bias, acknowledged by the authors in the methodology of their study. The addition of quantitative analysis based on mean hue histogram values calculated for the region of interest restricted to the focal pancreatic mass (not the entire elastography region of interest) yielded a sensitivity, specificity, and accuracy of differentiation of benign and malignant masses of 91.4%, 87.9%, and 89.7%, respectively.[35] Furthermore, multilayer perceptron neural networks with both one and two hidden layers of neurons (3-layer perceptron and 4-layer perceptron) can be trained to learn how to classify focal lesions as benign or malignant, thus yielding an excellent testing performance of 95% accuracy on average, for multiple computer runs of the neural network model. These results were confirmed in a recent multicenter trial of EUS elastography that included 212 patients with focal pancreatic masses (pancreatic cancer and inflammatory masses), indicating a sensitivity of 92.6%, a specificity of 71.7%, and an overall accuracy of 87.4%, based on a cut-off value of 175 for mean hue histogram values.[36]

Although the data are still limited and await further multicenter validation studies, EUS elastography might provide complementary information to conventional EUS imaging. The value of EUS elastography might be crucial in negative EUS-FNA cases in which a strong suspicion of malignancy still persists. Moreover, EUS elastography can be combined with contrast-enhanced EUS examinations, proving that both techniques are complementary and might help in EUS-FNA–negative cases.[37]

Contrast-enhanced EUS

Description of the technique. The use of intravenous UCAs has become standard practice in transabdominal US for the diagnosis and follow-up of hepatic and pancreatic diseases.[38] Experience with the use of UCAs in EUS is limited in comparison to transabdominal US. Nevertheless, the potential indications for the use of UCAs with EUS are multiple, including the characterization of solid tumor vascularization in the pancreas, the differential diagnosis of lymph nodes, and the prediction of malignant behavior of GI stromal tumors.

Several challenges have been overcome to produce microbubbles small enough to cross the lung bed and to prolong their survival. First, the gases were encapsulated in a resistant shell that can enhance the pressure that a small bubble can tolerate. Second, heavy gases were used, such as perfluorocarbons, which are less water soluble and less likely to leak out.[39] When a gas microbubble is hit by an US wave, it vibrates, producing a strong backscattered acoustic signal that can be detected by the US probe and reproduced as a white echo signal in the monitor. The mechanical index is an arbitrary value reflecting the probability of cavitation of the microbubbles: the higher the mechanical index, the faster all the microbubbles are destroyed.

Contrast-enhanced EUS can be performed by using color or power Doppler as a generic signal intensifier or, more appropriately, by using a dedicated contrast harmonic: contrast harmonic–enhanced EUS (CHE-EUS).

Many publications in the literature dealt with the use of UCAs with color and power Doppler. The first demonstration that pancreatic-ductal adenocarcinoma was hypoenhancing by contrast-enhanced EUS dates back more than 10 years.[40] Subsequently, larger experiences with the use of the contrast agent Levovist (Bayer AG, Leverkusen, Germany) were published. Dietrich et al[41] used contrast-enhanced (color Doppler) EUS to investigate patients with undetermined pancreatic tumors. Ductal adenocarcinoma of the pancreas showed hypovascularity in 57 of 62 cases, whereas all other pancreatic lesions revealed an isovascular or hypervascular pattern (20 neuroendocrine tumors, 10 serous microcystic adenomas, and 1 teratoma). In their experience, hypovascularity as a sign of malignancy in contrast-enhanced EUS demonstrated 92% sensitivity and 100% specificity. Regarding the usefulness of contrast-enhanced EUS to differentiate inflammation (focal pancreatitis) from pancreatic carcinoma, Hocke et al[42] reported that the sensitivity of EUS was increased from 73% to 91% by the use of Sonovue (sulfur hexafluoride MBs; Bracco International BV, Amsterdam, The Netherlands). The diagnostic yield of contrast-enhanced EUS also was found to be significantly superior to multidetector CT in the differentiation between small pancreatic adenocarcinomas (≤2 cm) from other tumors (sensitivity 83% for contrast-enhanced EUS vs only 50% for multidetector CT).[43]

Contrast-enhanced EUS also has been adopted in the investigation of pancreatic cystic neoplasms. Particularly, intraductal papillary mucinous neoplasms present difficult diagnostic challenges when malignancy is to be detected inside or among the cysts and the dilated Wirsung duct. Ohno et al[44] analyzed intracystic mural nodules with contrast-enhanced EUS and found it to be very useful in this setting. In fact, although nonneoplastic mural vegetations (such as mucus plugs) were completely unenhanced, adenomas and adenocarcinomas showed mild vascular enhancement. Given the suboptimal diagnostic yield of EUS-FNA in this disease, further research with contrast-enhanced EUS is advocated.

Because of their highly vascular internal structure, pancreatic endocrine tumors can be visualized nicely with contrast-enhanced EUS. Ishikawa et al[45] studied 41 patients with pancreatic endocrine tumors with contrast-enhanced EUS. Not only was contrast-enhanced EUS more sensitive than multidetector CT in identifying these small tumors, but also it allowed for the prediction of malignancy by detecting filling defects (seen as heterogeneous hypoechoic and anechoic areas), which corresponded to hemorrhage or necrosis on pathologic examination.

