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Endoscopic ultrasonography: Enhancing diagnostic accuracy

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ABSTRACT

Endoscopic ultrasound (EUS) is an essential technique for the management of several diseases. Over the years, new technologies have been developed because to improve and overcome certain limitations related to EUS guided tissue acquisition. Among these new methods, EUS guided elastography and contrast enhanced EUS has arisen as the most widely recognized and available. We will review in this manuscript the different techniques of elastography and contrast enhancement. Nowadays, there are well establish indications for advance imaging, mainly for supporting the management of pancreatic diseases (diagnosis of chronic pancreatitis and differential diagnosis of solid and cystic pancreatic tumors) and characterization of lymph nodes. However, there are more data on new potential indications for the near future.

1. Introduction

The introduction of endoscopic ultrasound (EUS) into clinical practice was an important advancement in the management of several diseases, with clear clinical indications [1]. EUS has significantly changed the management of up to 50% of patients [2–5]. Nevertheless, an accurate diagnosis cannot always be determined using only conventional B-mode EUS imaging. Although new ultrasound systems associated to EUS provide highly accurate images in almost any indication (biliopancreatic indications, evaluation of lymph nodes, study if liver diseases or analysis of gastrointestinal lesions, for instance), to distinguish between different diseases can be real challenging. In many cases, EUS-guided tissue acquisition (TA) is needed. Nowadays, the accuracy of EUS-guided TA is very high, with sensitivities ranging between 80 and 85%, and specificities approaching 100%, mainly related to the development of EUS specific devices, among them, EUS needles [6, 7]. There has been a great evolution from standard cytological needles to the new histological ones, which are able to provide with more and better samples. In fact, it possible to obtain not only a cyto-histological diagnosis, but also specific information on lesion type, based on immunohistochemistry, molecular profiling [8–10]. However, EUS-guided TA is technically demanding, and in certain occasions multiple punctures may be necessary to obtain the diagnosis; and even after repeated sampling, cytohistologic assessment can be falsely negative [11], especially in the case of solid pancreatic masses in patients with advanced chronic pancreatitis [12, 13]. Hence, new methods associated to EUS have emerged, allowing a more accurate and noninvasive characterization of lesions, limiting the need for EUS-guided TA and guiding biopsies from areas with the highest suspicion of malignancy.

2. EUS guided advance imaging

Some techniques have emerged to increase the diagnostic capabilities of EUS. Among them, EUS-guided elastography (EUS-E) and contrast enhanced harmonic EUS (CEH-EUS) have raised over others, having demonstrated its accuracy in different clinical scenarios.

We will focus on the technique, for subsequently analyzed accepted clinical applications, in which they have increased the diagnostic yield of standard B-mode EUS.

2.1. EUS guided strain elastography

EUS-E is a noninvasive technique that measures elasticity in real time by registration of differences in distortion of the EUS image after application of slight pressure by the EUS probe. The elasticity modulus can be calculated from the strain and the stress of the evaluated structures. And extended combined autocorrelation method have been designed, allowing the reconstruction of the tissue elasticity of the

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Table 1
EUS guided elastographic classification and/or significance.

	Stiffness	Malignancy
Qualitative Elastography		
Homogenous blue predominant	Hard	Yes
Heterogeneous blue predominant	Hard	Yes
Heterogeneous green predominant	Intermediate	No
Homogenous green predominant	Intermediate-soft	No
Heterogeneous green and blue without predominance	Intermediate-hard	Undetermined
Quantitative Elastography		
SR > 10	Hard	Yes
SR < 10	Intermediate	No
SH > 150	Intermediate-soft	No
SH 50-150	Intermediate	No
SH < 50	Hard	Yes

different structures based on a 3-dimensional finite element model. This allows a highly accurate estimation of tissue elasticity distribution and adequate compensation of sideslips. The basis for elastography is that different pathologic processes, including inflammation, fibrosis, and cancer, all induce alterations in tissue stiffness [14–16]. Strain elastography analysis can be evaluated in a qualitative manner, based on color map distribution, or quantitively, by evaluating the strain ratio (SR) and strain histogram (SH).

- Qualitative EUS Elastography

For the elastographic analysis, a region of interest (ROI) is manually selected to include the whole targeted lesion, when possible, as well as surrounding tissues. Maximal sensitivity for elastographic registration is recommended. Elasticity (on a scale of 1–255) is depicted using a color map (red–green–blue), wherein hard tissue is shown in dark blue, medium hard tissue in cyan, tissue with intermediate hardness in green, medium soft tissue in yellow, and soft tissue in red. The elastography pattern is demonstrated by superimposing the color pattern on a conventional B-mode picture. Usually, a two-panel image is used for presentation, with the conventional grey-scale B-mode image on the right side and the elastographic image on the left. Elastographic software, to avoid bias on manual selection of the imagen allows performing a frame average evaluation. The system also selects the optimal frames to analyze. Table 1 summarizes the elastographic patterns and its signification [14].

- Quantitative EUS elastography

There are two options for quantitative elastography evaluation: a strain histogram and strain-ratio. In both cases, the first step is to obtain a stable elastographic images, as previously described [14].

2.1.1. *Strain histogram*

The strain histogram is a graphical representation of the color distribution in a selected image field. SH are based on the qualitative EUS-E data for a manually selected ROI within the standard elastography image. The x-axis represents the elasticity of the tissue, from 0 (hardest) to 255 (softest). The y-axis represents the number of pixels in each elasticity level in the ROI. The mean value of the histogram corresponds to the global hardness or elasticity of the lesion [14]. Table 1 summarizes the SH values and its correlation.

