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Imaging in the diagnosis of chronic pancreatitis

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Abstract: *Chronic pancreatitis is characterised by progressive and irreversible damage of the pancreatic parenchyma and ductal system, which leads to chronic pain, loss of endocrine and exocrine functions. Clinically, pancreatic exocrine insufficiency becomes apparent only after 90% of the parenchima has been lost. Despite the simple definition, diagnosing chronic pancreatitis remains a challenge, especially for early stage disease. Because pancreatic function tests can be normal until late stages and have significant limitations, there is an incresing interest in the role of imaging techniques for the diagnosis of chronic pancreatitis. In this article we review the utility and accuracy of different imaging methods in the diagnosis of chronic pancreatitis, focusing on the role of advanced imaging (magnetic resonance imaging, endoscopic retrograde cholangiopancreatography and endoscopic ultrasound).*

INTRODUCTION

Chronic pancreatitis is represented by a progressive inflammation and fibrosis of the pancreas, resulting in permanent structural damage and loss of function. Regarding its epidemiology, incidence and prevalence worldwide varies depending on the frequency of risk factors (rates mainly paralelling alcohol consumption) and on the diagnostic method used (with higher incidence and prevalance rates where diagnosis was based on advanced imaging techniques – a study in Japan using advanced diagnostic tools reported a prevalence of 45.4 and incidence of 12.4/100.000, compared to 10-15 and respectively 3.5-4 in western countries). Etiology is represented by heavy alcohol consumption, ductal obstruction (post-traumatic fibrosis, stones, pseudocyst, tumors, pancreas divisium, Oddi sphicter dysfunction), genetic causes (hereditary pancreatitis), tropical pancreatitis, autoimmune pancreatitis or systemic disease (lupus, hyperparathyroidism).

The natural history of c hronic pancreatitis evolves with a slowly progressing subclinical phase, followed by recurrent episodes of abdominal pain and finally, when over 90% of the pancreatic parenchyma is lost, exocrine insufficiency appears. Although it is not yet known if early diagnosis of chronic pancreatitis can alter its natural history and change the outcomes of this disease, efforts should be made for earlier detection of the disease.

In real-life there are two main diagnostic issues regarding this disease: on one hand it's over-diagnosed by considering a hyperechoic pancreas on

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ultrasound as chronic pancreatitis, and on the other hand it's under-diagnosed in early stages when patients don't have exocrine insufficiency but present with recurrent abdominal pain and abdominal dis tention, symptoms which are frequently attributed to irritable bowel syndrome (IBS).

On clinical grounds, early chronic pancreatitis can be asymptomatic or paucisymptomatic; moreover, early symptoms are nonspecific, of low intensity and often attributed to IBS. The classic steathoreea appears late in the evolution of the disease, but our aim is to detect chronic pancreatitis before overt exocrine insufficiency develops.

Diagnostic tests for chronic pancreatitis are separated in two: those that evaluate pancreatic function and those that detect structural changes[2].

Pancreatic function tests (PFT) can be classified as direct (which directly measure pancreatic secretions) and indirect (which measure either the pancreatic enzymes in blood or stool or the effect/lack of effect of the pancreatic enzymes, by administering a substrate which requires pancreatic enzymes for digestion and measuring the metabolites of the substrate in stool, urine, blood or breath). Direct PFT is done by collecting and measuring intraduodenal bicarbonate and lipase levels after stimulation with a secretagogue (secretin-cholecystokinin); this method has a sensitivity of 96% (which means a normal result can accurately rule out chronic pancreatitis) and specificity of 37%, but it has major limitations – it's not standardized, not widely available, it depends on the patient to tolerate the oroduodenal tube/endoscope for an hour (here we add the costs and risks of prolonged sedation) and it has many false positive results (in Billroth II anastomosis, diabetes mellitus, celiac disease, cirrhosis and recent acute pancreatitis)[2]. Other PFT such as fecal elastase, fecal chymotrypsin or serum trypsinogen have proven useful only for advanced disease[2].

Histopathological examination of the pancreas could be diagnostic in the early stages, however tissue sampling in chronic pancreatitis is rarely used because of many reasons: histopathological changes are non-specific (chronic inflammation and fibrosis), sampling can be nonrepresentative in focal disease, normal aging can produce changes similar to those seen in chronic pancreatitis and pancreatic biopsy has a high risk of complications (acute pancreatitis, fistula, pseudocyst).