Contrast harmonic–enhanced EUS

CHE-EUS is able to detect signals from microbubbles in vessels with very slow flow without the burden of Doppler-related artifacts, such as ballooning and overpainting, which are common with contrast-enhanced EUS. In seminal studies from Germany[46] and Japan,[47] it was shown that low values of mechanical index allowed good visualization of the early arterial phase, parenchymal perfusion, and microvasculature in the pancreas, unlike contrast-enhanced EUS, which did not depict the parenchymal perfusion images and branching vessels.

Among the available UCAs, Sonovue and Sonazoid (perfluorobutane; GE Healthcare, Little Chalfont, Buckinghamshire, UK; not available in USA and Europe) are the most commonly used in this setting. For an optimal visualization of the Sonovue microbubbles, we use a mechanical index of 0.25 with the radial (GF-UE160; Olympus) and linear (GF-UCT180; Olympus) echoendoscopes in conjunction with the Alfa 10 unit (Aloka, Tokyo, Japan). However, the settings differ from manufacturer to manufacturer and, for instance, a mechanical index of 0.08 to 0.09 can be used for best results with the Pentax-Hitachi Preirus system. Of note, it is the authors' experience that

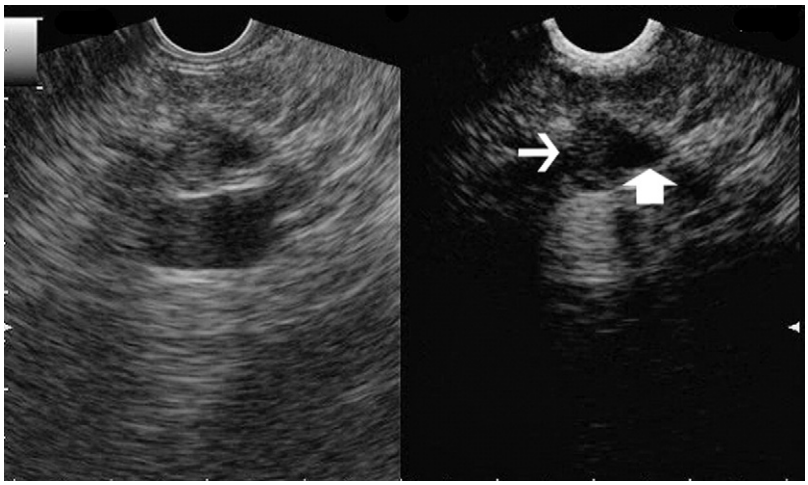

Figure 4. Contrast harmonic-enhanced EUS of a small pancreatic body adenocarcinoma *(thin arrow)*. A dilated Wirsung duct *(thick arrow)* is visible proximal to the lesion. The lesion is hypoenhanced in comparison with the surrounding parenchyma.

no difference in image quality is appreciated by using the full vial of Sonovue (4.8 mL) or half of it; thus, 2.4 mL as a standard dose in EUS is exactly analogous to the practice in transabdominal US.[38]

After a complete EUS examination is done in B-mode, the echoendoscope is placed in front of the lesion of interest and switched to the CHE mode. The intermittent modality of the monitor is activated to keep a reference B-mode image beside the CHE image. After injection, Sonovue uptake and washout are evaluated for at least 120 seconds.

The CHE screen is almost black at baseline. When the contrast material is infused intravenously, the microbubbles emit a strong echo signal depicting large and small vessels, both within the surrounding parenchyma and into the lesions. As a result, the microvasculature is clearly visualized. Perfusion of the lesions is continuous, with dynamic observation of the shift from the unenhanced phase to the contrast-enhanced phase. The enhancement pattern is dependent on the internal vascular architecture of the lesion and is differentiated into 3 uptake patterns (hyperenhancement, isoenhancement, hypoenhancement) and 2 distribution patterns (homogeneous, inhomogeneous). We recommend recording the examination in digital format for later review.

Analysis of the literature. We have reported that CHE-EUS increases the accuracy of EUS for the diagnosis of solid pancreatic tumors.[48] The finding of a hypoenhancing mass with an inhomogeneous pattern was a sensitive (96%) and accurate (82%) identifier of patients with adenocarcinoma; the vast majority of patients with primary pancreatic adenocarcinoma had hypoenhancing masses that were inhomogeneous and had fast washouts (Fig. 4; Video 2, available online at www.giejournal.org). This finding was more accurate in diagnosis than the finding of a hypoechoic lesion when standard EUS was used. Hyperenhancement specifically excluded adenocarcinoma (98%), although sensitivity was low (39%). Of neuroendocrine tumors, 11 of 13 were nonhypoenhancing (9 hyperenhancing, 2 isoenhancing) (Fig. 5; Video 3, available online at www.giejournal.org). Interestingly, CHE-EUS allowed detection of small lesions in 7 patients who had uncertain standard EUS findings because of biliary stents or chronic pancreatitis. Targeted EUS-FNA revealed malignancy in all these lesions.