2.1.2. *Strain ratio*

The calculation of SR, which analyzes the elastographic picture of

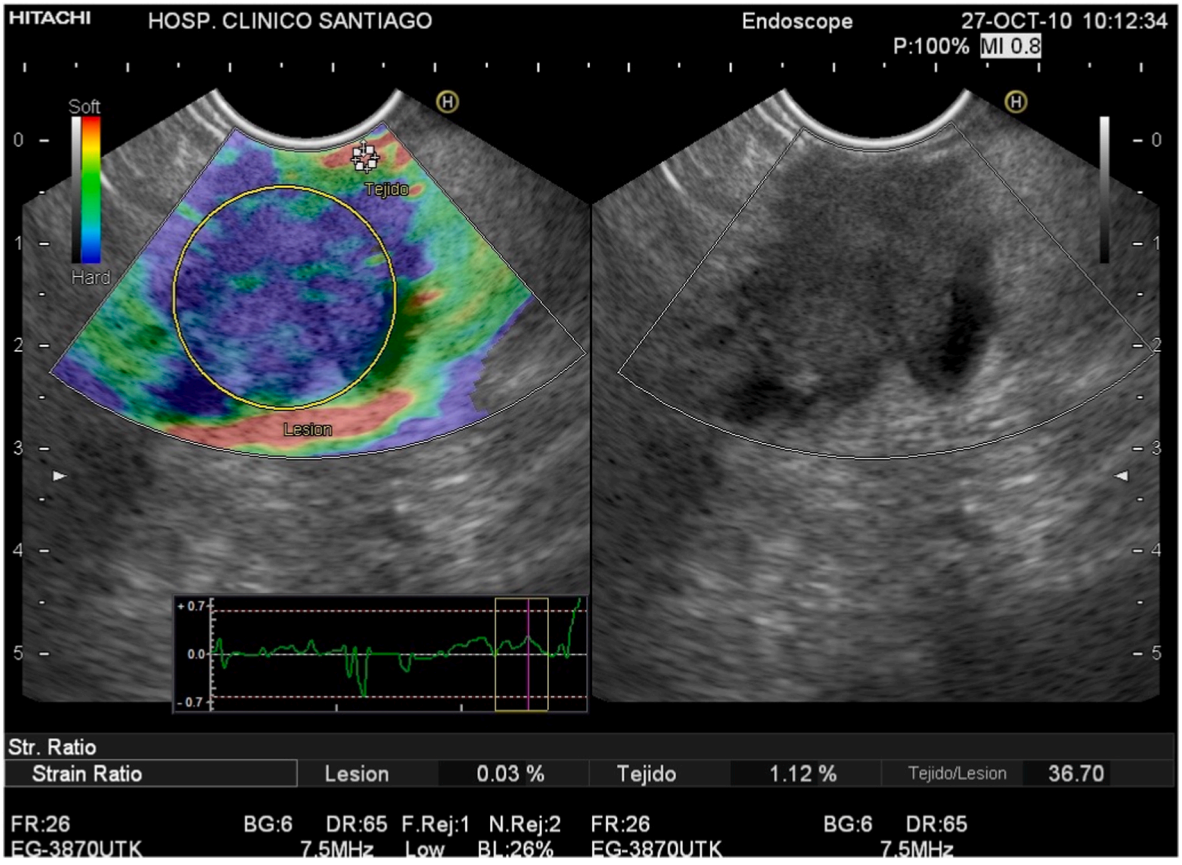

Fig. 1. EUS guided elastographic evaluation of a solid pancreatic tumor, with a heterogeneous blue predominant pattern and a SR of 36.70, corresponding to a pancreatic adenocarcinoma. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

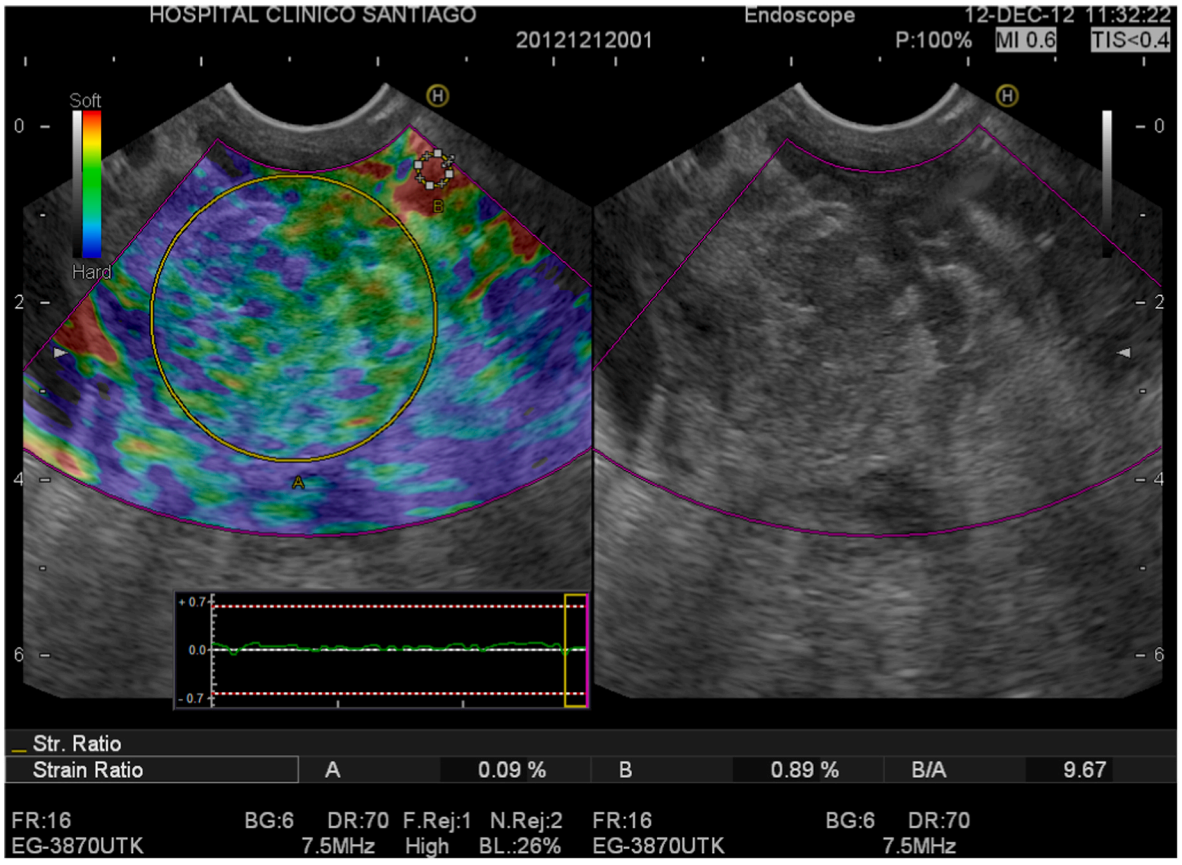

Fig. 2. EUS guided elastographic evaluation of a solid pancreatic tumor, with a heterogeneous green predominant pattern and a SR of 9.67, corresponding to a mass forming chronic pancreatitis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the target lesion in relation to the surrounding tissues, is an attempt to address this problem. As for the hue histogram, SR calculation is based on standard qualitative EUS-E data. Two different areas (A and B) are selected for quantitative elastographic analysis. Area A is selected to include as much of the target lesion as possible, without including the surrounding tissues. Area B is selected within a soft (red) reference area outside the target lesion, preferably the gut wall. The SR is calculated as the quotient of B/A. An assumption of this method is that the investigated disease does not significantly alter the hardness of the reference connective or fat tissues [15]. Table 1 summarizes the SR values and its correlation.

