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EUS in the diagnosis of early-stage chronic pancreatitis

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Chronic pancreatitis (CP) is a progressive inflammatory disease that is difficult to diagnose due to the paucity of a diagnostic gold standard. For almost two decades, early-stage CP has been recognised in the context of endoscopic ultrasound (EUS) when a patient presents with typical pancreatic-type pain, normal conventional imaging examinations, and subtle findings of CP by EUS. Whether these EUS findings represent true early-stage CP that will progress or whether they are false positive findings remain unclear. The key to enhancing the diagnostic precision of EUS in CP is to use objective, widely-accepted criteria that are reproducible. The Rosemont Criteria is a significant step towards achieving this goal and needs to be validated in conjunction with long-term studies of early-stage CP.

Introduction

Chronic pancreatitis (CP) is characterised by irreversible morphologic changes often associated with pain, and sometimes with loss of exocrine and/or endocrine function. In the context of endoscopic ultrasound (EUS), the terms 'early-stage' or 'minimal change' CP first emerged in a case series of a syndrome complex consisting of pancreatic-type pain and normal transabdominal ultrasound and computed tomography (CT), but with subtle histologic changes of chronic inflammation [1]. Although the inflammatory changes seen in the pancreas can be both focal and diffuse, they were seemingly out of proportion to the degree of symptoms manifested by the patients described. One of the earliest papers on the use of EUS in early-stage CP showed all patients with abnormal features of CP by ERCP also had abnormal EUS, but several patients with abnormal EUS had normal ERCP [2]. These abnormal

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EUS findings were not seen among healthy volunteers, suggesting either the presence of early-stage CP or perhaps false positive results.

Since its introduction, EUS has remained clinically relevant and arguably unrivalled over the years in terms of its ability to quantitatively diagnose CP in a minimally invasive manner with almost no complication. EUS can image the pancreas at higher frequencies without intervening bowel gas, providing high-resolution real-time images of pancreatic duct and parenchyma. However, it is difficult to assess the operating characteristics of EUS for diagnosing CP, as there is no universally-accepted test to which one can compare it to. CP is not unlike several medical conditions clinicians encounter in practice where a gold standard diagnostic test does not exist. Pancreatic function tests are difficult to validate as they are not widely used in the community, and reproducibility data between centres are scarce. ERCP can be abnormal in a number of patients who end up with normal pancreas on autopsy [3]. Non-invasive imaging modalities such as CT scan cannot rule out early-stage chronic pancreatitis [4]. Histology, itself is far from perfect because in early-stage CP the inflammatory changes could be patchy and conventional image-guided biopsy can miss pathology. Also, at this time there is lack of consensus among pathologists for standardised criteria for CP [5].

Evolution of EUS criteria for chronic pancreatitis

Minimal-change CP by EUS can be an arbitrary term to endosonographers in terms of the diagnostic threshold for quantity of EUS features. Each terminology is also subject to substantial inter-observer variability making interpretation difficult. Thus a brief discussion on the history of EUS-based diagnostic criteria is mentioned here to better understand the strengths and pitfalls of how CP, no matter the spectrum of the disease, is diagnosed by EUS. Realising the difficulty in assessing the performance characteristics of EUS, early investigators used ERCP as proxy gold standard, being the most sensitive available method at the time. Wiersema et al [2] prospectively compared EUS with ERCP and pure pancreatic juice (PPJ) collection for diagnosing CP. Twenty healthy subjects provided normative data for two basic endosonographic features: 1) Ductal (narrowing, dilation, irregularity, duct wall echogenicity, calculi, and side-branch dilation); and 2) Parenchymal (echogenicity; echogenic foci, cysts, and accentuated lobularity). Among subjects with early CP (no or minimal changes on ERCP), the sensitivity was 86% vs 50% for EUS and ERCP, respectively ($p = 0.01$). Using an ROC curve, the authors recommended a minimum of three EUS features to diagnose CP.