Napoleon et al[49] reported similar figures by using the same apparatus (ie, Olympus echoendoscopes in conjunction with Aloka alfa 10, CHE-EUS performed after injection of Sonovue) in 35 patients presenting with solid pancreatic lesions. The sensitivity, specificity, and accuracy of hypoenhancement for diagnosing pancreatic adenocarcinoma were 89%, 88%, and 89%, respectively, compared with corresponding values of 72%, 100%, and 86% for EUS-FNA. Interestingly, 4 of 5 adenocarcinomas with false-negative results at EUS-FNA were hypoenhanced at CHE-EUS (thereby raising the suspicion of cancer and mandating further investigation).

CHE-EUS also has been used for the characterization of abdominal lesions by Xia et al,[50] who analyzed 43 extraintestinal hypoechoic masses of uncertain origin. After histopathologic evaluation, the majority of these masses turned out to be both inflammatory and malignant lymph nodes. Interestingly, CHE-EUS with Sonazoid was very useful in discriminating between malignant (heterogeneous pattern, in which the distorted tumor vessels could be visualized clearly) and benign (homogeneous pattern, mainly hyperenhanced) lymph nodes. Because the benign and malignant lesion groups differed significantly in terms of enhancement ($P < .001$), we speculate that CHE-EUS might prove useful in selecting which lymph nodes should be targeted first for obtaining tissue analysis (Fig. 6). Other interesting studies have been published recently, reporting the use of CHE-EUS in mixed clinical conditions, including the

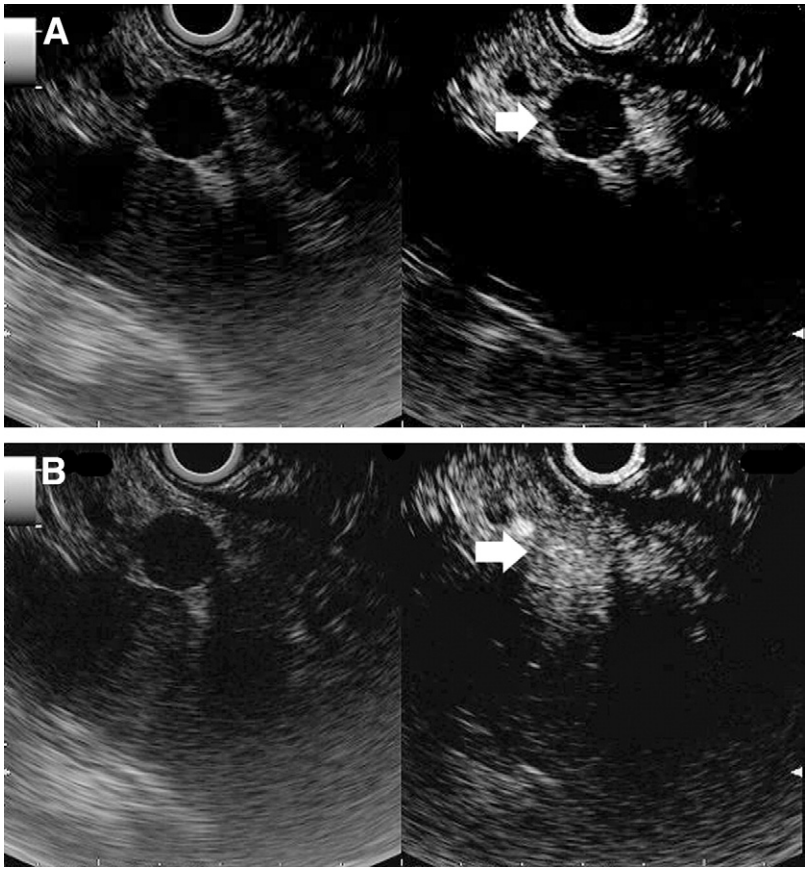

Figure 5. Contrast harmonic–enhanced EUS of a small, pancreatic body neuroendocrine tumor *(arrow)*. **A,** At baseline, the lesions appears almost black. **B,** A few seconds after contrast agent injection, the lesions become markedly hyperenhanced, with a homogeneous internal vascular pattern.

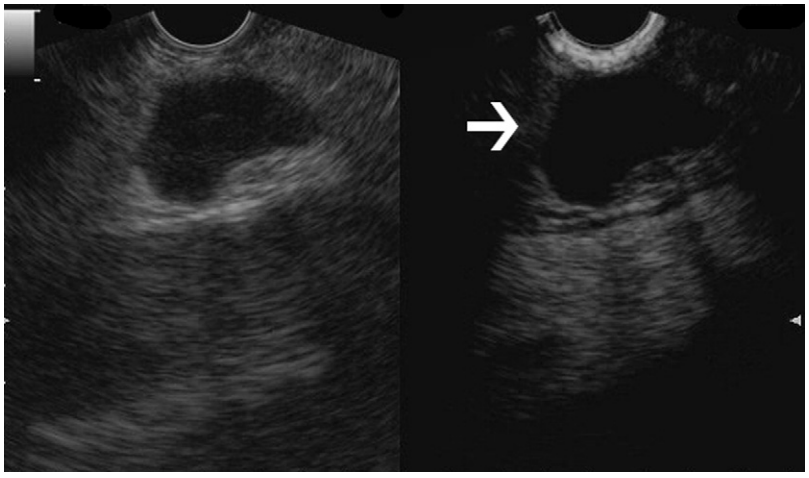

Figure 6. A metastatic lymph node seen behind the pancreas in a patient with rectal cancer. Contrast harmonic–enhanced EUS shows a markedly hypoenhanced lymph node, predictive of a malignant nature *(arrow)*. EUS-guided FNA confirmed malignancy.