2.2. EUS guided shear wave elastography

EUS-guided shear wave elastography (SWE) has been available since 2019 and use absolute values to objectively calculate tissue elasticity [17]. This modality involves a doppler-like ultrasound technique to monitor shear-wave propagation and to measure the velocity of the shear wave. Theoretically, greater tissue elasticity corresponds to faster shear-wave propagation. As an elastic module, the shear-wave velocity (Vs) is measured in a target lesion. The Vs is displayed in meters per second (m/s) or kilopascals (kPa) with Young's modulus $E = 3(Vs2\ \rho)$ where E is Young's modulus, Vs is the shear-wave velocity and ρ is the tissue density. Stiffer tissue is associated with faster shear-wave propagation. Using the reliability index, the percentage of the net amount of effective shear-wave velocity (VsN, %) is calculated to determine whether shear-wave propagation is detected correctly and whether unnecessary components other than those generated by shear-wave propagation existed in the ROI according to predefined rejection conditions. The ROI is 5 × 10 mm (height x width) and is set at a site close to the tissue or lesion that is evaluated, avoiding structures such as cystic components, blood vessels and calcifications as much as possible. The measurement is performed at a time with as little respiratory fluctuation as possible to avoid breathing artifacts [17–19].

2.3. Contrast enhanced EUS

CEH-EUS is another methodology to improve the EUS-based differential diagnosis in different indications [20, 21]. 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 [22]. The principle of contrast-enhanced ultrasound imaging is to selectively depict signals arising from microbubbles of ultrasound contrast agents 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. The use of low mechanical index, 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, has led to a big improvement in the method, increasing its usefulness and diagnostic yield [23].

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. After intravenous injection, the arterial phase occurs within 15–30 s before a venous phase starts approximately 30–45 s after injection. 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 (homogenous or heterogeneous) [24]. Besides qualitative descriptions, the intensity of

Table 2
Summary of results of EUS guided elastography in solid pancreatic tumors.

Reference	Patients	Methodology	Sensitivity (%)	Specificity (%)
Giovannini et al., 2006 [57]	24	Qualitative	100	67
Saftoiu et al., 2008 [71]	43	Hue Histogram	91	87
Iglesias-Garcia et al., 2009 [72]	130	Qualitative	100	85
Giovannini et al., 2009 [58]	121	Qualitative	92	80
Iglesias-Garcia et al., 2010 [73]	86	Strain-ratio	100	92
Saftoiu et al., 2011 [74]	258	Hue Histogram	93	66
Figueiredo et al., 2012 [75]	47	Strain-ratio	90	75
Dawwas et al., 2012 [76]	111	Strain-ratio	100	22
Havre et al., 2014 [77]	48	Strain-ratio	67	71
Opacic et al., 2015 [78]	149	Histogram	98	50
Mayerle et al., 2016 [79]	85	Strain-ratio	96	43
Okasha et al., 2017 [80]	172	Qualitative & Strain-ratio	98	77
Rustemovic et al., 2017 [81]		Strain-ratio	100	95
Iglesias-Garcia et al., 2017 [27]	62	Strain-ratio Strain-Histogram	100	92.3
Ignee et al., 2018 [30]	218 (<15 mm)	Qualitative Strain-ratio	84	68
Ohno et al., 2021 [33]	64	SWE Strain-Histogram		
Kataoka et al., 2021 [82]	126	Qualitative	94	23

depicted contrast signals can be quantified by the calculation of time–intensity curves both during the wash-in and wash-out phases. 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 [25].

3. Clinical applications of EUS guided advance imaging

Advance imaging has supposed a clear add-value in many of these indications. We will summarize its role in those indications.

3.1. Pancreatic diseases

3.1.1. Solid pancreatic tumors

EUS-E has been shown to be highly accurate for the differential diagnosis of solid pancreatic tumors [15]. A homogeneous green pattern usually represents normal pancreatic parenchyma; a heterogeneous, predominantly green pattern with slight yellow and red lines is present in inflammatory pancreatic masses; a heterogeneous, predominantly blue pattern with small green areas and red lines and a geographic appearance is present mainly in pancreatic malignant tumors, while a homogeneous blue pattern is found in pancreatic neuroendocrine malignant lesions (Table 1). Thus, pancreatic cancer (PC) shows an almost unequivocally very stiff pattern in comparison to the surrounding pancreatic parenchyma, thus showing a typical blue pattern. PC can be excluded with high accuracy when a predominantly soft (green) pattern is seen. Chronic pancreatitis (CP) can be differentiated from PC by a difference in the elastography appearance in most of the cases [15]. It is important to highlight the different pattern in cases of autoimmune pancreatitis, since this entity shows a characteristically diffuse stiff pattern in the whole pancreatic parenchyma, not just in the focal mass [26].

Regarding quantitative EUS-E, malignant pancreatic masses and neuroendocrine tumors produce higher SR and lower SH than inflammatory masses and normal parenchyma. It has been suggested that a SR $>$ 10 or a mean SH value of $<$50 is associated with malignancy (Fig. 1), whereas the presence of a SR $<$ 10 or a mean SH value of $>$50 is associated with benign diseases (Fig. 2) [15, 27].

