

## REVIEW

# Endoscopic ultrasound in the diagnosis of chronic pancreatitis

Julio Iglesias-García<sup>1</sup>, José Lariño-Noia<sup>1</sup>, Björn Lindkvist<sup>1,2</sup> and J. Enrique Domínguez-Muñoz<sup>1</sup>

<sup>1</sup>Department of Gastroenterology and Foundation for Research in Digestive Diseases (FIENAD). Hospital Universitario de Santiago. Santiago de Compostela. A Coruña, Spain. <sup>2</sup>Institute of Medicine. Sahlgrenska Academy. University of Gothenburg. Gothenburg, Sweden

## ABSTRACT

Diagnosis of chronic pancreatitis (CP) remains a challenge. Endoscopic ultrasound (EUS) can be considered nowadays as the technique of choice for the morphological diagnosis of this disease. More than three or four EUS defined criteria of CP need to be present for the diagnosis of the disease. The development of the more restrictive Rosemont classification aims to standardize the criteria, assigning different values to different features but its impact on the EUS-based diagnosis of CP is debatable. A combined use of endoscopic function test and EUS has even increased the diagnostic yield. Elastography and FNA may be also of help for diagnosing CP. EUS also provides with very valuable information on the severity of the disease, giving key information that may influence in the treatment. Differential diagnosis of solid pancreatic masses in the context of a CP is also challenging, EUS plays a key role in this context. It provides with the possibility of obtaining specimens for histopathological diagnosis. Nowadays, new developed techniques associated to EUS, like elastography and contrast enhancement, are also showing promising results for the differentiating between these pancreatic lesions.

**Key words:** Endoscopic ultrasound. Diagnosis. Chronic pancreatitis.

## INTRODUCTION

Chronic pancreatitis (CP) is a progressive and irreversible inflammation of the pancreatic gland that ultimately leads to fibrosis and destruction of normal tissue resulting in morphological alterations and exocrine as well as endocrine dysfunction (1). The diagnosis is easy to establish in advanced stages of the disease, when the presence of pancreatic calcifications, atrophy of the gland and pancreatic

duct dilation can be visualized by conventional imaging techniques such as abdominal ultrasound and computed tomography. Early CP, on the other hand, remains a major diagnostic challenge today. Pathological specimens from the pancreas are very difficult to obtain and there is no clear international consensus of a histological or clinical definition of CP.

Endoscopic retrograde cholangiopancreatography (ERCP) has previously been considered as the gold standard for the diagnosis of CP. However, due to the possible and serious complications related to the procedure and the fact that the parenchyma is not visualized, ERCP is no longer considered the method of choice (2). Among pancreatic function tests, the secretin test has been demonstrated to have a high sensitivity and specificity for CP (3). The use of this test has been limited since it is difficult to perform and not widely available (4). Endoscopic ultrasonography (EUS) has emerged as a promising diagnostic technique for pancreatic disease since it is able to detect pancreatic parenchymal and ductal changes with high sensitivity. Furthermore, fine needle biopsies can be obtained by EUS for cytological or histological evaluation, and CP related complications could be treated with EUS guided interventions. The use of EUS for the diagnosis of CP will be reviewed in this article.

## EUS IN THE DIAGNOSIS OF CHRONIC PANCREATITIS

EUS has the ability to produce high-resolution ultrasonography images of the pancreas due to the proximity of the transducer to the gland, avoiding interference by air in the intestine. EUS diagnosis of CP is based on specific criteria that have been described by the International Working Group for Minimum Standard Terminology in Gastrointestinal Endoscopy (5). These comprise five parenchymal criteria (hyperechoic foci, hyperechoic strands, parenchymal

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*Correspondence:* Julio Iglesias-García. Gastroenterology Department. Foundation for Research in Digestive Diseases (FIENAD). Hospital Universitario de Santiago. c/ Choupana, s/n. 15706 Santiago de Compostela. A Coruña, Spain  
e-mail: julio.iglesias.garcia@sergas.es