characterization and estimation of malignant potential of GI stromal tumors.[51,52]

CHE-EUS has been used as a qualitative method so far. Although evaluations of interobserver agreement are currently underway to assess the reproducibility of the technique, quantitative assessment of CHE-EUS might prove useful. Seicean et al[53] presented a preliminary experience of analyzing the index of the contrast agent uptake ratio, which was significantly lower in adenocarcinomas than in mass-forming chronic pancreatitis, with a sensitivity of 80%, a specificity of 92%, a positive predictive value of 93%, and a negative predictive value of 78%.

Software-assisted image analysis

Pixel analysis by dedicated software. EUS images are composed of individual pixels, based on the resolution of each specific US system. Digital image analysis includes a variety of mathematical and statistical parameters derived from the distribution of pixels in an image.[54] These usually represent subtle architectural changes of tissues induced by pathological conditions, consequently, several mathematical models can be further used to enhance and improve the differential diagnosis. Image analysis can be performed with various software programs, including ImageJ (free JAVA image analysis software available from the National Institute of Health at http://rsbweb.nih.gov/ij/).

The most useful analysis is texture analysis, which analyzes blocks of pixels represented by coordinates and gray-level intensity between 0 and 255 (8-bit images). Image analyses thus yield a large number of parameters, which can be reduced through different statistical techniques.[55] All these parameters can be further fed to artificial intelligence models needed to apply standard machine learning algorithms. Furthermore, automatic decision systems consisting of forward/backward stepwise models easily can be designed based on machine learning algorithms and used to determine the focal pancreatic diagnostic classes, based on as little as possible information.[56]

Integration with EUS. Digital image analysis was used to some extent for the analysis of gray-scale images in EUS, mostly for the differential diagnosis of focal pancreatic masses. A simplified version of image analysis, based on single EUS gray-scale images, was initially tested with a "self-teaching" neural network program intended to differentiate chronic pancreatitis and pancreatic adenocarcinoma.[57] Although this initial feasibility study was based on a small number of patients with chronic pancreatitis (N = 14) and pancreatic cancer (N = 21), the accuracy was similar, being 80% for computer analysis, 83% for blinded videotape assessment, and 85% for assessment of EUS images during the procedure. Improved methodology with analysis of a large number of texture parameters is a distinct advantage offered by recent advances in software and hardware. Thus, a recent study included patients with normal pancreas (N = 22), chronic pancreatitis (N = 12), and pancreatic cancer (N = 22), whose cases were analyzed by extraction of 228 features, with only 11 retained by principal component analysis.[54] An artificial neural network was subsequently built, based on the multilayer perceptron architecture with a back-propagation algorithm. The sensitivity and specificity for the differential diagnosis of pancreatic cancer were 93% and 92%, with an area under the receiver operating characteristic curve of 0.93. The same group published a subsequent article, used for the EUS differential diagnosis of malignant GI subepithelial lesions, including GI stromal tumors, carcinoid tumors, and lipomas.[58] The model was regarded as "good" for the differentiation of carcinoid tumors and GI stromal tumors and "excellent" for the differentiation of lipomas, with areas under the receiver operating characteristic curve of 0.86, 0.89, and 0.92, respectively. The support vector machine theory was used with a sequential forward selection process to build, train, and validate a predictive model, which achieved high values of sensitivity, specificity, and accuracy for the diagnosis of pancreatic cancer, that is, 98%, 94.3%, and 97.8%, respectively. The data used in the model were obtained from 153 patients with pancreatic cancer, 43 patients with chronic pancreatitis, and 20 patients with normal pancreas, examined by mechanical radial EUS.

Another approach would be to enhance tissue characterization through the use of additional information based on spectral analysis from the raw backscattered radiofrequency spectrum.[59] Spectral analysis of backscattered US uses information discarded in the EUS gray-scale images/movies, dependent on the size and concentration of scatterers, as well as the density and sound speed in the tissues. The authors used US spectrum analysis to differentiate normal pancreas, chronic pancreatitis, and pancreatic cancer and also benign and malignant intra-abdominal and mediastinal lymph nodes in a feasibility study based on 21 patients. Although this approach is very interesting, it certainly awaits further clinical validation in large, multicenter trials and even inclusion in the traditional EUS systems.[60]

There are of course several limitations of software-assisted analysis applications in EUS, the most important being the small number of patients included in a limited number of centers/research groups. Also, the methodology is not yet validated in multiple centers because of lack of reproducibility in different clinical settings or different EUS systems (different manufacturers, mechanical vs digital, radial vs linear, gray-scale vs spectral analysis vs elastography and/or contrast enhancement, etc). The ideal digital image analysis approach should be easy to use and embedded in the EUS system during real-time imaging, whereas the indications in the clinical decision-making process should be firmly established, either for the differential diagnosis or for selection of better targets for EUS-FNA. Examples of such technologies recently embedded in state-of-the-art US systems include time-intensity-curve analysis during second-generation contrast harmonic-enhanced EUS or hue histogram analysis averaged over several compression cycles in EUS elastography.[61] However, all these technological advances should be further tested in randomized, multicenter trials, which should include machine learning technologies and even intelligent automatic decision systems.