Different meta-analyses have evaluated the diagnostic performance of EUS-E for the characterization of malignant pancreatic tumors. EUS-E showed a high sensitivity (92%–98%), but a low specificity (67%–76%) in this clinical application [28, 29]. In a recent multicenter study, 50% of solid pancreatic lesions $\leq$15 mm proved to be soft, and the probability of a soft lesion to be malignant was negligible [30]. Therefore, due to its very high negative predictive value for malignancy EUS-E may have a specific value for small pancreatic lesions. However, there is a reason for the low specificity of this methodology, the difficult interpretation of cases with calcific CP. Calcifications presents a hard blue pattern, as expected, so it is extremely important to evaluate the areas in CP cases where there are no calcifications. This may lead to an increase in the diagnostic yield of elastography in this particular indication. An additional value is the role of elastography in detecting blue spots (hard tissue) inside the mass-forming CP and directing the area of sampling. However, recent studies failed to show any impact of EUS-guided TA guided by elastography [31, 32]. Recent studies have evaluated SWE in this clinical setting.

Ohno et al., compared SWE with the SH in solid pancreatic tumors. The Vs (m/s) values of were 2.19 for PC, 1.31 for pancreatic neuroendocrine neoplasm, 2.56 for mass-forming pancreatitis and 1.58 for metastatic tumors. Vs showed no significant difference based on the disease. The mean strain values were 45.5 for PC, 47.3 for neuroendocrine tumors, and 74.5 for inflammatory process. In the comparison of tissue elasticity between PC and inflammatory lesions, Vs showed no significant difference ($p = 0.5687$); however, the mean strain value was significantly lower in PC cases (45.4 vs 74.5: $p = 0.0007$) [33].

We summarize in Table 2 the diagnostic accuracy of EUS-E.

Elastography has also shown to have impact in the staging of PC. Yamada et al. [34] evaluated the vascular staging in 44 patients who underwent both dynamic CT and EUS-B mode. Sensitivity, specificity, and accuracy were 0.733, 0.697 and 0.708 on dynamic- CT; and 0.733, 0.606 and 0.646 in EUS B-mode. When performing an elastographic analysis, these results increased to 0.917, 0.900 and 0.906. In 27 subjects with a tumor contacting a vessel with no vascular obstruction or stenosis on dynamic-CT, the sensitivity, specificity, and accuracy were 0.556, 0.750 and 0.690 on dynamic-CT; 0.667, 0.700 and 0.690 in EUS B-mode; and 0.889, 0.850 and 0.862 in elastography. These results suggest a potential role of EUS-E to optimize local staging of PC.

CEH-EUS can differentiate the nature of solid pancreatic lesions, particularly PC that is typically hypoenhanced (Fig. 3). In this regard, PC differs from other solid lesions such as neuroendocrine tumors and pancreatic metastases, that usually appear as hyperenhancing lesions (Fig. 4), or from pseudotumoral (mass forming) focal CP, typically present as isoenhanced lesions. CEH-EUS can be successfully used for evaluation and diagnostic workup of focal pancreatic masses [21–24]. Table 3 shows the different CEH-EUS patterns and correlation to final diagnosis.

Some meta-analyses have shown the accuracy of this methodology in the differential diagnosis of solid pancreatic tumor, mainly for the detection of PC. Sensitivities ranges from 85 to 90%, and specificities from 80 to 90% [35–37]. A large multicenter trial with 167 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 CP and PC. Using a model of artificial neural networks, authors found an increased sensitivity (94%) and specificity (94%) [38].

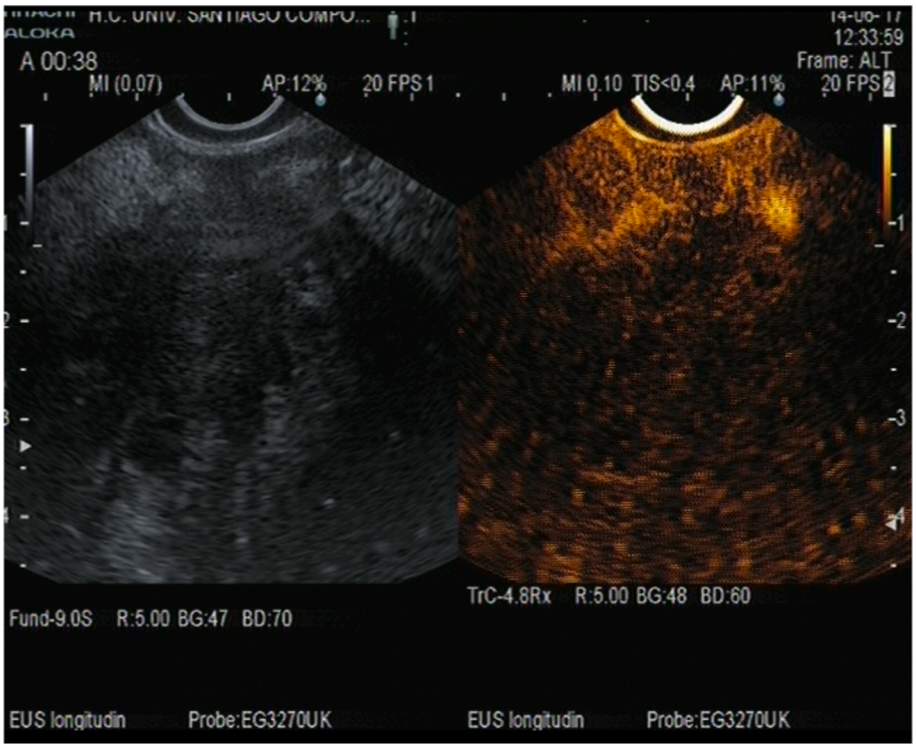

Fig. 3. Contrast enhanced harmonic EUS evaluation of a solid pancreatic tumor, presenting an hypovascular pattern, corresponding to a pancreatic adenocarcinoma.