In this setting, imagery has emerged as a very valuable tool for evaluation of chronic pancreatitis.

Imaging methods used for the diagnosis and staging (with regard to severity and complications) consist of: plain abdominal x-ray, transabdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) and secretin stimulation (S-MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS).

Plain abdominal X-Ray

Plain abdominal radiography can reveal diffuse calcifications on the projection area of the pancreas, which are considered pathognomonic of chronic pancreatitis[3].

Abdominal ultrasound (US)

Abdominal ultrasound is a simple, non-invasive, widely available imaging tool. Its limitations are represented by the fact that it's highly examiner-dependent and patient-dependent (excessive adipose tissue, history of upper GI tract surgery or overlying gas can lead to a poor view of the pancreas).

Examination is done using a convex probe, with a frequency of 3.5-5 Mhz, using epigastric and left subcostal approaches. To optimise visualisation of the pancreas, some recommend drinking 500 ml of water before the examination, to make the stomach an acoustic window.

Ultrasound can show atrophy/enlargement of the pancreas, inhomogenous echostructure (by hyperechoic areas corresponding to fibrosis), irregular gland border, pancreatic duct changes (dilatation, irregularity or stones), cysts and pseudocysts. US has a sensitivity of 60-70% and specificity of 80-90% in diagnosing chronic pancreatitis3. Although its role in positive diagnosis is limited, US is very useful in follow-up: it can assess

position of intraductal or pseudocystogastric stent and it can evaluate the efficacy of extracorporeal lithotripsy by showing the disappearance of stones and reduction in pancreatic duct diameter.

Computed tomography (CT)

From its first use in chronic pancreatitis back in 1976, CT is now widely used for the evaluation of pancreatic pathology. Computed tomography has a reported sensitivity of 75-90% and specificity of 85% in the diagnosis of chronic pancreatitis, but it can be normal in patients with early stage disease[3,6].

CT scan can reveal chages in size (enlargement, atrophy) and contour (irregularity of the anterior border) of the pancreas, calcifications (with higher detection rates than ultrasound, being the imaging method of choice for calcifications), dilatation of the main pancreatic duct or common bile duct, alterations in peripancreatic fat – see figures 1, 2. It can also detect complications such as pseudocysts, arterial pseudoaneuyrisms or splenic vein thrombosis[6].

Contrast-enhanced computed tomography

(CECT) is also useful in differentiating pseudotumoral chronic pancreatitis from pancreatic cancer[6].

The disadvantages of the CT scan consist of irradiation, risk of contrast-induced nephropathy and its contraindication in patients with iodine-allergy[6].

Endoscopic retrograde cholangiopancreatography (ERCP)

ERCP is a very useful tool for detecting morphological changes in the pancreatic ductal system. It is done using a lateral-view endoscope by cannulating the main pancreatic duct from the duodenum and injecting contrast to create a pancreatogram. The pancreatogram can show structural changes (dilatation, narrowing, irregularity, stones, leaks) of the pancreatic duct, abnormal side branches, communicating pseudocysts, which are reported in a standardized manner, using the Cambridge criteria, (Table 1). In interpreting the pancreatogram, one should keep in mind that focal ductal changes can follow an episode of severe acute pancreatitis,. Also a normal pancreatogram does not exclude early chronic pancreatitis.

Table 1 Cambridge Classification for ERCP (Banks PA. J Gastroenterol 2007)

Grade	Main duct	Abnormal side branches
Normal	Normal	None
Equivocal	Normal	< 3
Mild	Normal	> 3
Moderate	Abnormal	> 3
Marked	Abnormal with at least one additional feature: large cavity (>10 mm), obstruction, filling defects, severe dilatation or irregularity	> 3

The main disavantages of ERCP are represented by the fact that it's strongly operator dependent, it's an invasive technique with potential serious complications (pancreatitis, hemorrhage, infection) and it only reveals ductal changes[6]. Over the last years, ERCP has become a primarily therapeutic tool, so that diagnostic studies have been abandoned in favor of other imaging methods such as MRI/MRCP or EUS. However, ERCP remains of great importance in pancreatic endotherapy (pancreatic sphincterotomy, stenting and cyst drainage).

Magnetic resonance imaging (MRI). Magnetic resonance cholangiopancreatography (MRCP)

Due to its noninvasivity and lack of irradiation, MRI with MRCP, gadolinium enhancement and secretin stimulation is being increasingly seen as the imaging method of choice in the evaluation of pancreatic disease. MRI can be used in renal impairment and in patients with iodine allergy, in whom CECT cannot be performed[7]. One of the drawbacks of MRI is represented by the artefacts caused by respiratory movements, but this has improved with the latest technology.