Tridimensional EUS

Types of probes and miniprobes. Tridimensional EUS (3-D-EUS) allows the capture of a complete data set volume, with visualization of spatial relationships between the lesions and neighboring structures, together with accurate calculations of volume.[62] Tridimensional EUS has been used with radial and linear transducers, both with

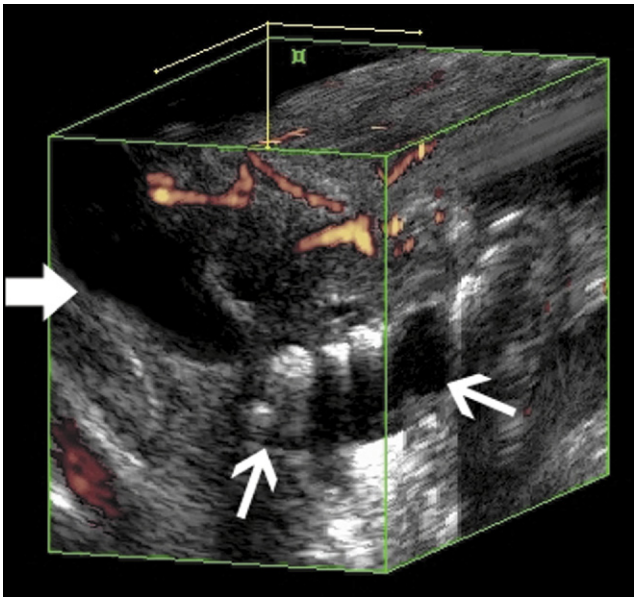

Figure 7. Tridimensional picture of advanced chronic pancreatitis, with a dilated common bile duct *(thick arrow)* and Wirsung duct, with intraductal stones (up to 10 mm) *(thin arrows)*.

freehand and automatic acquisition techniques (Fig. 7). Controlled pullback of radial scanning probes has been applied initially in several studies, with good results.[63] Miniprobes were used extensively, especially with systems with radial-linear switchable probes that provide helical scanning and dual-plane reconstructions.[64-69] Also, linear scanning echoendoscopes have been used with freehand techniques or electromagnetic tracking devices, based on rotation of the scope along its long axis.[70,71] Different studies also used rigid rectal probes for 3-D endorectal US, enabling pull-back or automatic volume scanning at transverse and longitudinal scan angles.[72-74]

Analysis of the literature. Tridimensional EUS was used with the initial purpose of improving the staging of esophageal, gastric, pancreaticobiliary, or rectal tumors, because it enhances anatomical interpretation and definition of vascular structures, which is needed to evaluate staging and resectability of tumors.[62] Recent studies showed a good delineation of tumor stage in esophagogastric cancer[66,68] as well as pancreaticobiliary cancer[67,71] or rectal cancer.[69,72,73] However, the number of patients was small, and the methodology was not designed to derive firm conclusions.

Accurate volume measurements usually are possible with 3-D EUS, being useful for treatment planning and monitoring of tumor response.[65,71] However, based on the limited published data, it is not yet clear whether the results obtained by 3-D EUS are significantly better as compared with the results of 2-dimensional EUS. Consequently, 3-D EUS should be validated in blinded, multicenter studies including large numbers of patients, in comparison with other cross-sectional imaging methods (eg, magnetic resonance imaging) and pathology validation.

Finally, there is well-established data on the utility of 3-D US in the evaluation of anorectal fistulas.[75,76] In particular, 3-D US is considered useful for the preoperative evaluation of trans-sphincter fistulas, contributing to planning of surgery, with a subsequent decrease in postoperative incontinence symptoms.[77] The method is especially useful for recurrent or complex fistulas, improving visualization of tracts and internal openings. Although the immediate impact for diagnosis is not clear, volume rendering offers improved visualization, especially for defining anatomical structures in the pelvis, the extension of anal sphincter defects, the anatomy of complex fistulous tracts, and the presence of submucosal invasion in early rectal cancer.[77]

CONCLUSIONS

We provided a comprehensive, updated overview of the available techniques of image enhancement in EUS. In particular, insights into both the technical and the clinical aspects of basic and advanced techniques were given. Power Doppler, tissue harmonic imaging, EUS elastography, and CHE-EUS are already part of the endosonographer's everyday armamentarium. Others techniques, such as 3-D EUS and digital image analysis are still mainly experimental. However, all these methodologies rely on sophisticated software programs that are actively upgraded by their developers. It is likely that their further evolution will be very fast, both for the qualitative and quantitative analysis of EUS pictures. We speculate that this evolution will result in better care of our patients.