Our group evaluated 80 patients with acute recurrent pancreatitis who underwent EUS, ERCP, and secretin test [6]. We found complete concordance between ERCP and EUS for normal results and severe disease but only 17% agreement for mild disease. Several years later another group [7] produced similar results with EUS and pancreatic function test noting discrepant results among patients with presumed early-stage CP. Combining the results of three studies [2,6,8] on CP, EUS had a sensitivity of 87% and specificity of 75% where we defined early-stage CP as less than three EUS features using conventional criteria [9].

The question remains whether 'early-stage' or 'mild disease' represents misclassification (i.e., erroneously categorising healthy patients to have early disease) or a genuine entity that will progress into obvious CP if given the opportunity of long-term follow-up. A few preliminary studies have attempted to answer this question. In a study [10] of 319 patients with abdominal pain and 26 asymptomatic patients without risk factors for pancreatic disease or alcohol use who underwent EUS, there was significantly fewer patients with zero to three EUS criteria for CP in the symptomatic group (46% versus 80%, respectively; $P = 0.001$). Thus it is possible, albeit less likely, to see minimal changes of CP by EUS even among patients who have no apparent pancreatic disease. Our group [8] retrospectively studied patients with minimal change CP by EUS for at least six years (mean 8.5 years). Patients were included if they had normal baseline CT, ERCP, and secretin tests and had at least two EUS examinations more than two years apart. The follow-up examination consisted of at least two of the three (CT, ERCP, and secretin test). Of the 37 patients with minimal criteria for CP, 20 developed worse CP by repeat EUS including 14 moderate and six severe diseases. Based on this finding, subtle abnormalities detected by EUS among patients with pancreatic-type pain appear to represent true pathology that could progress over several years. However, it is difficult to reach a conclusion from these studies on early-stage CP because the populations are heterogeneous with regards to aetiology, risk factors, and treatment rendered for pancreatic disease.

Although traditional EUS criteria mentioned up to this point give equal weigh to each EUS features for diagnosing CP, experts generally agree these features are in fact not uniformly predictive of CP. Clearly there are EUS features such as pancreatic duct calculi that by itself have more predictive power for CP than others such as hyperechoic foci (Table 1) [11]. As noted previously, there is inconsistency as well with regards to minimum number of diagnostic criteria for CP (some authors require greater than three [2] criteria, while others greater than five [12]).

In an effort to modify the existing classification of CP into an EUS-based system, and to standardise endosonographic features that is more clinically relevant and reproducible, the Rosemont Criteria [13] was established (Tables 2 and 3) [13]. This consensus-based diagnostic system is divided into Major and Minor features according to perceived predictive accuracy for diagnosing CP. For example, finding two Major A features (hyperechoic foci with shadowing and main pancreatic duct calculi) and no other features is enough to assign the term 'consistent' with CP. In most cases pancreatic duct stones would have been associated with other EUS features in a patient with CP, however theoretically using the new system it would have been possible to diagnose a patient with CP by EUS with just two features, which would not have been possible with conventional classification systems. On the other hand, a patient may have four EUS features consisting of hyperchoic foci without shadowing, irregular main pancreatic duct contour, main pancreatic duct dilation, and hyperechoic MPD margin yet still be 'indeterminate' for CP using the new criteria.

Apart from the need for validation, the Rosemont Criteria has certain limitations. It is far from simple and therefore post-procedure documentation will prove challenging for an endosonographer using the detailed system without the aid of a checklist readily available in the dictation area. Due to the wide inter-observer variability for individual features of CP, the goal was to produce criteria that will be highly predictive of CP. And to accomplish this, the criteria must be objective, quantifiable, and precise without being cumbersome. Another limitation is that it does not specifically address early-stage CP. In its current form it remains unresolved whether 'indeterminate' for CP represents early-stage CP, although answering this question was certainly not the main intention of creating the Rosemont Criteria. At the present time our group arbitrarily defines 'early-stage' or 'minimal-change' CP as a patient with pancreatic-type pain, normal CT, ERCP, and secretin test, but indeterminate for CP using the Rosemont Criteria (Fig. 1, Tables 2 and 3).

