Imaging in chronic pancreatitis: State of the art review

Rohan Kamat, Pankaj Gupta, Surinder Rana

Department of Radiodiagnosis and Imaging and Gastroenterology, PGIMER, Chandigarh, India

Correspondence: Dr. Pankaj Gupta, Department of Gastroenterology, Section of Radiology, PGIMER, Chandigarh, India.
E-mail: pankajgupta959@gmail.com

Abstract

Chronic pancreatitis (CP) is an important gastrointestinal cause of morbidity worldwide. It can severely impair the quality of life besides life-threatening acute and long-term complications. Pain and pancreatic exocrine insufficiency (leading to malnutrition) impact the quality of life. Acute complications include pseudocysts, pancreatic ascites, and vascular complications. Long-term complications are diabetes mellitus and pancreatic cancer. Early diagnosis of CP is crucial to alter the natural course of the disease. However, majority of the cases are diagnosed in the advanced stage. The role of various imaging techniques in the diagnosis of CP is discussed in this review.

Key words: Chronic pancreatitis; diagnosis; imaging

Introduction

Clinically, morphologically, and histologically, pancreatitis can be categorized into acute and chronic.[1] Chronic pancreatitis (CP) is characterized by relentless inflammatory and fibrotic changes of the gland, eventually leading to exocrine and endocrine dysfunction.[2] CP due to alcoholism constitutes about 70-90% of cases in western countries. Malnutrition is a rare cause of CP now.[3,4] Other important risk factors are genetic predisposition, smoking, high protein diet, hypercalcemia, hyperparathyroidism, congenital lesions like abnormal pancreaticobiliary junction and pancreatic divisum, pancreatic or peripancreatic neoplasms, and ampullary stricture. Rarer causes of CP include hereditary pancreatitis, autoimmune pancreatitis, and chronic renal failure.[2] Gall stones are major causes of acute pancreatitis. However, they are not considered as risk factors for chronic pancreatitis.[5] CP most commonly presents with abdominal pain. It can also present with steatorhea and diabetes.[2] Early diagnosis of CP is difficult. Biochemical studies do not help in definitive diagnosis in the early stages.[6] Diagnosis at this stage is suspected based on a combination of clinical symptoms, pancreatic function tests, and radiological investigations.[7] Definitive diagnosis of CP is established in advanced cases with a destruction of greater than 90% of parenchyma.[8] Several imaging modalities have been used to assess the pancreas such as abdominal radiographs, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic retrograde cholangiopancreatography (ERCP).[2] With the evolution of several newer techniques such as pancreatic CT protocol with a multi-detector scanner, magnetic resonance cholangiopancreatography (MRCP) with secretin stimulation (S-MRCP), endoscopic ultrasound (EUS) and shear wave elastography (SWE), early detection and management of CP has been possible.[9] In the early phases of CP, functional and morphological disturbances can be seen at the ductal level, with delayed discharge of pancreatic

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enzymes in response to secretin (functional) or ectasia and irregularities of the main/branch ducts (morphological).\[2,9\]

Chronic inflammation of the pancreas results in fibrosis of the gland with loss of exocrine tissue. Edema, inflammation, and necrosis may superimpose on this background. Pancreatic biopsy is not usually performed as it may result in several complications such as acute pancreatitis, fistulae, and hemorrhage. It may also yield false negative results due to sampling of normal pancreatic tissue.\[9\] In this review, we will discuss the role of various imaging modalities in CP.

Pancreatic functional tests

Functional assessment of the pancreas can be carried out directly by assessing the volume of secretions, bicarbonate, and measuring the enzyme levels in blood and stools. Pancreatic enzymes play a key role in digestion. Hence, indirect evaluation involves studies on mal-digestion to prove pancreatic insufficiency.\[10,11\]

Overall, noninvasive tests are useful only in moderate to severe pancreatic insufficiency.\[12\] None of these tests are useful in mild stage of the disease. Mixed triglyceride breath test is one such test which has shown a promising role in monitoring of the patients on enzyme replacement.\[10\] But like other breath tests, it is not useful in identifying the disease at an early stage. Secretin-cholecystokinin and endoscopy-based functional testing are useful in the diagnosis of CP when morphological assessment cannot yield the diagnosis in early stages of the disease. These tests however are invasive, expensive, time consuming, nonstandardized, and are available only in a few centres. They are also not suitable for monitoring the patients on replacement therapy. Hence, they are not widely being used.\[10,13\] Recent improvements in MRI such as S-MRCP have helped in morphological evaluation of the pancreatic duct along with the assessment of pancreatic secretions.\[13\]