REFERENCES

1. Eloubeidi MA, Varadarajulu S, Desai S, et al. A prospective evaluation of an algorithm incorporating routine preoperative endoscopic ultrasound-guided fine needle aspiration in suspected pancreatic cancer. J Gastrointest Surg 2007;11:813-9.
2. Soriano A, Castells A, Ayuso C, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. Am J Gastroenterol 2004;99:492-501.
3. Agarwal B, Abu-Hamda E, Molke KL, et al. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. Am J Gastroenterol 2004;99:844-50.
4. Eloubeidi MA, Jhala D, Chhieng DC, et al. Yield of endoscopic ultrasound-guided fine-needle aspiration biopsy in patients with suspected pancreatic carcinoma. Cancer 2003;99:285-92.
5. Eisen GM, Dominitz JA, Faigel DO, et al; American Society for Gastrointestinal Endoscopy. Guidelines for credentialing and granting privileges for endoscopic ultrasound. Gastrointest Endosc 2001;54:811-4.
6. Fusaroli P, Manta R, Fedeli P, et al. The influence of endoscopic biliary stents on the accuracy of endoscopic ultrasound for pancreatic head cancer staging. Endoscopy 2007;39:813-7.
7. Bhutani MS, Gress FG, Giovannini M, et al. The No Endosonographic Detection of Tumor (NEST) Study: a case series of pancreatic cancers missed on endoscopic ultrasonography. Endoscopy 2004;36:385-9.
8. Fritscher-Ravens A, Brand L, Knöfel WT, et al. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in