Early-stage CP tend to be a focal, inconsistent disease that could prove elusive to conventional image-guided biopsies. EUS-guided FNA [14] or EUS-guided Trucut biopsy [15] have limited accuracy and is associated with complications. Therefore at this time, diagnostic EUS without tissue aspiration or biopsy is the preferred method for diagnosing CP. A few studies have attempted to correlate EUS

Table 1
Comparison of EUS features of chronic pancreatitis among representative authors: Wiersema (1993), Catalano (1998), Sahai (1998), Wallace (2001), and DeWitt (2005) and colleagues (adapted from Hernandez and Bhutani, 2008) [11].

	Wiersema et al	Catalano et al	Sahai et al	Wallace et al	DeWitt et al
Ductal features					
Dilation	X	X	X	X	X
Irregularity					
Hyperechoic wall					
Calculi			X		
Side branch dilation					
Narrowing		X	X	X	X
Parenchymal features					
Hypoechoic foci			X	X	
Hyperechoic Foci (>3 mm)					
Cysts (>3 mm)					
Lobularity					
Prominent interlobular septae	X		X	X	X
Heterogenous	X		X	X	X
Hyperechoic strands	X	X			
Shadowing calcifications	X	X		X	X
Total # of Features	10	11	9	9	10

Table 2
Parenchymal and ductal features of chronic pancreatitis by rosemont criteria [13].

Rank	Feature	Major criteria	Minor criteria
Parenchymal features			
1	Hyperechoic foci with shadowing	Major A	
2	Lobularity		
	A. With honeycombing	Major B	
	B. Without honeycombing		Yes
3	Hyperchoic foci without shadowing		Yes
4	Cysts		Yes
5	Stranding		Yes
Ductal features			
1	MPD calculi	Major A	
2	Irregular MPD contour		Yes
3	Dilated side branches		Yes
4	MPD dilation		Yes
5	Hyperechoic MPD margin		Yes

findings with histology. Chong et al [16] studied 71 patients with presumed CP and underwent EUS within one year of pancreatic surgery. Although there was data on whether or not calcifications were seen on imaging tests, there was no sub-group analysis on early-stage CP. The authors found a correlation between pancreatic fibrosis and number of EUS criteria, and interestingly noted several patients with calcifications on EUS that was missed by conventional imaging. A strong correlation between EUS and histologic findings were also noted by another group in a prospective study [17] on 42 patients with noncalcific CP.

The definitive way to prove correlation between subtle EUS findings and histology is surgical resection of the entire pancreas right after an EUS examination. Bhutani and colleagues [18] elucidated this issue with the use of a canine model. The authors inserted a stent into the pancreatic duct and then two and four weeks later performed EUS examination, immediately followed by euthanasia and histologic examination of the entire pancreas by a pathologist blinded to EUS findings. Among the EUS features they noted post-stenting were lobularity, hyperechoic foci, and pancreatic duct irregularity which were confirmed histologically as moderate to severe inflammation and fibrosis. Therefore, this validated model can be used for assessing new technologies such as computer-aided digital-image analysis which can minimise operator bias and improve diagnostic accuracy in early-stage CP. EUS elastography, which translates tissue elasticity into coloured spectrum, is another potentially useful modality for early-stage CP, rendering honeycombing features more obvious in some cases of CP [19]. Of note, digital-image analysis and EUS elastography are still in its experimental stage and are not recommended for use outside a research setting.

Table 3
Diagnosis of chronic pancreatitis based on rosemont criteria [13].