Pancreatic parenchyma can be best examined on T1-weighted, fat-suppressed sequences, where it reveals a high signal due to the high-protein content (enzymes, hormones). In chronic pancreatitis, the pancreatic signal decreases (due to loss of exocrine

function) and there is a delayed enhancement after gadolinium administration (due to fibrosis, blood flow inside the pancreas is altered and the gland peaks in the venous phase instead of the arterial one)6. MRI is inferior to CT in detecting calcifications, because they are seen as signal void.

Pancreatic ductal system is best evaluated by magnetic resonance cholangiopancreatography.

MRCP images are obtained without injecting contrast medium, by using heavily T2-weighted sequences.

On T2-weighted images, fluid from the bilio-pancreatic system has a bright signal and by adding fat-supression, the signal of fluid within the ducts becomes more pronounced[6]. MRCP can show dilatation, strictures, irregularities in the Wirsung duct or similar changes in the side-branch ducts – see figures 3,4.

The advantages of MRCP over ERCP are lack of instrumentation of the Wirsung duct and lack of need for sedation during the procedure; however, MRCP is only diagnostic, whereas ERCP is therapeutic. Another difference between the two is that while during ERCP the collapsed secondary branches are distended by the contrast agent, MRCP visualizes the ductal system in a physiologic state, thus being less acurate for small duct disease. To overcome this difference a combined functional-structural test has been developped, called MRCP-S (magnetic resonance cholangiopancreatography with secretin stimulation): secretin stimulates secretion in the ductal system and it also increases the tonus of the Oddi sphincter (preventing the release of secretion in the duodenum), thus filling in the collapsed branches and better delineating minimal duct changes in patients in whom MRCP showed no abnormalities under physiological conditions; the study of Manfredi et al. showed that visualization of the secondary branches improved significantly in both patients with severe disease (from 71% to 100%) and those with a mild-moderate disease (from 4% to 63%). MRCP-S also allows for calculation of the change in pancreatic duct size before and after secretin stimulation (index called pancreatic duct compliance, PDC), which is reduced in chronic pancreatitis[6].

Table 2. Rosemont criteria for chronic pancreatitis

	Rank	Criteria	Feature	Definition
Parenchymal features	1	Major A	Hyperechoic foci with shadowing	Echogenic structures ≥ 2 mm in length and width that shadow
	2	Major B	Lobularity with honeycombing	Well-circumscribed, ≥ 5 mm structures with enhancing rim and relatively echo-poor center, contiguous ≥ 3 lobules
		Minor	Lobularity without honeycombing	Same as above, noncontiguous lobules
	3	Minor	Hyperechoic foci without shadowing	Echogenic structures foci ≥ 2 mm in both length and width with no shadowing
	4	Minor	Cysts	Anechoic, rounded/elliptical structures with or without septations
	5	Minor	Stranding	Hyperechoic lines of ≥ 3 mm in length in at least 2 different directions with respect to the imaged plane
Ductal features	1	Major A	MPD calculi	Echogenic structure(s) within MPD with acoustic shadowing
	2	Minor	Irregular MPD contour	Uneven or irregularoutline and ectatic course
	3	Minor	Dilated side branches	3 or more tubular anechoic structure seach measuring ≥1 mm in width,budding from the MPD
	4	Minor	MPD dilation	≥3.5-mm body or >1.5-mm tail
	5	Minor	Hyperechoic MPD margin	Echogenic, distinct structure greater than 50% of entire MPD inthe body and tail

Endoscopic ultrasound (EUS)

Endoscopic ultrasound is done using a linear/radial transducer integrated into the tip of the scope, using 7.5-12 Mhz frequencies. It is a great method of evaluating the pancreas, considering that the transducer gets in very close range of the gland, from which is separated only by the digestive tract wall.

EUS is especially useful for early chronic pancreatitis, being able to reveal small structural changes. Its advantage over ERCP is that it detects both parenchymal and ductal changes and doesn't use ionizing radiation. One of the disadvantages of EUS is that it's operator-dependent.