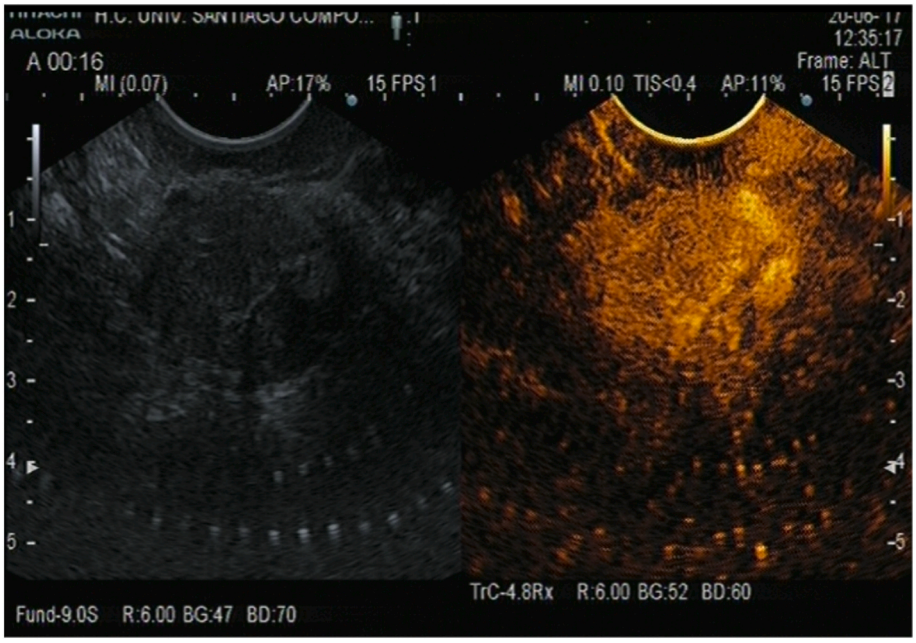

Fig. 4. Contrast enhanced harmonic EUS evaluation of a solid pancreatic tumor, presenting an hypervascular pattern, corresponding to a neuroendocrine tumor.

Table 3
CEH-EUS patterns and its correlation to final diagnosis of pancreatic solid tumors.

CEH-EUS Pattern	Type of pancreatic tumor
Hypovasular/Hypo-enhancement	Pancreatic adenocarcinoma
Isovascular/Iso-enhancement	Inflammatory process
Hypervasular/Hyper-enhancement	Neuroendocrine Tumor
	Metastasis

The diagnostic yield of CEH-EUS for the diagnosis of PC versus non-PC lesions below 15 mm has been confirmed in a multicenter trial (219 patients), yielding an overall 89% accuracy [39]. Recently, time–intensity curve analysis has also been used with a diagnostic accuracy of 91% [25].

CEH-EUS can be used for targeting EUS-TA. A metanalysis, showed that CEH-EUS guided-TA seems to be superior to standard sampling in pancreatic solid lesions [40]. However, a recent study showed that diagnostic rates were not significantly different, however it led to a lower number of needles passes needed to reach diagnosis [41].

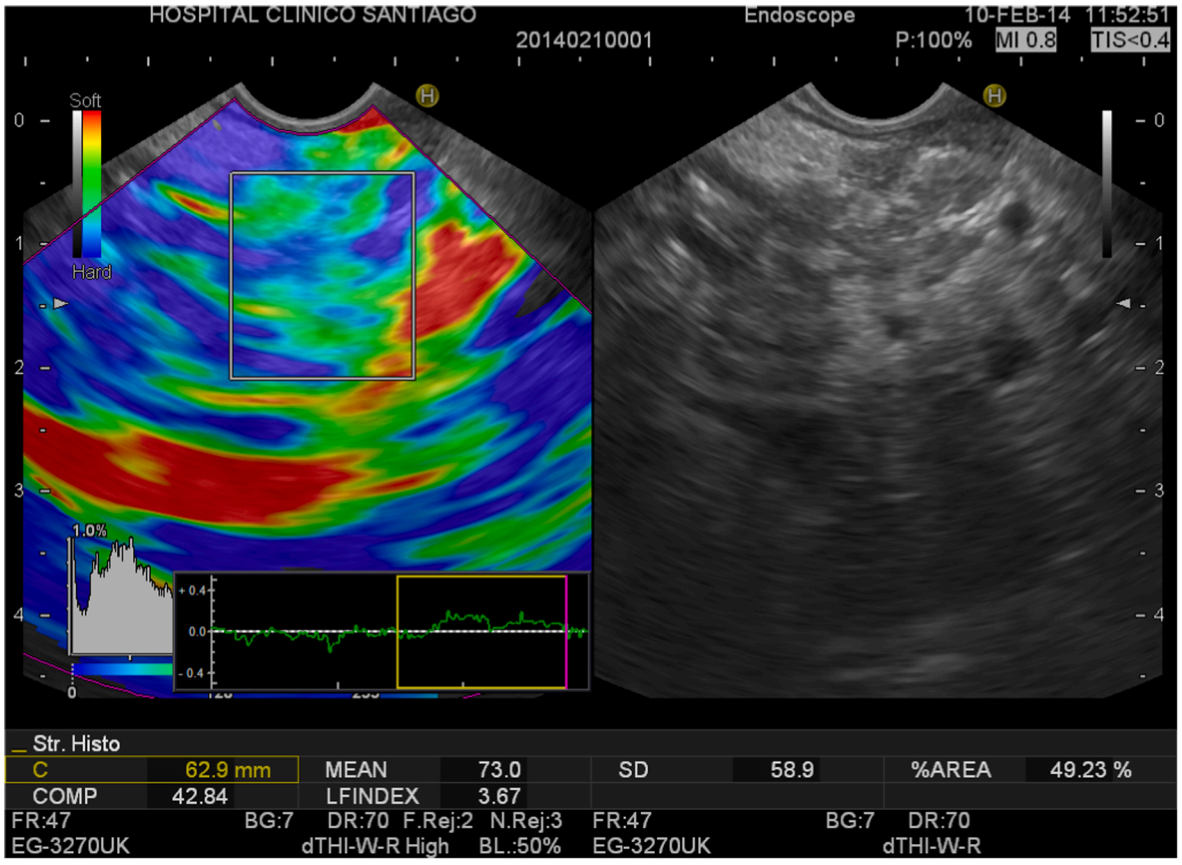

Fig. 5. EUS guided elastographic evaluation showing the typical heterogenous green pattern in a case of early chronic pancreatitis, with a strain histogram with a mean of 73. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

CEH-EUS can also optimize the staging of PC, either by better evaluation of vascular invasion [42], but also highlighting the presence of small liver metastasis [43].