Imaging modalities

Radiographs: Radiograph is now an obsolete tool for the diagnosis of CP. The utility of radiographs in CP is restricted to detection of focal calcifications along the course of pancreas, in the epigastric region [Figure 1]. Calcifications in CP is the most specific feature, however, it occurs late in the course of the disease. Radiographs have a poor sensitivity in the diagnosis of CP.\[2\]

Ultrasonography: Pancreas is a retroperitoneal organ. Ultrasonography of pancreas is challenging due to the bowel gas shadows obscuring part or whole of the pancreas. Sonography of pancreas is also dependent on the patient’s body habitus and the radiologist’s skill. Pancreas should always be assessed in fasting status as this can restrict the obscuration of the gland by bowel gases. Graded compression can help to displace the bowel gases and result in better visualization of the pancreas. Several manoeuvres have been used to assess the pancreas such as distending the stomach with fluids or scanning the patient in oblique position using spleen as the acoustic window. This technique especially helps in visualization of the tail of the pancreas. Other techniques are asking the patient to blowing the abdomen during the scan and scanning in sitting position. However, as ultrasound is easily available, cheap, and has no risk of ionizing radiation, it is used as the first line tool in the radiological assessment of pancreas.\[2,6,10\] Pancreas is usually iso/hyperechoic compared with normal hepatic parenchyma. In early stages of CP, ultrasound is seldom useful.\[4,5\] In later stages of the disease, there are focal hypoechoic areas and hyperechoic areas within the gland representing inflammatory and fibrotic tissues, respectively. Hence, CP gives a heterogenous appearance to the pancreas. Pancreatic parenchyma shows progressive atrophy in CP. Irregular progressive dilatation of the main and the branch pancreatic ducts is seen over time. Discontinuous strictures within the duct may give a “chain of lakes” appearance. Punctate calcifications with or without posterior acoustic shadowing, in the pancreatic parenchyma and the ducts, is the hallmark of CP, seen in about 40% cases [Figure 2].\[5,14-16\] Tiny calcifications not seen on routine sonogram can be identified with color Doppler as a result of twinkling artifacts.\[14\] Associated pancreatic ductal calci may be seen which might obstruct the ducts resulting in repeated attacks of pancreatitis. Other important findings in CP that can be detected with sonography are pseudocysts, thrombosis of the splenoportal axis, and portosystemic collaterals and arterial complications like aneurysms most commonly of splenic artery or gastroduodenal artery.\[17\]

Endoscopic Ultrasonography (EUS): Transabdominal sonography has a limited scope in the assessment of...
pancreas in obese individuals and gaseous abdomen. This limitation is overcome by EUS, as the high frequency transducer (5-12.5 MHz) in EUS is in close proximity to the pancreas, hence visualizing it better.\[10,14\] EUS like ERCP and S-MRCP helps in diagnosing CP at early stages. Normal pancreas in EUS shows homogenous appearance, smooth margins, and is slightly hyperechoic to liver (salt pepper appearance). Normal main pancreatic duct is tubular with anechoic walls. Normal side branches can be seen in about 32% patients.\[11,14\] Certain features of CP seen in EUS besides the usual features seen in TAS and CT are subtle lobularity of the gland borders, tiny cystic changes within the glandular parenchyma, echogenic foci/strands representing areas of fibrosis [Figure 3A], side branch ectasia, and echogenic margins of main pancreatic duct [Figure 3B]. EUS due to its superior resolution compared with TAS and CT helps in early diagnosis of CP by detecting the subtle parenchymal and ductal changes.\[10\] Differentiation of mass forming pancreatitis is difficult with EUS per se, like other modalities. However, EUS has the ability to sample the tissue by guided fine needle aspiration (EUS-FNA).\[14,15,16,20\] In a retrospective analysis by Agarwal et al., it was found that EUS-FNA had a sensitivity of 88.8% and specificity of 100% for diagnosis of mass forming pancreatitis.\[21\] In comparison with ERCP, EUS is relatively less invasive, assesses both parenchymal and ductal abnormalities, can be used for celiac plexus blockade, and drainage of collections.\[18\] It has a sensitivity and specificity of 83% and 80%, respectively, for the diagnosis of CP.\[22\] Drawbacks of EUS are its inter/intraobserver variability and false positivity, as a few findings of CP like echogenic septations can be normally seen with aging, in smokers and in alcoholics.\[15\] A few studies have shown that EUS is more sensitive than ERCP.\[23\] Kahl et al. conducted a study comparing EUS with ERCP and found that 69% of patients detected by EUS and negative on ERCP in the initial study eventually showed abnormal pancreatograms.\[23\]