Add-on modules such as elastography and contrast-enhanced EUS (CEEUS) provide further details in evaluating pancreatic disease. Moreover, linear EUS can also provide tissue sampling (to differentiate an inflammatory mass from adenocarcinoma) and can guide therapy in chronic pancreatitis (celiac plexus neurolysis for unresponsive pain, pseudocyst drainage, main pancreatic duct drainage).

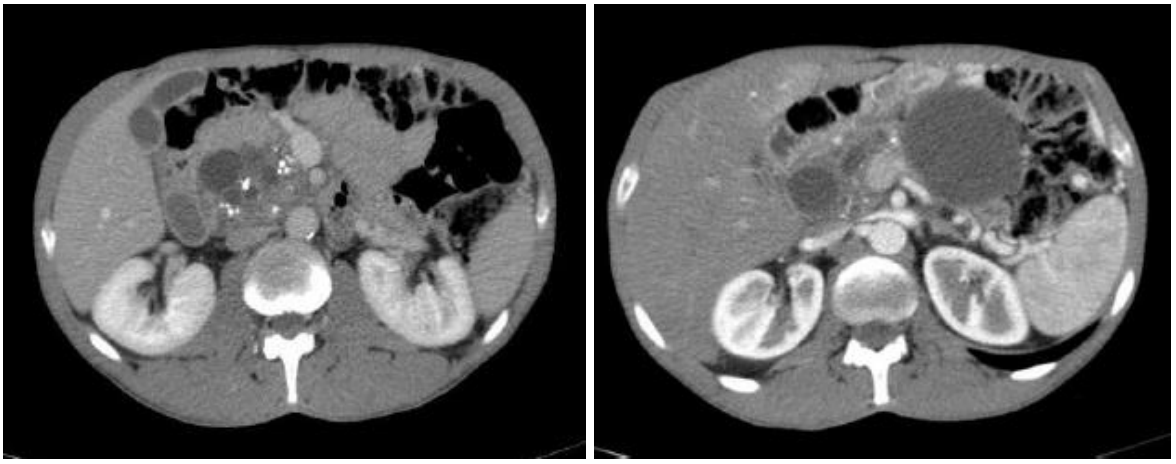
EUS characteristics of chronic pancreatitis have been grouped into ductal and parenchymal, focusing on 9 criteria which correspond to histopathological changes: 5 of them are parenchymal (hyperechoic foci, hyperechoic strands, lobularity, cysts/ pseudocysts, calcifications) and 4 are ductal (dilated pancreatic duct, irregular pancreatic duct, hyper-echoic pancreatic duct walls, visible side branches) – see figures 5,6,7,8. Because not all of these criteria have the same importance in the diagnosis of chronic pancreatitis, these sonographic features have been redefined as major and minor features in a consensus classification called Rosemont.

According to the Rosemont criteria, EUS result can be23: consistent with chronic pancreatitis (1 major A feature + ≥3 minor features, or 1 major A feature + major B feature, or 2 major A features), suggestive of chronic pancreatitis (1 major A feature + <3 minor features, or 1 major B feature + ≥3 minor features, or ≥5 minor features), indeterminate for chronic pancreatitis (3 to 4 minor features, no major features or major B feature alone or with <3 minor features) or normal (no major features, ≤ 2 minor features – excluding cysts, dilated MPD, hyperechoic non-shadowing foci, dilated side branch).

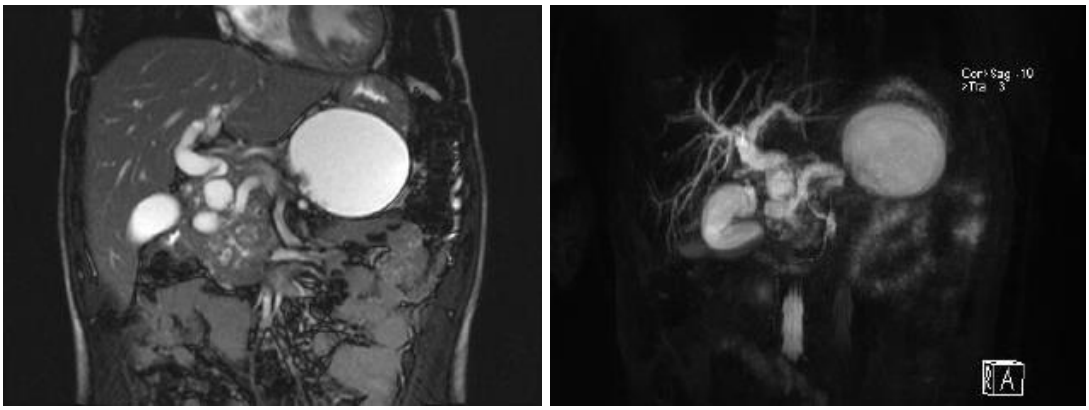
Table 3. Sensitivity and specificity of imaging studies for the diagnosis of chronic pancreatitis[10]