The combine use of all EUS technologies have shown to even improve the management of patients with solid pancreatic lesions. A recent meta-analysis of 17 studies to showed a pooled sensitivity and specificity for qualitative elastography of 97% and 67%, respectively; for SR 98% and 62%; for contrast enhancement 90% and 76%: and for TA 84% and 96% [44]. Iglesias-Garcia et al. [27] showed that overall accuracies for the determination of malignancy using elastography, CEH-EUS, their combination, and EUS-guided TA were 98.4%, 85.5%, 91.9% and 91.5% respectively. Importantly in this study the combination of advance imaging provided information for stablishing the malignant potential. In the study from Costache et al. [45] EUS-E showed a sensitivity, specificity and accuracy of 100%, 29.63% and 80.41%, respectively. For CEH-EUS (considering hypoenhencement as malignant) were 98.57%, 77.78%, and 92.78%, respectively. Combining CEH-EUS and EUS-E, sensitivity, specificity, and accuracy were 98.57%, 81.48%, and 93.81%, respectively. Best values were obtained using a sequential clinical algorithm based on the initial use of elastography, followed by contrast enhancement.

3.1.2. *Chronic pancreatitis*

In our experience, normal pancreas shows a homogeneous green pattern, whereas a heterogeneous green predominant pattern is typical in CP. Normal pancreas usually presents lower SR levels compared to inflammatory and malignant lesions. As a measure of the degree of pancreatic fibrosis in CP, Iglesias-Garcia et al. found a significant direct linear correlation between the number of EUS criteria for CP and the SR ($r = 0.813$; $p < 0.0001$). Accuracy of EUS-E for diagnosing CP was 91.1%, and the SR also varied significantly among the different Rosemont classification groups (1.80 normal pancreas, 2.40 indeterminate group, 2.85 suggestive of CP, 3.62 consistent with CP, $p < 0.001$) [46]. Fig. 5 shows a elastographic in early CP. Itoh et al. [47] demonstrated a high correlation between the histological fibrosis score and the EUS-E, yielding an area under the curve of 0.90 in all stages. EUS-E is also useful for establishing the severity of the disease, so as higher the SR, as higher the possibility of exocrine pancreatic insufficiency [48]. Our group have developed the EUS multimodal test for the evaluation of suspected CP [49]. This method includes EUS criteria for CP, SR, and endoscopic pancreatic function test (ePFT) with the distensibility of the main pancreatic duct. SR was abnormally high in all patients. Peak bicarbonate concentration was decreased in 81.1% and compliance was reduced in 77.3%. The presence of abnormal morphological and functional evaluation of the pancreas could support the clinical suspicion of early CP in the appropriate clinical setting. We have recently published that the degree of pancreatic fibrosis as evaluated by elastography correlates with the ePFT in patients with clinical suspicion of CP and inconclusive EUS findings ($r = 0.715$, $p < 0.0001$). Using the ePFT as gold-standard, EUS-E yielded a diagnostic accuracy of 93.4% for CP [50].

EUS-guided SWE has also been tested in CP. Yamashita et al. showed a correlation between the shear-wave velocity and the Rosemont classification and certain EUS features of CP. Shear-wave velocity was consistent with CP (2.98 m/s) and were suggestive of CP (2.95 m/s). The results were significantly higher than those found for normal tissue (1.52 m/s). This methodology also showed high accuracy for diagnosing CP, with the area under the curve of 0.97. The velocity cut-off of 2.19 m/s showed 100% sensitivity and 94% specificity for CP.