I. Consistent with chronic pancreatitis
  A. 1 MAJOR A Feature (+) ≥3 MINOR Features
  B. 1 MAJOR A Feature (+) MAJOR B Feature
  C. 2 MAJOR A Features

II. Suggestive of chronic pancreatitis
  A. 1 MAJOR A (+) <3 MINOR Features
  B. MAJOR B Feature (+) ≥3 MINOR Features
  C. ≥5 MINOR Features (Any)

III. Indeterminate for chronic pancreatitis
  A. 3 to 4 MINOR features, no MAJOR features
  B. MAJOR B alone or with <3 MINOR features

IV. Normal
  ≤2 MINOR Features, no MAJOR features

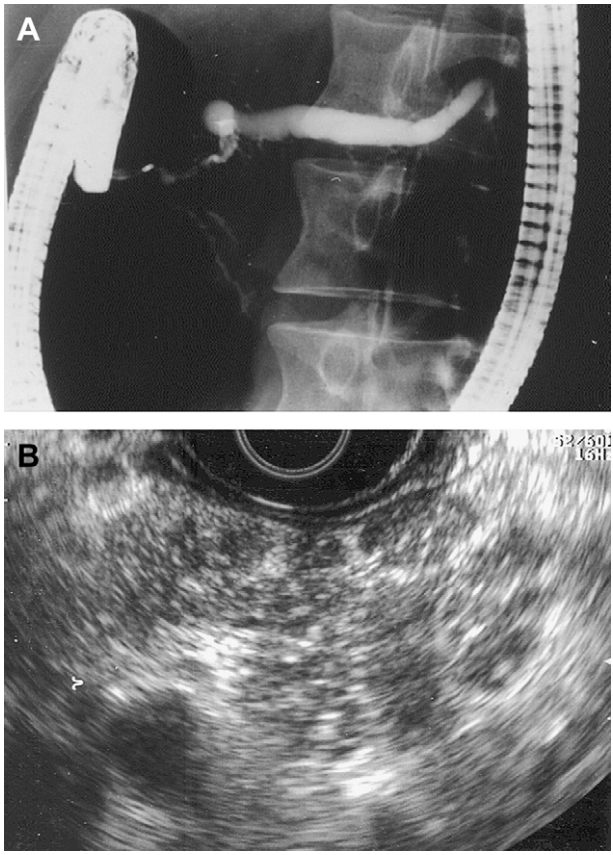

Fig. 1. Representative image of a normal pancreatogram (A) of a patient with pancreatic type pain. (B) Shows an endoscopic ultrasound (EUS) image of the body of the pancreas showing subtle findings of chronic pancreatitis characterised by parenchymal lobularity with noncontiguous lobules. These aggregate findings are consistent with early-stage chronic pancreatitis.

Presenting clinical problem

We are not aware of any epidemiologic data that allows us to identify patients most likely to have early-stage CP. In our experience, there are specific clinical scenarios where early-stage chronic pancreatitis emerges in the differential diagnosis. Patients with obscure pancreatic-type pain and acute recurrent pancreatitis of unknown aetiology (Table 4) [20] are among the core groups at highest risk to have early-stage CP whom we consider for EUS. In essence, the high sensitivity and low specificity of EUS (using data from conventional endosonographic criteria) allows us to rule out early-stage CP if it turns out normal.

There are certain patient features that may alter test performance of EUS such as gender, age, smoking, and alcohol. Male gender is an independent predictor of CP based on EUS perhaps to a greater degree than older age [21]. This was confirmed in a recent autopsy series [22] of male patients (median age 65 years) dying of all causes without known pancreatic disease where the authors observed a high prevalence of CP with three or more EUS features using conventional criteria. This leads some authors to adjust their criteria to higher cut-off level when they encounter elderly male patients. However, it appears that some these factors were not adjusted for confounding in many studies to the point that several experts in the Rosemont conference felt that the Rosemont Criteria can be used independently of these patient features.