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mal lobularity, cysts, calcifications) and five ductal criteria (pancreatic duct dilation, pancreatic duct irregularity, hyperechoic pancreatic duct walls, visible pancreatic side branches, intraductal calcifications) (Fig. 1). The number of criteria that is needed to establish the diagnosis of CP and the relative weight of each criterion has been a matter of debate for several years. The first attempts to create an integrated evaluation of EUS based CP findings simply used the sum of positive criteria and defined EUS findings consistent with CP as a certain minimum number of positive criteria (6,7). In an attempt to allow for differentiated weighting of CP criteria and to harmonize EUS based diagnosis of CP, the Rosemont classification was published in 2009 (8). The Rosemont classification is a definition of EUS based CP criteria produced by a group of endosonography experts at an international consensus conference. Ductal and parenchymal EUS findings are divided into major A, major B and minor criteria (Table I). As opposed to the previous simple counting of criteria, the Rosemont classification gives different weight to different findings. Based on the number and character of positive EUS criteria, EUS evaluation is classified as "consistent with CP", "suggestive of CP", "indeterminate for CP", or "normal" (8) (Table II). This system agrees with the standard classification in 74% of cases, increasing to 84% when "suggestive of CP" was included as CP (8).

One of the most important weaknesses of EUS in the diagnosis of CP is concern about poor interobserver agreement (9). Interobserver agreement differs between EUS criteria. Duct dilation and lobularity (10) was demonstrated to have the highest agreement in one study while hyperechoic strands and parenchymal cysts were found to have the highest agreement in another study (11). Interobserver agreement for standard EUS classification *versus* Rosemont classification for CP has been evaluated in a

multicenter study. Fourteen experts evaluated 50-recorded videos using the standard EUS criteria (CP diagnosis if  $\geq 3$ ) and the Rosemont classification (considering "suggestive of CP" and "consistent with CP" as positive findings). Kappa score for inter observer agreement on the Rosemont classification was 0.65, and the kappa score for standard classification was 0.54 (n.s.). Best agreement was noted for calcifications (standard scoring), pancreatic duct calcifications (Rosemont classification) and pancreatic duct dilation (both systems). The poorest agreement was seen for lobularity without honeycombing (Rosemont classification). Patients were correctly classified as definite CP in 91.2% of cases according to standard scoring and 83.5% according to Rosemont classification; as mild CP in 50% according to standard scoring and 42.9% according to Rosemont classification; and not CP in 83.3% and 95.2% of cases respectively (12). The inability of the Rosemont classification to improve inter-observer agreement compared to standard EUS criteria has thereafter been confirmed in a recent study (13). The use of radial or linear echoendoscopes does not have a significant impact on inter observer agreement ( $k = 0.50$  and  $0.61$  respectively) (14).

### EUS vs. pancreatic function test and EUS plus endoscopic function test

Pancreatic function test have been used for diagnosis of early CP. The pancreatic function test with the highest sensitivity for CP is the secretin/cholecystokinin (CCK) stimulation test with aspiration of duodenal content by a dreilling tube or an endoscope during at least 45-60 minutes. The sensitivity and specificity of this test for diagnosing CP both exceed 90% (4). A high agreement between EUS and the secretin test has been demonstrated in several studies.