	Sensitivity (%)	Specificity (%)
Ultrasound	60-70	80-90
CT	75-90	85
MRI/MRCP	85	100
ERCP	75-95	90
EUS	97	60

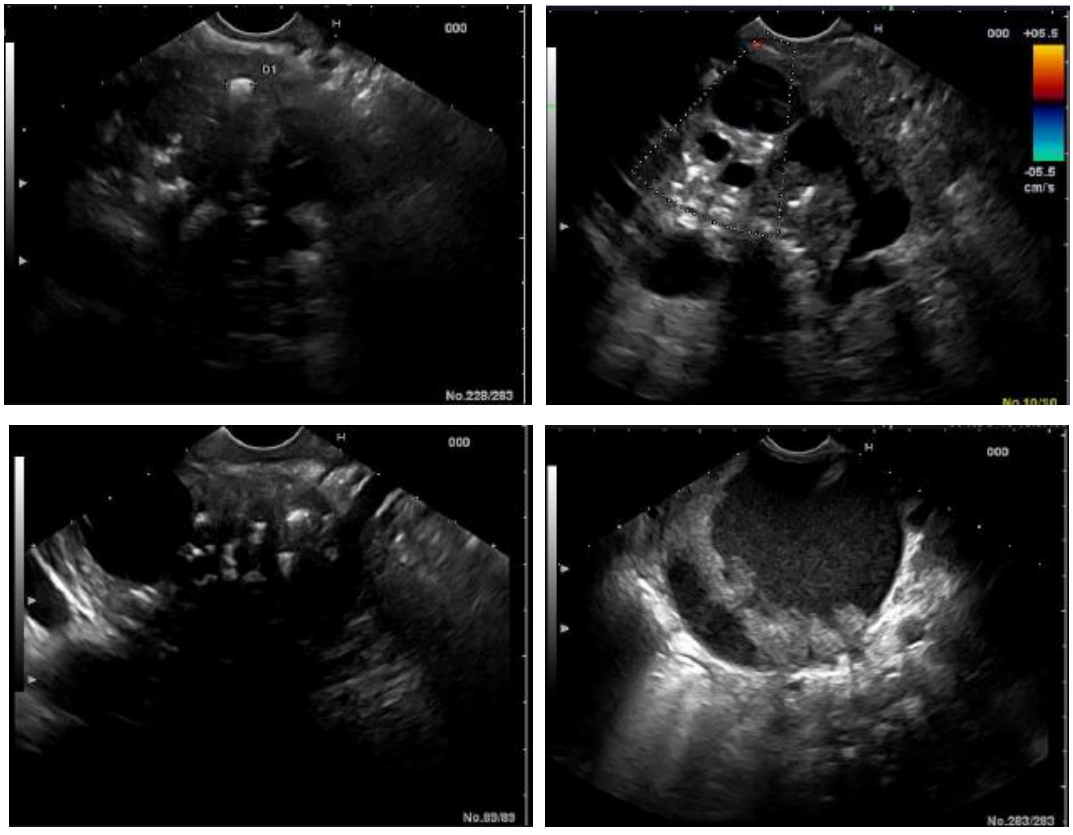
Figures 1,2: CT scan of a 40 years-old male, smoker, with chronic alcohol intake and history of multiple episodes of acute pancreatitis: Enlarged head of the pancreas with multiple cystic structures (up to 3 cm, compressing the CBD) and calcifications; large pseudocyst (8/7 cm) in the body-tail.



Figures 3,4: MRI and MRCP, same patient: Pseudotumoral chronic pancreatitis, 9/7 cm pseudocyst in the bodytail with splenic vein occlusion



Figures 5-8: EUS examination, same patient: Inhomogeneous head of the pancreas with multiple calcifications (up to 6 mm) and cystic structures; large cystic lesion in the body of the pancreas with hyperechoic debris



CONCLUSIONS

Imaging is becoming more and more important in the evaluation of chronic pancreatitis.

Among the imaging methods, plain abdominal radiograph is useful when calcifications are present and abdominal ultrasound is valuable for follow-up.