Table 4
Presenting clinical scenarios where early-stage chronic pancreatitis is in the differential diagnoses (Definitions: 1) Pancreatic-type pain*: based on Rome III criteria20; 2) IRAP: two or more attacks of well-documented acute pancreatitis of unclear cause despite an exhaustive work-up).

Unexplained abdominal pain suspected to be of pancreatic origin*, especially if there is a history of alcohol abuse
Acute pancreatitis of unclear etiology or idiopathic acute recurrent pancreatitis (IRAP)
Unexplained weight loss
Chronic diarrhoea, especially steatorrhea of unclear etiology
Equivocal findings of the pancreas on non-invasive imaging (for example, CT scan showing dilated pancreatic duct or subtle pancreatic calcifications)
New-onset diabetes in a patient without family history of diabetes

Clearly, we need to look further in improving diagnostic accuracy of EUS in early-stage CP. However, we also need to ask what the benefits are to our patients by doing so. Do patients diagnosed to have CP by EUS in its early stage have better health outcomes than those diagnosed much later in its natural history? Knowing there is no proven therapy for early-stage CP, we believe offering pancreatic enzymes and advising patients to minimise alcohol is a reasonable option that is a relatively benign form of intervention. So why not just treat patients with pancreatic-type pain and normal findings on CT scan and spare them from undergoing EUS? Diagnosing CP carries with it certain social, economic (insurability), and psychological repercussions and may subject patients to unnecessary treatments and invasive procedures. Thus we believe one must be selective and reasonably thorough in taking steps to be confident in the diagnosis of early-stage CP.

Practice points

- CP is a progressive disease with scant epidemiologic studies and no diagnostic gold standard making the evaluation of EUS in early-stage CP difficult.
- The Rosemont Criteria is an important step towards improving objectivity and diagnostic precision of CP, and can be used independently of age and gender of the patient.
- Our group arbitrarily defines ‘early-stage’ CP as a patient with pancreatic-type pain, normal CT, ERCP, and secretin test, but ‘indeterminate’ for CP using the Rosemont Criteria.
- Preliminary studies suggest that patients with early-stage CP appear to have demonstrable progression of EUS features of CP.

Research agenda

- Validation studies comparing Rosemont Criteria with conventional criteria are needed.
- The Rosemont Criteria can be used to assess emerging technologies that will further enhance EUS imaging of the pancreas and to document natural progression of disease among those with early-stage CP over the long-term.
- We anticipate future revisions of the Rosemont Criteria based on above findings.

Conflict of interest

No conflict of interest has been declared by the authors.