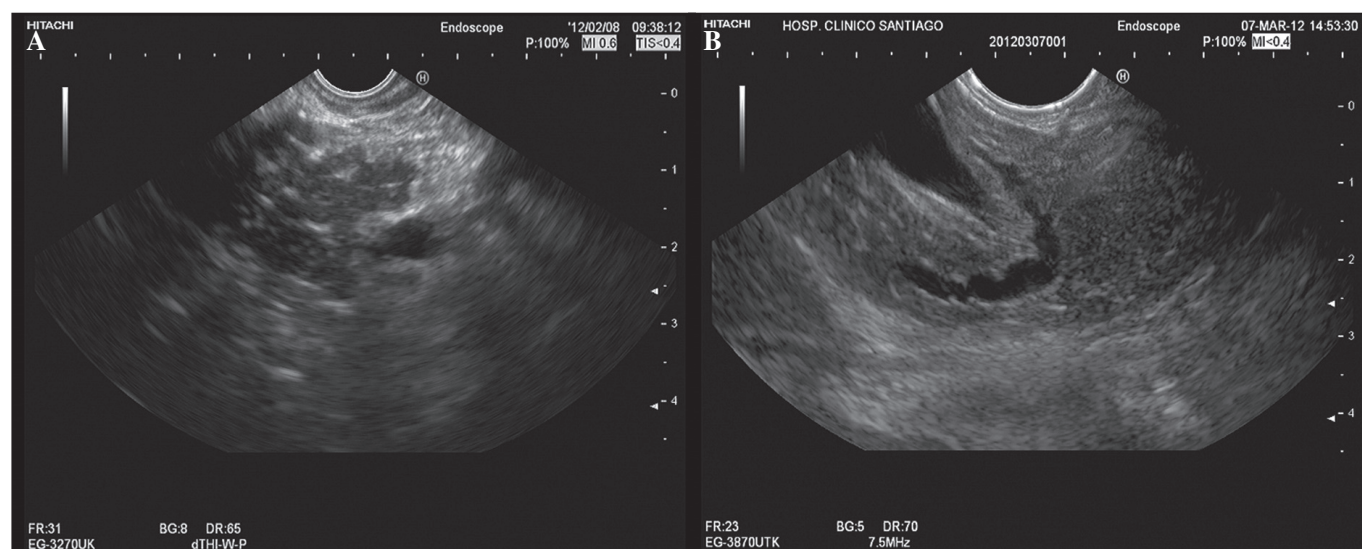


Fig. 1. Different EUS criteria in a patient diagnosed of chronic pancreatitis (parenchymal: Lobularity, strands and foci [A]; ductal: Irregular MPD with hyperchoic wall [B]).

**Table I. Consensus-based parenchymal and ductal features of CP according to the new Rosemont classification (adapted from reference 8)**

Feature	Definition	Major criteria	Minor criteria
Hyperechoic foci with shadowing	Echogenic structures $\geq 2$ mm in length and width that shadow	Major A	
Lobularity	Well-circumscribed, $\geq 5$ mm structures with enhancing rim and relatively echo-poor center		
A. With honeycombing	Contiguous $\geq 3$ lobules	Major B	
B. Without honeycombing	Noncontiguous lobules		Yes
Hyperechoic foci without shadowing	Echogenic structures $\geq 2$ mm in both length and width with no shadowing		Yes
Cysts	Anechoic, rounded/elliptical structures with or without septations		Yes
Stranding	Hyperechoic lines of $\geq 3$ mm in length in at least 2 different directions with respect to the imaged plane		Yes
MPD calculi	Echogenic structure(s) within MPD with acoustic shadowing	Major A	
Irregular MPD contour	Uneven or irregular outline and ectatic course		Yes
Dilated side branches	3 or more tubular anechoic structures each measuring $\geq 1$ mm in width, budding from the MPD		Yes
MPD dilation	$\geq 3.5$ -mm body or $\geq 1.5$ -mm tail		Yes
Hyperechoic MPD margin	Echogenic, distinct structure greater than 50% of entire MPD in the body and tail		Yes

**Table II. EUS diagnosis of chronic pancreatitis (CP) based on Rosemont consensus (adapted from reference 8)**

<i>I. Consistent with CP</i>	A. 1 major A feature (+) $\geq 3$ minor features
	B. 1 major A feature (+) major B feature
	C. 2 major A features
<i>II. Suggestive of CP</i>	A. 1 major A feature (+) $< 3$ minor features
	B. 1 major B feature (+) $\geq 3$ minor features
	C. $\geq 5$ minor features (any)
<i>III. Indeterminate for CP</i>	A. 3 to 4 minor features, no major features
	B. major B feature alone or with $< 3$ minor features
<i>IV. Normal</i>	$\leq 2$ minor features, no major features

By using 1-2 EUS criteria for mild pancreatitis, 3-5 for moderate pancreatitis, and  $> 5$  for severe forms, agreement between classic secretin test and EUS was 100% for normal parenchyma and severe disease, 50% for moderate CP, and 13% for mild disease (3). Stevens et al used 4 EUS criteria as cut-off and observed a sensitivity of around 70% and a specificity of around 90% of EUS for prediction of a pathological endoscopic function test, depending on if CCK or secretin was used to simulate pancreatic secretion (15). Comparison of EUS (3-5 criteria for diagnosis) and

ERCP showed quite similar sensitivity (72% vs. 68%) and specificity (76% vs. 79%) for either mild or severe CP with the endoscopic secretin test as the reference. EUS worked significantly better for establishing the presence of pancreatic exocrine insufficiency (PEI) (16). Six criteria were needed to obtain the best specificity and best negative predictive value, however sensitivity decreased to only 26% (17,18).