patients with normal parenchyma and chronic pancreatitis. Am J Gastroenterol 2002;97:2768-75.
9. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc 2005;62:728-36.
10. Krishna NB, Mehra M, Reddy AV, et al. EUS/EUS-FNA for suspected pancreatic cancer: influence of chronic pancreatitis and clinical presentation with or without obstructive jaundice on performance characteristics. Gastrointest Endosc 2009;70:70-9.
11. Eloubeidi MA, Varadarajulu S, Desai S, et al. Value of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. J Gastroenterol Hepatol 2008;23:567-70.
12. Anderson MA, Scheiman JM. Initial experience with an electronic radial array echoendoscope: randomized comparison with a mechanical sector scanning echoendoscope in humans. Gastrointest Endosc 2002;56:573-7.
13. Niwa K, Hirooka Y, Niwa Y, et al. Comparison of image quality between electronic and mechanical radial scanning echoendoscopes in pancreatic diseases. J Gastroenterol Hepatol 2004;19:454-9.
14. Papanikolaou IS, Delicha EM, Adler A, et al. Prospective, randomized comparison of mechanical and electronic radial endoscopic ultrasound systems: assessment of performance parameters and image quality. Scand J Gastroenterol 2009;44:93-9.
15. Caletti G, Brocchi E, Baraldini M, et al. Assessment of portal hypertension by endoscopic ultrasonography. Gastrointest Endosc 1990;36:S21-7.
16. Caletti GC, Bolondi L, Zani E, et al. Detection of portal hypertension and esophageal varices by means of endoscopic ultrasonography. Scand J Gastroenterol 1986;21:74-7.
17. Sato T, Yamazaki K, Toyota J, et al. Experience with electronic radial endoscopic Color Doppler ultrasonography in esophageal variceal patients. Digestive Endoscopy 2003;15:275-9.
18. Sato T, Yamazaki K, Toyota J, et al. Usefulness of electronic radial endoscopic color Doppler ultrasonography in esophageal varices: comparison with convex type. J Gastroenterol 2006;41:28-33.
19. Sato T, Yamazaki K, Toyota J, et al. Observation of gastric variceal flow characteristics by endoscopic ultrasonography using color Doppler. Am J Gastroenterol 2008;103:575-80.
20. Sato T, Yamazaki K, Toyota J, et al. Endoscopic ultrasonographic evaluation of hemodynamics related to variceal relapse in esophageal variceal patients. Hepatol Res 2009;39:126-33.
21. Săftoiu 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.
22. Ishikawa H, Hirooka Y, Itoh A, et al. A comparison of image quality between tissue harmonic imaging and fundamental imaging with an electronic radial scanning echoendoscope in the diagnosis of pancreatic diseases. Gastrointest Endosc 2003;57:931-6.
23. Frey H. Real-time elastography. A new ultrasound procedure for the reconstruction of tissue elasticity. Radiologe 2003;43:850-5.
24. Săftoiu A, Vilmann P. Endoscopic ultrasound elastography—a new imaging technique for the visualization of tissue elasticity distribution. J Gastrointestin Liver Dis 2006;15:161-5.
25. Shiina T, Nitta N, Ueno EI, et al. Real-time tissue elasticity imaging using the combined autocorrelation method. J Med Ultrason 2002;29:119-28.
26. Giovannini M, Hookey L, Bories E, et al. Endoscopic ultrasound elastography: the first step towards virtual biopsy? Preliminary results in 49 patients. Endoscopy 2006;38:344-8.
27. Giovannini M, Botelberge T, Bories E, et al. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. World J Gastroenterol 2009;15:1587-93.
28. Săftoiu A, Vilmann P, Hassan H, et al. Analysis of endoscopic ultrasound elastography used for characterisation and differentiation of benign and malignant lymph nodes. Ultraschall Med 2006;27:535-42.
29. Janssen J, Dietrich CF, Will U, et al. Endosonographic elastography in the diagnosis of mediastinal lymph nodes. Endoscopy 2007;39:952-7.
30. Săftoiu A, Vilmann P, Ciurea T, et al. Dynamic analysis of EUS used for the differentiation of benign and malignant lymph nodes. Gastrointest Endosc 2007;66:291-300.
31. Janssen J, Schlörer E, Greiner L. EUS elastography of the pancreas: feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. Gastrointest Endosc 2007;65:971-8.
32. Hirche TO, Ignee A, Barreiros AP, et al. Indications and limitations of endoscopic ultrasound elastography for evaluation of focal pancreatic lesions. Endoscopy 2008;40:910-7.
33. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, et al. EUS elastography for the characterization of solid pancreatic masses. Gastrointest Endosc 2009;70:1101-8.
34. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, et al. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. Gastroenterology 2010;139:1172-80.
35. Săftoiu A, Vilmann P, Gorunescu F, et al. Neural network analysis of dynamic sequences of EUS elastography used for the differential diagnosis of chronic pancreatitis and pancreatic cancer. Gastrointest Endosc 2008;68:1086-94.
36. Săftoiu A, Vilmann P, Gorunescu F, et al; on behalf of the European EUS Elastography Multicentric Study Group. Accuracy of endoscopic ultrasound elastography used for differential diagnosis of chronic pancreatitis and pancreatic cancer: a multicentric study. Endoscopy 2011. In press.
37. Săftoiu A, Iordache S, 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.
38. Claudon M, Cosgrove D, Albrecht T, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS)—update 2008. Ultraschall Med 2008;29:28-44.
39. Sanchez MV, Varadarajulu S, Napoleon B. EUS contrast agents: What is available, how do they work, and are they effective? Gastrointest Endosc 2009;692(suppl):S71-7.
40. Hirooka Y, Naitoh Y, Goto H, et al. Usefulness of contrast-enhanced endoscopic ultrasonography with intravenous injection of sonicated serum albumin. Gastrointest Endosc 1997;46:166-9.
41. Dietrich CF, Ignee A, Braden B, et al. Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. Clin Gastroenterol Hepatol 2008;6:590-7.
42. Hocke M, Schulze E, Gottschalk P, et al. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. World J Gastroenterol 2006;12:246-50.
43. Sakamoto H, Kitano M, Suetomi Y, et al. Utility of contrast-enhanced endoscopic ultrasonography for diagnosis of small pancreatic carcinomas. Ultrasound Med Biol 2008;34:525-32.
44. Ohno E, Hirooka Y, Itoh A, et al. Intraductal papillary mucinous neoplasms of the pancreas: differentiation of malignant and benign tumors by endoscopic ultrasound findings of mural nodules. Ann Surg 2009;249:628-34.
45. Ishikawa T, Itoh A, Kawashima H, et al. Usefulness of EUS combined with contrast-enhancement in the differential diagnosis of malignant versus benign and preoperative localization of pancreatic endocrine tumors. Gastrointest Endosc 2010;71:951-9.
46. Dietrich CF, Ignee A, Frey H. Contrast-enhanced endoscopic ultrasound with low mechanical index: a new technique. Z Gastroenterol 2005;43:1219-23.
47. Kitano M, Sakamoto H, Matsui U, et al. A novel perfusion imaging technique of the pancreas: contrast-enhanced harmonic EUS. Gastrointest Endosc 2008;67:141-50.
48. 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.
49. Napoleon B, Alvarez-Sanchez MV, Gincoul R, et al. Contrast-enhanced harmonic endoscopic ultrasound in solid lesions of the pancreas: results of a pilot study. Endoscopy 2010;42:564-70.
50. Xia Y, Kitano M, Kudo M, et al. Characterization of intra-abdominal lesions of undetermined origin by contrast-enhanced harmonic EUS (with videos). Gastrointest Endosc 2010;72:637-42.