CT is best for identifying pancreatic calcifications and for evaluating complications of chronic pancreatitis.

ERCP can accurately detect changes in the ductal system, but it's nowadays accepted only for therapeutic purposes. MRI with MRCP and EUS are currently the imaging methods of choice for the evaluation of chronic pancreatitis.

References:

1 Tandon RK, Sato N, Garg PK. Chronic pancreatitis. Asia-Pacific consensus report. J Gastroenterol Hepatol 2002; 17: 508-518.

2 Feldman M. Friedman LS, Brandt LJ. Chronic pancreatitis. In: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Elsevier 2010.

3 Steer ML, Waxman I, Freedman S. Chronic pancreatitis. N Engl J Med 1995; 332:1482-1490.

4 Forsmark C, Adams PC. Pancreatic function testing – valuable but underused. Can J Gastroenterol. 2009; 23: 529–530.

5 Parsi MA, Conwell DL, Zuccaro G, et al. Findings on endoscopic retrograde cholangiopancreatography and pancreatic function test in suspected chronic pancreatitis and negative cross-sectional imaging. Clin Gastroenterol Hepatol. 2008; 6:1432-1436.

6 Choueiri NE, Balci NC, Alkaade S, Burton FR. Advanced imaging of chronic pancreatitis. Curr Gastroenterol Rep. 2010; 12:114-120.

7 Munoz JED: Chronic pancreatitis. In Clinical Pancreatology for Practicing Gastroenterologists and Surgeons. Malden: Blackwell; 2006: 180–253.

8 Badea R, Diaconu B. Contributions of US to the diagnosis of chronic pancreatitis and to evaluating its main complications. Rom J Gastroenterol 2005; 14:183-189.

9 Haaga JR, Alfidi RJ, Zelch MG, et al. Computed tomography of the pancreas. Radiology 1976; 120:589–595.

10 Nair JR, Lawler L, Miller MR. Chronic pancreatitis. Am Fam Physician. 2007; 76:1679-1688.

11 Malfertheiner P, Büchler M. Correlation of imaging and function in chronic pancreatitis. Radiol Clin North Am. 1989; 27:51-64.

12 Axon ATR, Classen M, Cotton PB, Cremer M, Freeny PC, Lees WR. Pancreatography in chronic pancreatitis: International definitions. Gut 1984; 25:1107-1112.

13 Banks PA. Classification and diagnosis of chronic pancreatitis. J Gastroenterol 2007; 42 (Suppl XVII): 148–151.

14 Angelini G, Cavallini G, Pederzoli P, et al. Long term outcome of acute pancreatitis: A prospective study with 118 patients. Digestion 1993; 54: 143–147.

15 Tandon RK, Sato N, Garg PK and The Consensus Study Group. Chronic pancreatitis: Asia–Pacific consensus report. Journal of Gastroenterology and Hepatology 2002; 17: 508–518.

16 Remer EM, Baker ME. Imaging of chronic pancreatitis. Radiol Clin North Am 2002; 40:1229–1242.

17 Sai JK, Suyama M, Kubokawa Y, Watanabe S. Diagnosis of mild chronic pancreatitis (Cambridge classification): comparative study using secretin injection-magnetic resonance cholangiopancreatography and endoscopic retrograde pancreatography. World J Gastroenterol 2008; 14:1218–1221.

18 Balci NC, Alkaade S, Magas L, Momtahen AJ, Burton FR. Suspected chronic pancreatitis with normal MRCP: findings on MRI in correlation with secretin MRCP. J Magn Reson Imaging 2008; 27:125–131.

19 Manfredi R, Costamagna G, Brizi MG, et al. Severe chronic pancreatitis versus suspected pancreatic disease: dynamic MR cholangio-pancreatography after secretin stimulation. Radiology 2000; 214:849–855.

20 Cappeliez O, Delhaye M, Devière J. Chronic pancreatitis: evaluation of pancreatic exocrine function with MR pancreatography after secretin stimulation. Radiology 2000; 215:358-364.

21 Seicean A. Endoscopic ultrasound in chronic pancreatitis: Where are we now? World J Gastroenterol. 2010; 16:4253–4263.

22 The International Working Group for Minimum Standard Terminology for Gastrointestinal Endosonography. Reproduction of minimal standard terminology in gastrointestinal endosonography. Dig Endosc 1998; 10:158-188.

23 Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc 2009; 69: 1251-1261.