A combined use of endoscopic function test and EUS has recently been brought forward as a sensitive and accurate method for early diagnosis of CP (19,20). The concept is theoretically appealing since both morphology and exocrine function is evaluated. A standard EUS is performed, secretin is administered intravenously and duodenal fluid is subsequently collected at 15, 30, and 45 min. In a study including 252 patients for suspected minimal change CP (no calcifications), 160 (63.5%) had both normal EUS and endoscopic function test results, excluding CP. Thirty-two patients (12.7%) had abnormal EUS and abnormal endoscopic test results, confirming the diagnosis. The remaining 60 patients had discordant results (21). Patients with abnormal EUS and normal endoscopic function test may have CP with preserved exocrine function, or a false positive result of EUS for CP. The significance of normal EUS with abnormal function test is uncertain, but may suggest a very early form of CP prior to the development of structural changes, or a false positive result of function test for

CP (21). Pancreatic morphology can also be dynamically evaluated with EUS after secretin stimulation. The pancreatic duct dilates after secretin stimulation in the normal pancreas. Dynamic EUS has demonstrated reduced pancreatic duct compliance as a consequence of duct fibrosis in CP, most pronounced in the tail of the pancreas, and duct compliance is negatively associated with bicarbonate secretion (22).

### **EUS vs. ERCP**

ERCP has previously been considered as the reference method for early diagnosis of CP. Early studies on EUS have used ERCP as gold standard for diagnosis of CP. These studies have demonstrated a good overall agreement between the tests and a sensitivity of 70-100% and a specificity of 80-100% of EUS (using > 2 criteria cut-off) (6,18). Ductal stones and parenchymal calcifications are the EUS findings that are associated with the highest probability of an abnormal ERCP. Later studies have demonstrated that ERCP may not be the appropriate reference method for early diagnosis of CP and that EUS actually may be more sensitive than ERCP (23). Kahl et al. identified 38 patients with normal ERCP but EUS findings suggesting CP in a cohort of 130 patients evaluated for known or suspected CP. During follow-up, 69% of these patients with initially normal findings on ERCP developed an abnormal pancreatogram (24).

### **EUS vs. magnetic resonance imaging**

Magnetic resonance imaging (MRI) enhanced by gadolinium contrast after secretin stimulation together with magnetic resonance cholangiopancreatography (MRCP) is a highly accurate method for evaluation of CP (25). EUS has been compared with MRI/MRCP for the diagnosis of CP and similar sensitivity but a slightly superior specificity of EUS has been indicated (26). In the presence of both abnormal EUS and MRI/MRCP the specificity for CP diagnosis was 100% in that study (26). In our experience, there is a very good correlation between EUS and secretin MRCP in the evaluation of patients with a suspected CP both in the global evaluation for diagnosing the disease (both for parenchymal and ductal analysis). In fact, in 81% of the cases, information provided by both techniques was equivalent.

### **EUS vs. histology**

Compared to pancreatic specimens, > 3 EUS standard criteria predict histological findings of CP (27). However, these EUS features have also been demonstrated in elderly persons without signs of CP (28) and in 59% of asymptom-

atic alcohol abusers (20). Using histologic findings from surgical specimens as reference, > 5 *versus* > 3 standard EUS criteria diagnosed CP with a sensitivity of 60% *versus* 87% and specificity of 83% *versus* 64% (29). Varadarajulu et al. demonstrated in a similar study where EUS findings were compared to histology from surgical specimens that hyperechogenic foci, stranding, lobularity or any ductal aberrations were the EUS features that were significantly associated with histological findings of CP. Four or more standard criteria was the cut-off for CP diagnosis that provided the best accuracy in that study (30). In yet another study on EUS findings *versus* surgical specimens, Chong et al. found that 3 or more criteria was the cut-off that best differentiated abnormal from normal pancreas (27). Standard EUS criteria appear as a poor predictor of histological severity in these studies. Varadarajulu et al. did not find any correlation between the number of EUS criteria and histological severity and Chong et al. found only a weak, although statistically significant, correlation between the number of EUS criteria and the histological fibrosis score (27,30). However, in a recent study, Leblanc et al. showed that certain EUS criteria were associated with a severe CP, as correlated with histological findings. These criteria were lobularity with honeycombing, hyperechoic foci with shadowing, dilated MPD, irregular MPD, and dilated side branches. Authors also state that the importance of pancreatic ductal changes should not be minimized in the evaluation of CP (31).