51. Romagnuolo J, Hoffman B, Vela S, et al. Accuracy of contrast-enhanced harmonic EUS with a second-generation perflutren lipid microsphere contrast agent (with video). Gastrointest Endosc 2011;73:52-63.
52. Sakamoto H, Kitano M, Matsui S, et al. Estimation of malignant potential of GI stromal tumors by contrast-enhanced harmonic EUS (with videos). Gastrointest Endosc 2011;73:227-37.
53. Seicean A, Badea R, Stan-Iuga R, et al. Quantitative contrast-enhanced harmonic endoscopic ultrasonography for the discrimination of solid pancreatic masses. Ultraschall Med 2010;31:571-6.
54. Das A, Nguyen CC, Li F, et al. Digital image analysis of EUS images accurately differentiates pancreatic cancer from chronic pancreatitis and normal tissue. Gastrointest Endosc 2008;67:861-7.
55. Zhang M, Yang H, Jin ZD, et al. Differential diagnosis of pancreatic cancer from normal tissue with digital imaging processing and pattern recognition based on a support vector machine of EUS images. Gastrointest Endosc 2010;72:978-85.
56. Gorunescu F, Gorunescu M, Saftoiu A, et al. Competitive/collaborative neural computing system for medical diagnosis in pancreatic cancer detection. Expert Systems. Epub 2010 November 14.
57. Norton ID, Zheng Y, Wiersema MS, et al. Neural network analysis of EUS images to differentiate between pancreatic malignancy and pancreatitis. Gastrointest Endosc 2001;54:625-9.
58. Nguyen VX, Nguyen CC, Li B, et al. Digital image analysis is a useful adjunct to endoscopic ultrasonographic diagnosis of subepithelial lesions of the gastrointestinal tract. J Ultrasound Med 2010;29:1345-51.
59. Kumon RE, Olowe K, Faulx AL, et al. EUS spectrum analysis for in vivo characterization of pancreatic and lymph node tissue: a pilot study. Gastrointest Endosc 2007;66:1096-106.
60. Bhutani MS. Digital analysis of EUS images: "promising" method, but is it ready for "prime time"? Gastrointest Endosc 2008;67:868-70.
61. Săftoiu A. State-of-the-art imaging techniques in endoscopic ultrasound. World J Gastroenterol 2011. In press.
62. Săftoiu A, Gheonea DI. Tridimensional (3D) endoscopic ultrasound—a pictorial review. J Gastrointestin Liver Dis 2009;18:501-5.
63. Molin S, Nesje LB, Gilja OH, et al. 3D-endosonography in gastroenterology: methodology and clinical applications. Eur J Ultrasound 1999;10:171-7.
64. Tokiyama H, Yanai H, Nakamura H, et al. Three-dimensional endoscopic ultrasonography of lesions of the upper gastrointestinal tract using a radial-linear switchable thin ultrasound probe. J Gastroenterol Hepatol 1999;14:1212-8.
65. Yoshino J, Nakazawa S, Inui K, et al. Volume measurement using tissue characterization of three-dimensional endoscopic ultrasonographic images. Endoscopy 2000;32:624-9.
66. Watanabe M, Kida M, Yamada Y, et al. Measuring tumor volume with three-dimensional endoscopic ultrasonography: an experimental and clinical study (including video). Endoscopy 2004;36:976-81.
67. Inui K, Miyoshi H, Yoshino J. Bile duct cancers: What can EUS offer? Intraductal US, 3D-IDUS? FNA—is it possible? Endoscopy 2006;38(suppl 1):S47-9.
68. Futawatari N, Kikuchi S, Sakuramoto S, et al. A new diagnostic method for early gastric cancer: volume measurement by 3-dimensional endoscopic ultrasonography in early gastric cancer and its clinical significance. Anticancer Res 2008;28:2907-12.
69. Abe T, Kakemura T, Fujinuma S, et al. Successful outcomes of EMR-L with 3D-EUS for rectal carcinoids compared with historical controls. World J Gastroenterol 2008;14:4054-8.
70. Sumiyama K, Suzuki N, Kakutani H, et al. A novel 3-dimensional EUS technique for real-time visualization of the volume data reconstruction process. Gastrointest Endosc 2002;55:723-8.
71. 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.
72. Hünerbein M, Pegios W, Rau B, et al. Prospective comparison of endorectal ultrasound, three-dimensional endorectal ultrasound, and endorectal MRI in the preoperative evaluation of rectal tumors: preliminary results. Surg Endosc 2000;14:1005-9.
73. Kim JC, Cho YK, Kim SY, et al. Comparative study of three-dimensional and conventional endorectal ultrasonography used in rectal cancer staging. Surg Endosc 2002;16:1280-5.
74. West RL, Dwarkasing S, Briel JW, et al. Can three-dimensional endoanal ultrasonography detect external anal sphincter atrophy? A comparison with endoanal magnetic resonance imaging. Int J Colorectal Dis 2005;20:328-33.
75. Murad-Regadas SM, Regadas FS, Rodrigues LV, et al. The role of 3-dimensional anorectal ultrasonography in the assessment of anterior transsphincteric fistula. Dis Colon Rectum 2010;53:1035-40.
76. Buchanan GN, Bartram CI, Williams AB, et al. Value of hydrogen peroxide enhancement of three-dimensional endoanal ultrasound in fistula-in-ano. Dis Colon Rectum 2005;48:141-7.
77. Santoro GA, Fortling B. The advantages of volume rendering in three-dimensional endosonography of the anorectum. Dis Colon Rectum 2007;50:359-68.

Received February 7, 2011. Accepted March 25, 2011.

Current affiliations: Department of Clinical Medicine (P.F., M.G.M., G.C.), Gastroenterology Unit, University of Bologna/Hospital of Imola, Bologna, Italy; Research Center of Gastroenterology and Hepatology (A.S.), University of Medicine and Pharmacy, Craiova, Romania; American University of Beirut (M.A.E.), Medical Center, Beirut, Lebanon.

Reprint requests: Dr. Pietro Fusaroli, University of Bologna/AUSL di Imola, Ospedale di Castel S. Pietro Terme (BO), Viale Oriani 1, 40024 Italy.