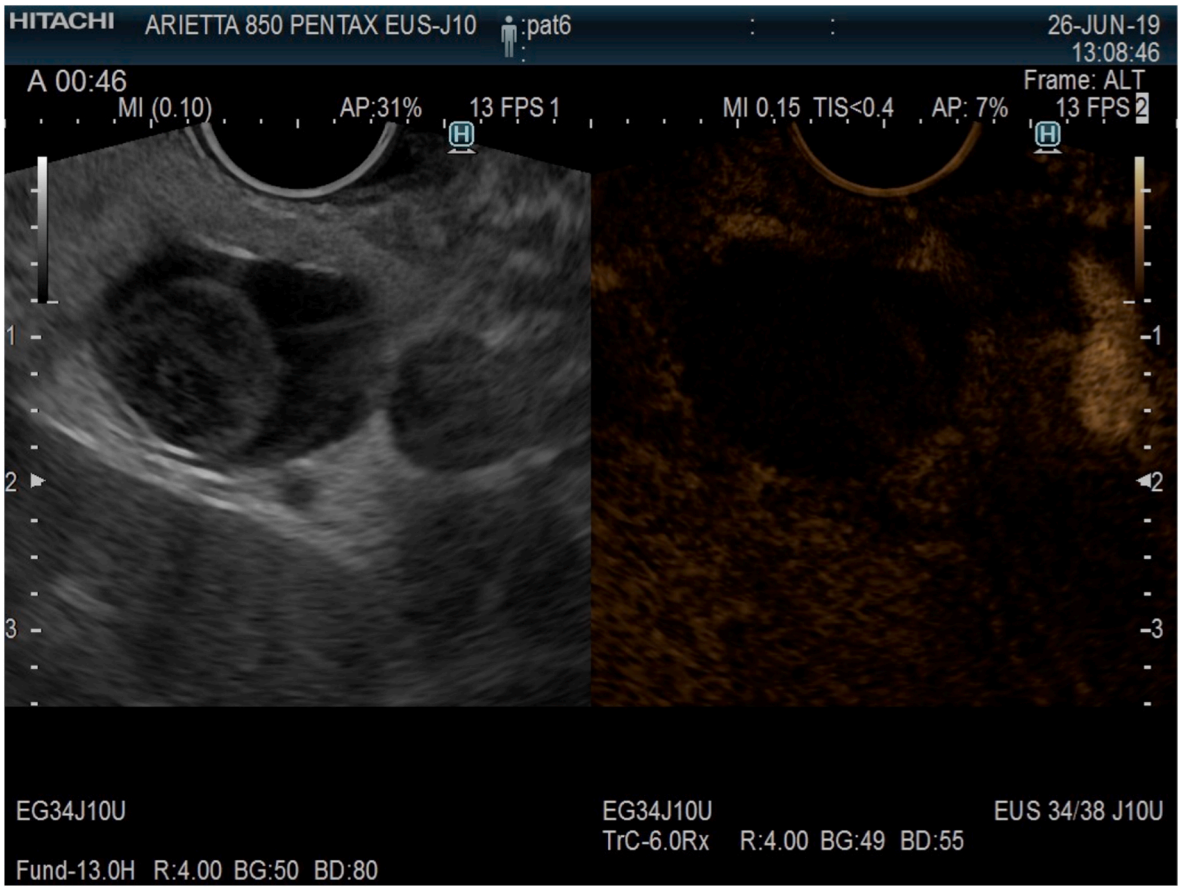

Fig. 6. Contrast enhanced harmonic EUS evaluation of a cystic pancreatic tumor, with a suspected mural nodule in B-mode, but without contrast uptake, finally corresponding to a mucin plug.

3.2. Cystic pancreatic tumors

Cystic pancreatic tumors (CPT) are a frequent incidental finding. CEH-EUS allows for distinguishing between pseudocysts and real CPT (among them mucinous cystic tumors) based on the demonstration of the vascularization of the septa of the lesion and nodules [23]. In this setting, it is crucial to characterize a lesion as benign, premalignant, or malignant. CEH-EUS appears as a very useful tool, with the capability to identify high-risk stigmata and/or worrisome features, by enabling the assessment of the vascularization of different structures such as cyst walls, septa, or mural nodules. Discrimination of contrast-enhancing mural nodules from non-enhancing mucin plugs has become one of the main indications of CEH-EUS in CPT (Fig. 6).

Harima et al. reported a diagnostic accuracy for mural nodules of 92% for CT, 72% for EUS, and 98% for CEH-EUS, being CEH-EUS clearly superior to CT ($p < 0.05$) or EUS ($p < 0.01$) [51]. Kamata et al. compared CEH-EUS and B-mode EUS for the differential diagnosis of CPT, depending on the presence of mural nodules. They found a 75% specificity for CEH-EUS, superior to the 40% for B-mode EUS [52]. Fujita et al. observed that CT, MRI, and EUS were able to detect mural nodules in 86%, 71%, and 100% of cases, respectively [53]. However, B-mode EUS was not able to differentiate mucin plugs from real mural nodules. Based on CEH-EUS, authors could correctly classify all cases based on the vascular pattern. Similar results have been reported by Fusaroli et al., showing how CEH-EUS correctly detects mural nodules as solid components with features of hyperenhancement [54]. A recent systematic review and meta-analysis finally confirmed this topic, showing how it increases the diagnostic yield for the identification and characterization of malignant mural nodules [55].

3.3. Lymph nodes

Several studies have shown the role of EUS-E in lymph nodes (LN) evaluation, summarize in a review from Dietrich et al. [56]. Initial studies were conducted by Giovannini et al. [57]. In their first study, sensitivity and specificity for malignancy were 100 and 50%, respectively. A subsequent multicenter trial showed, considering benign lesions tests as negative and indeterminate and malignant lesion tests as positive, a sensitivity, specificity and overall accuracy for malignancy of 91.8%, 82.5% and 88.1% [58]. In the study from Janssen et al. three examiners evaluating the cases had accuracies ranging from 81.8 to 87.9% for benign LN and from 84.6 to 86.4% for malignant ones. Interobserver agreement yielded a $\kappa = 0.84$ [59]. Puga-Tejada et al. evaluated 121 patients, showing that with SR cutoff values of >14.0 and > 155, sensitivity and specificity for malignancy were 90.9% and 95.2%, respectively [60]. One meta-analysis, including 7 studies with 368 patients and 431 LN reported a pooled sensitivity of EUS-E of 88%, with a specificity of 85%. Thus EUS-E is a useful method to differentiate malignant from benign LN, complementary to EUS-guided TA (Fig. 7) [61].

CEH-EUS also plays a role in this setting. Combination of patterns with a quantitative analysis yielded a high accuracy. In TIC analysis, the velocity of reduction for homogeneous lesions showed a significant difference between malignant and benign lesions ($p = 0.0011$), and ROC curved cut-off value of 0.149 dB/s [62]. A meta-analysis published by Lisotti et al. analyzing 210 studies, with 336 patients, showed a pooled sensitivity of 87.7% and a pooled specificity of 91.8% for determining the malignant potential of the studied LN [63].