### **EUS-guided fine needle aspiration and/or fine needle biopsy**

EUS-guided fine needle aspiration (FNA) and/or fine needle biopsy (FNB) has a clear and well investigated role in the differential diagnosis between mass forming chronic pancreatitis and pancreatic cancer but studies on the use of EUS guided tissue sampling in differentiating early CP from normal tissue are scarce. The possible and severe complications related to the procedure and the lack of a generally agreed histologic definition of CP further limits today the use of EUS-guided FNA/FNB in the diagnosis of early CP. Hollerbach et al investigated the value of adding a 22-gauge needle FNA to standard EUS evaluation in a series of 37 patients with a suspicion of CP with ERCP as reference method. The addition of EUS-guided FNA improved the negative predictive value of EUS (32). In a small series of fourteen patients with alcohol related CP undergoing EUS-guided FNA, we have observed presence of inflammatory cells in all cases (33). Preserved pancreatic acini were observed in patients with mild to moderate EUS changes of CP. In contrast, biopsies from more severe cases (8-10 EUS criteria) showed only ductal epithelium and fibrosis (33). Thus, it is possible that EUS-guided FNA can be useful for both diagnosis and staging of CP. However, to date it is not clear if the benefits of FNA/FNB out-



weighs the risks for complications related to the procedure and the clinical use of FNA/FNB for diagnosis and staging of CP remains to be established.

### EUS-guided elastography and contrast enhancement

Elastography evaluates tissue strain resulting from compression and that strain is smaller in harder tissue than in softer tissue. Different tissue elasticity patterns are marked supplementary on the grey-color scale with different colors (blue for hard tissue and red for soft tissue). Today elastography can also be evaluated in a quantitative manner by calculating the ratio between the strain in the region of interest and a reference area in surrounding soft tissue (strain ratio) (34). The typical finding on qualitative elastography in CP is a heterogeneous coloration with green areas and blue strands, as opposed to normal pancreas that presents a homogeneous, predominantly green and yellow pattern (35). The accuracy of quantitative EUS-elastography for the diagnosis of CP has been recently investigated. A high correlation was found between the number of EUS criteria and the pancreatic strain ratio. In addition, a significant difference in strain ratio between different Rosemont classification categories was observed, with increasing strain ratio when passing from normal pancreas to indeterminate for CP to suggestive for CP to consistent for CP (36,37) (Fig. 2). More recently, a new study has shown a very good correlation between the strain ratio, as evaluated by quantitative EUS-elastography, and the probability of suffering from exocrine pancreatic insufficiency (38). The role of contrast enhanced EUS for the diagnosis of CP has not been yet well established. Only one study has evaluated the role of contrast enhanced EUS in this setting. Contrast enhanced EUS enhances the lobular pattern seen by con-

ventional EUS in CP patients. Furthermore, the washout of contrast is markedly faster in CP patients compared to controls.

### EUS for evaluating the severity degree of chronic pancreatitis

Visible side branches, duct dilation, duct irregularity, and calcifications have been demonstrated to be associated with severe CP on ERCP (39) according to the Cambridge classification (40). One study has shown that odds ratio for pancreatic exocrine insufficiency (PEI) (severe CP) by EUS was, in the presence of minimal and severe structural changes 4.9 and 24, respectively (16). In a recent study, the probability of PEI in relation to EUS criteria of CP was analyzed. The percentage of patients with PEI increased linearly with the number of EUS criteria. The presence of intraductal calcifications, hyperechogenic foci with shadowing, and dilation of the main pancreatic duct were significantly and independently associated to PEI (Fig. 3). The probability of PEI in the presence of calculi in the main pancreatic duct is 80% and increases to 82.8% if, in addition, the main duct is dilated. Thus EUS allows predicting the probability of PEI and thus need for enzyme replacement therapy in patients with CP (41).