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References

[1] Walsh TN, Rode J, Theis BA, Russell RCG. Minimal change chronic pancreatitis. Gut 1992;33:1566–71.
[2] Wiersema MF, Hawes RH, Lehman GA, Kochman ML, Sherman S, Kopecky KK. Prospective evaluation of endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in patients with chronic abdominal pain of suspected pancreatic origin. Endoscopy 1993;25:555–64.
[3] MacCarty RL, Stephens DH, Brown Jr AL, Carlson HC. Retrograde pancreatography in autopsy specimens. Am J Roentgenol Radium Ther Nucl Med 1975 Feb;123(2):359–66.
[4] Luetmer PH, Stephens DH, Ward EM. Chronic pancreatitis: reassessment with current CT. Radiology 1989 May;171(2): 353–7.
[5] Shimizu M, Hirokawa M, Manabe T. Histological assessment of chronic pancreatitis at necropsy. J Clin Pathol 1996 Nov;49 (11):913–5.
[6] Catalano MF, Lahoti S, Geenen JE, Hogan WJ. Prospective evaluation of endoscopic ultrasonography endoscopic retrograde pancreatography, and secretin test in the diagnosi of chronic pancreatitis. Gastrointest Endosc 1998;48(1):11–7.
[7] Chowdhury R, Bhutani MS, Mishra G, Toskes PP, Forsmark CE. Comparative analysis of direct pancreatic function testing versus morphological assessment by endoscopic ultrasonography for the evaluation of chronic unexplained abdominal pain of presumed pancreatic origin. Pancreas 2005 Jul;31(1):63–8.
[8] Sahai AV, Zimmerman M, Aabakken L, Tarnasky P, Cunningham JT, van Velse A, et al. Prospective assessment of the ability of endoscopic ultrasound to diagnose, exclude, or establish the severity of chronic pancreatitis found by endoscopic retrograde cholangiopancreatography. Gastrointestinal Endosc 1998;48(1):18–25.
[9] Catalano MF, Kaul V, Pezanoski J, Guda N, Geenen N. Long-term outcome of endosonographically detected minimum criteria for chronic pancreatitis (MCCP) when conventional imaging and functional testing are normal. Gastrointestinal Endosc 2007 April;65(5):AB120.
[10] Sahai A, Pearson A, Wallace MB, Van Velse A, Hawes RH, Hoffman BJ. Endoscopic ultrasound (EUS) as a diagnostic tool in dyspepsia patients. A prospective study of EUS criteria for chronic pancreatitis in a consecutive series of dyspepsia patients and asymptomatic controls (abstract). Gastrointest Endosc; 1999:AB98.
[11] Hernandez LV, Catalano MF, Bhutani MS. EUS in chronic pancreatits. In: Bhutani MS, Deutsch J, editors. Atlas and textbook of EUS pathology. BC Decker; Jan 2008.
[12] Stevens T, Conwell DL, Zuccaro Jr G, Vargo JJ, Dumot JA, Lopez R. Comparison of endoscopic ultrasound and endoscopic retrograde pancreatography for the prediction of pancreatic exocrine insufficiency. Dig Dis Sci; 2007 Oct 13.
[13] Catalano MF, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, et al. EUS-based criterial for diagnosis of chronic pancreatitia: the rosemont classification. Gastrointest Endosc 2009 Jun;69(7):1251–61.
[14] Hollerbach S, Klamann A, Topalidis T, Schmiegel WH. Endoscopic ultrasonography (EUS) and fine-needle aspiration (FNA) cytology for diagnosis of chronic pancreatitis. Endoscopy 2001 Oct;33(10):824–31.
[15] DeWitt J, McGreevy K, LeBlanc J, McHenry L, Cummings O, Sherman S. EUS-guided Trucut biopsy of suspected nonfocal chronic pancreatitis. Gastrointest Endosc 2005 Jul;62(1):76–84.
[16] Chong KHA, Hawes RH, Hoffman BJ, Adams DB, Lewin DN, Romagnuolo J. Diagnostic performance of EUS for chronic pancreatitis: a comparison with histopathology. Gastrointest Endosc 2007;65(6):808–14.
[17] Varadarajulu S, Eltoum I, Tamhane A, Eloubeidi MA. Histopathologic correlates of noncalcific chronic pancreatitis by EUS: a prospective tissue characterization study. Gastrointest Endosc 2007;66(3):501–9.
[18] Bhutani MS, Ahmed I, Verma D, Xiao SY, Brining D. An animal model for studying endoscopic ultrasound changes of early chronic pancreatitis with histologic correlation: a pilot study. Endoscopy 2009;41:352–6.
[19] Janssen J, Schlorer 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(7):971–8.
[20] Behar J, Corazziari E, Guelrud M, Hogan W, Sherman S, Toouli J. Functional gallbladder and sphincter of oddi disorders. Gastroenterology 2006;130:1498.
[21] Yusoff IF, Sahai AV. A prospective, quantitative assessment of the effect of ethanol and other variables on the endosonographic appearance of the pancreas. Clin Gastroenterol Hepatol 2004 May;2(5):405–9.
[22] Bhutani MS, Arantes VN, Verma D, Moezzi J, Suryaprasad S, Kapadia AS, et al. Histopathologic correlation of endoscopic ultrasound findings of chronic pancreatitis in human autopsies. Pancreas 2009;38(7):820–4.