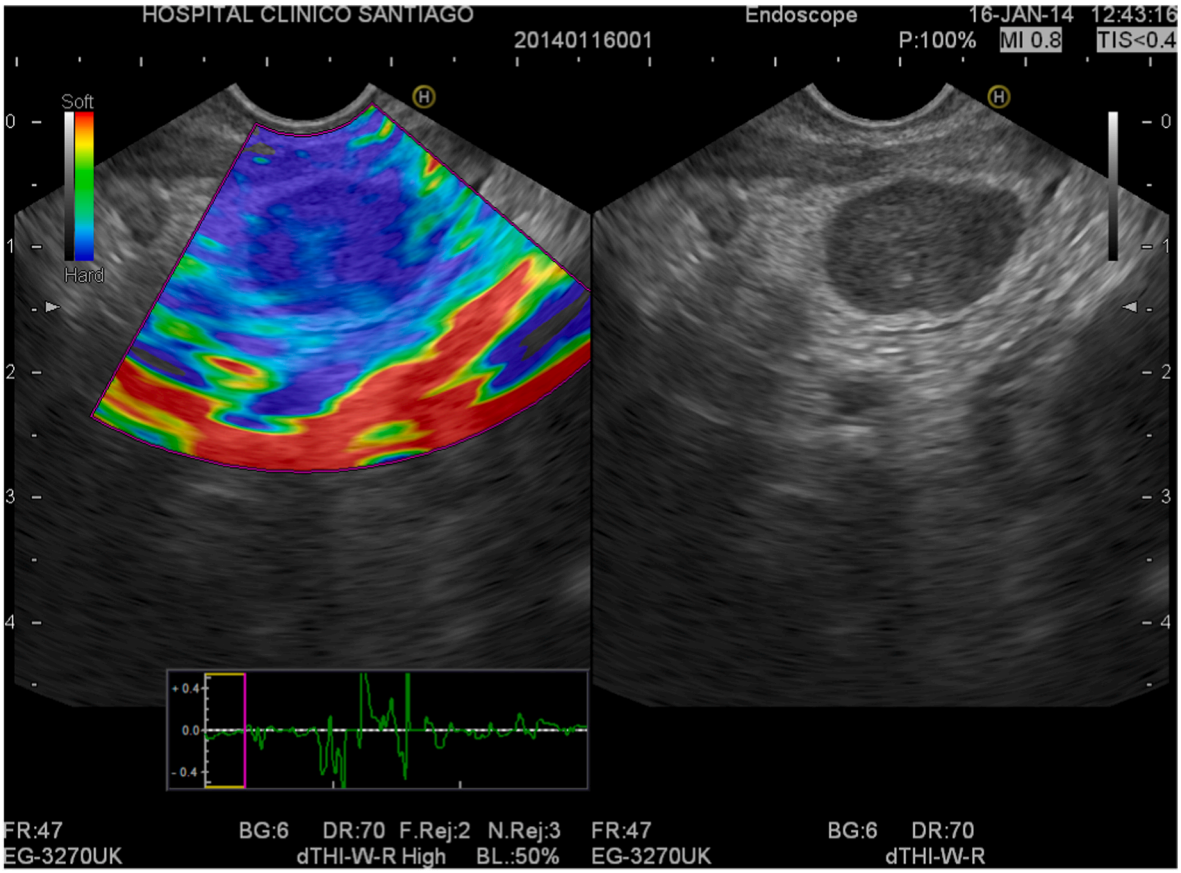

Fig. 7. EUS guided elastographic evaluation of an enlarged lymph node, presenting a heterogenous blue predominant pattern, finally confirmed to be malignant after tissue sampling. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.4. Gastrointestinal lesions

When facing a subepithelial lesions (SEL), differentiation between gastrointestinal stromal tumor (GIST) and other mesenchymal tumors such as leiomyoma or Schwannoma is essential. EUS-guided TA has shown good accuracy, however accessing small lesions is highly complex [64]. Therefore, differentiation by imaging is valuable for the management of these lesions.

Tsuji et al. used the elastic score to classify patterns of 25 gastric subepithelial lesions [65]. Their findings indicate that GIST are depicted as "hard" tissues compared with other SEL. In contrast, Ignee et al. reported difficulty in differentiating GIST from benign leiomyoma by pattern diagnosis using an elastic score [66]. The eventual usefulness of EUS-elastography in this field remains deserves further investigations.

Another potential and promising role of elastography is on the staging of esophageal and gastric cancer. Elastographic imagens might help to determine the degree of infiltration of the tumor, mostly to differentiate T3 from T4 lesions.

CEH-EUS has also shown a role in SEL. GIST tumors area usually hyperenhanced lesions, but with avascular areas inside, presenting a different patterns as compared to leiomyomas [66].

3.5. Transrectal EUS

EUS-E has demonstrated its usefulness in certain diseases that can be evaluated by transrectal EUS. Some studies showed its utility in pelvic endometriosis [67], fecal incontinence [68], or in rectal tumors. Catinean et al. showed that elastography offers higher sensitivity and specificity compared to B-mode EUS [69].

3.6. Other potential indications for EUS advance imaging

Given the current indications for conventional EUS, EUS advance imaging may be useful in evaluating solid lesions in left suprarenal glands, by differentiating between adenomas and metastases. Our preliminary unpublished data support this hypothesis. Another possible indication for EUS-E is differentiation between benign and malignant solid liver lesions [70]. Further studies soon will evaluate the usefulness of EUS advance imaging in diagnosing the aforementioned diseases and other indications. We believe both elastography and CEH-EUS will be an integral part of the EUS evaluation of any pathology that can alter tissue stiffness, including inflammation, fibrosis, and cancer.

4. Conclusion

EUS guided advance imaging, both elastography and contrast enhancement are well established techniques capable of differentiating fibrotic/inflammatory tissues from malignant lesions. They both EUS have demonstrated to differentiate between benign and malignant solid pancreatic masses, cystic pancreatic and lymph nodes with high accuracy, as well as to differentiate normal pancreatic tissues from early chronic pancreatitis. EUS-guided tissue sampling will still be needed in many situations. However, they can be useful for identifying cases in which biopsies are unnecessary and for directing biopsies to optimal areas in cases where histologic diagnosis is required.

5. Practice points

- EUS guided advance imaging are validated and useful tools for the evaluation of several diseases

- EUS guided elastography is very sensitive for the detection of pancreatic malignancy when a blue predominant patter and/or high levels of strain ratio and/or low levels of strain histogram are present
- Specific contrast enhanced vascular patterns are associated with specific pancreatic tumors (hypovascular - pancreatic cancer; hypervascular - pancreatic metastasis and neuroendocrine tumors; isovascular – inflammatory lesions)
- For cystic pancreatic lesions, contrast enhanced EUS is key in the differential diagnosis between mucin plugs and true mural nodules
- EUS guided elastography correlates with the severity of chronic pancreatitis
- Both techniques have shown it usefulness in determing the malignant potential of lymph nodes, when a blue pattern and a heterogeneous uptake of contrast is present.

6. Research agenda

- Analysis comparing the accuracy of EUS guided elastography analysis between strain ratio and strain histogram are needed in all accepted indications
- Protocolization and standardization of EUS shear wave elastography is mandatory to extend its use in clinical practice.
- For contrast enhance harmonic EUS, better contrast agents will be necessary, together with a simple and reproducible software for quantifications analysis
- Teaching EUS guided advance imaging is absolutely essential and needed for optimizing the usefulness of these 2 great techniques.

Declaration of competing interest

Julio Iglesias-Garcia MD, PhD; International Advisor and Teaching activities for Pentax Medical Company. Jose Lariño-Noia MD, PhD; Daniel de la Iglesia-García MD, PhD; J. Enrique Dominguez-Muñoz MD, PhD

No potential conflicts of interest relevant to this article.

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