### DIFFERENTIAL DIAGNOSIS OF MASS FORMING CHRONIC PANCREATITIS AND PANCREATIC CANCER

Differential diagnosis of solid pancreatic masses includes primary or secondary pancreatic tumor, focal

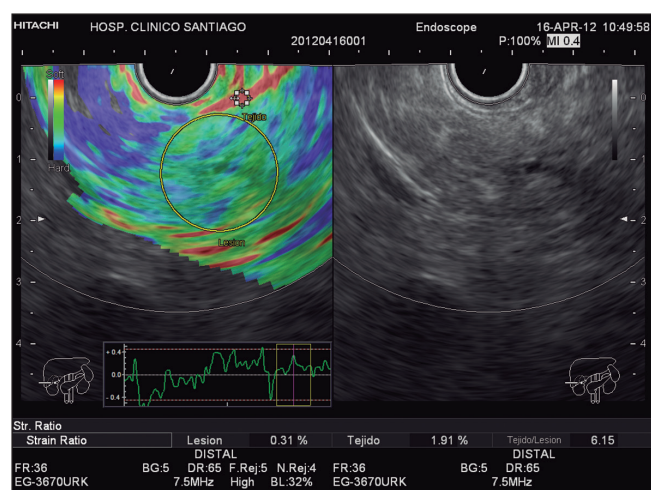


Fig. 2. Quantitative endoscopic ultrasound elastography in a patient with findings suggestive of chronic pancreatitis.

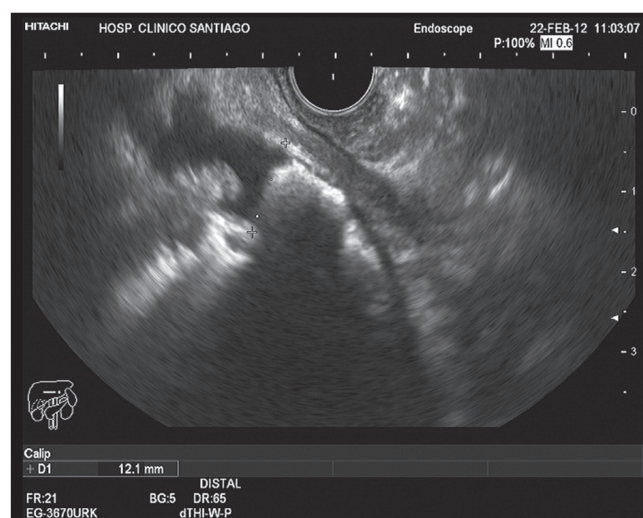


Fig. 3. Advanced chronic pancreatitis evaluated by EUS, showing diffuse calcifications, in patient diagnosis of pancreatic exocrine insufficiency.

CP and autoimmune pancreatitis. Despite high-resolution images produced by conventional EUS, differentiation between benign inflammatory masses and malignant tumors based on B-mode images remains a challenge. EUS-FNA/FNB, contrast enhanced harmonic EUS and EUS elastography are new tools to improve of the diagnostic accuracy of EUS for the evaluation of solid pancreatic masses.

### EUS-guided FNA and FNB

The role of EUS-guided FNA in the diagnosis of solid pancreatic tumors has been evaluated in several studies. Reported sensitivity and accuracy for malignancy ranges from 75 to 92% and from 79 to 92%, respectively (42). This accuracy may be even higher using on-site evaluation of the sample by an experienced pathologist (43). However, it should be kept in mind that the sensitivity of EUS-guided FNA for malignancy is lower (between 54% and 74%) if the lesion is detected in the context of CP compared to when the surrounding parenchyma is normal (44-47). Furthermore, in some cases EUS-guided FNA maybe not feasible due to technical difficulties or the EUS-FNA samples are of low quality for diagnosis. In total, EUS-guided FNA does not allow reaching the pathological diagnosis of pancreatic masses in 8% to 25% of cases (48). In order to optimize tissue retrieval of EUS-guided biopsy, various new needles, like Tru-Cut and the new Procore™ have been tested (49).

### EUS-guided elastography

Pathological processes like cancer and fibrosis alter tissue elasticity and will therefore induce changes in elastographic appearance. Qualitative elastography can differentiate malignant from benign solid pancreatic lesions with a sensitivity, specificity, positive and negative predictive values, and overall accuracy of 100%, 85.5%, 90.7%, 100% and 94.0%, respectively (50). Quantitative EUS-elastography is a more objective and accurate method than qualitative EUS-elastography. In a previous study including 86 consecutive patients with solid pancreatic masses, the sensitivity and specificity of quantitative EUS-elastography for the differentiation of malignant from benign lesions were 100% and 92.9% respectively (51) (Fig. 4). Mean hue histogram value is an alternative measure for quantitative elastography. A first study showed a sensitivity, specificity, and accuracy in differentiation of malignant from benign masses of 91.4%, 87.9%, and 89.7%, respectively (52). A multicenter study, using the same methodology, showed a sensitivity of 93.4%, a specificity of 66.0%, a positive predictive value of 92.5%, a negative predictive value of 68.9%, and an overall accuracy of 85.4% for the diagnosis of pancreatic malignancy (53).

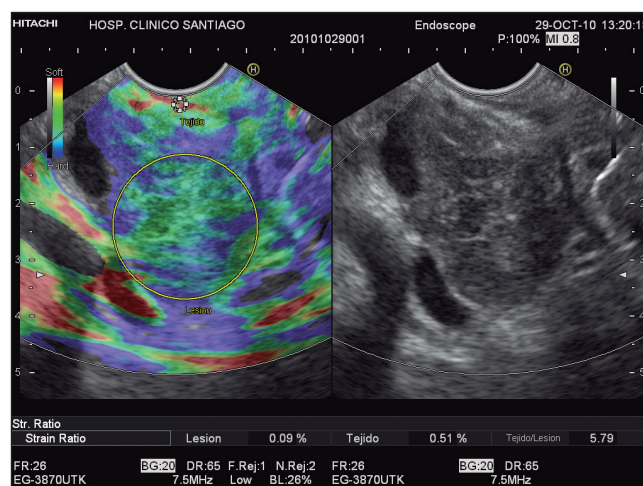


Fig. 4. Mass forming chronic pancreatitis at the pancreatic head, evaluated by EUS-elastography.

### Contrast enhanced EUS

Administration of contrast agents is another way to improve EUS-based diagnosis of solid pancreatic tumors. Today, the most widely used is contrast enhanced harmonic EUS (CEHEUS), technique that detects signals from micro bubbles delivered by new contrast agents in vessels with very slow flow without the burden of Doppler-related artifacts (54). With this technique pancreatic cancer appears as a low enhanced lesion with a rapid washout, while mass forming CP uses to appear as an isoenhanced lesion. A hypoenhanced pattern has a high sensitivity for adenocarcinoma (89-96%) but the specificity is lower since advanced mass-forming CP also may be hyperenhanced (55,56). Tissue perfusion after contrast administration can be quantified using time intensity curve analysis. A recent study has indicated that this quantitative method may have a high sensitivity and specificity for differentiation between pseudotumoral CP and pancreatic cancer (57). Further larger multicenter studies are warranted in order to investigate the role of quantitative and qualitative contrast enhanced EUS in the diagnosis of pancreatic cancer.

### CONCLUSIONS

Diagnosis of CP remains a challenge. EUS can be considered nowadays as the technique of choice for the morphological diagnosis of this disease. More than three or four EUS defined criteria of CP need to be present for the diagnosis of the disease. The development of the more restrictive Rosemont classification aims to standardize the criteria, assigning different values to different features but its impact on the EUS-based diagnosis of CP is debatable. A combined use of endoscopic function test and EUS has even increased the diagnostic yield for the diagnosis of CP.

Elastography and FNA may be of help for diagnosing CP. EUS also provides with very valuable information on the severity of the disease, giving key information that may influence in the treatment.

Differential diagnosis of solid pancreatic masses in the context of a CP is also challenging, EUS plays a key role in this context. It provides with the possibility of obtaining specimens for histopathological diagnosis, improving its diagnostic yield. Nowadays, new developed techniques associated to EUS, like elastography and contrast enhancement, are also showing promising results for the differentiating between these pancreatic lesions.

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