**Figure 2:** Abdominal ultrasound shows atrophic pancreas with dilated main pancreatic duct (short arrow) with intraductal calculi (arrow)

**Figure 3 (A and B):** EUS in a patient with chronic pancreatitis shows echogenic strands (arrow) in the head of pancreas (A). EUS in another patient with chronic pancreatitis (B) shows dilatation of main pancreatic duct (arrow) and side branches (short arrow)

Rosemont criteria for EUS diagnosis of CP is shown in Table 1.\[24\]

**Contrast enhanced-EUS (CE-EUS):** is an emerging technique in imaging the pancreas. It is particularly useful in patients with renal failure as the microbubble contrast agents are not nephrotoxic. The contrast resolution of EUS is further improved with the use of these contrast agents.\[25\] The lobular pattern seen in the conventional EUS is exaggerated by CE-EUS. CP patients have a faster wash-out of the contrast compared with normal individuals.\[26\] Pancreatic carcinoma appears as a hypoechoic lesion in CE-EUS showing rapid wash out. Mass forming CP usually appears as an isoechoic lesion. Hypoechoic character of the adenocarcinoma has a high sensitivity of 89-96%, but advanced mass forming CP can give a similar appearance [Figure 4]. Hyperenhancement of the lesion however rules out an adenocarcinoma.\[27\] EUS and MRI/S-MRCP have similar sensitivities for the diagnosis of CP. EUS has a slightly greater specificity. Combining both EUS and MRI/S-MRCP, the specificity was found to be 100%.\[28\]

**EUS-secretin pancreatic function test (EUS-PFT):** Demonstration of exocrine insufficiency is a functional evidence of CP, which may be present in a mild form even at the onset of pancreatic fibrosis. The gold standard for diagnosis of early exocrine insufficiency in CP is direct PFT using secretin and CCK. EUS-PFT allows a simultaneous structural and functional assessment of the pancreas. Following intravenous administration of synthetic secretin, duodenal aspirates are collected at 15, 30, and 45 min. A peak bicarbonate concentration less than 80 mM is suggestive of exocrine insufficiency.

**Elastography:** Elastography is a noninvasive ultrasound technique which helps to assess the stiffness of a tissue. Elastography can be qualitative or quantitative. The stiffness of the region of interest (ROI) can be quantified either by conventional strain elastography (SE) or by shear wave elastography (SWE). Fibrosis and malignant infiltration
can cause increase in the hardness of a tissue. As the first generation strain elastography was qualitative, second generation systems were developed, which gave the strain ratio (SR). ROIs are drawn over the target region and the surrounding reference region (preferably in the gut wall). Then the SR is calculated.\[^{21, 22, 25}\]

SWE quantitatively determines the stiffness of the tissue based on the velocity of shear waves in the tissues. Both SWE and SE yield elastograms, which are color maps superimposed on the gray-scale images. The color pattern determines the degree of stiffness (blue being towards the hard end of the spectrum and red towards the soft end).\[^{29}\]

Elastography can be used with TAS or EUS.\[^{30}\]

In CP, fibrosis of the gland leads to progressive increase in glandular stiffness [Figure 5A].\[^{31}\]

Focal pancreatic lesions can also be evaluated with EUS elastography to determine the nature based on the strain pattern.\[^{32}\]

EUS shows both focal pancreatic masses in CP as well as in adenocarcinomas as hypoechoic masses. Inflammatory masses of pancreas can show varied range of strain ratios [Figure 5B], however a hypoechoic lesion with higher strain suggesting softer tissue is unlikely to be malignant.\[^{14}\]

SR also helps in predicting the exocrine insufficiency of pancreas.\[^{33}\]

With progression of disease, there is corresponding decline in the exocrine activity of the gland. EUS elastography helps in predicting the enzymatic deficiency, suggesting requirement of enzyme replacement therapy in CP.\[^{34}\]

Table 1: Rosemont criteria for EUS diagnosis of CP\[^{24}\]

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor criteria</th>
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<tr>
<td>A. Hyperechoic foci with shadowing</td>
<td>Cysts</td>
</tr>
<tr>
<td>B. MPD calculi</td>
<td>MPD calibre ≥ 3.5 mm</td>
</tr>
<tr>
<td>C. Lobularity with honeycombing</td>
<td>Irregular ductal contour</td>
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I. Consistent with CP
A. 1 major A feature (+) ≥ 3 minor features
B. 1 major A feature (+) major B feature
C. 2 major A features

II. Suggestive of CP
A. 1 major A feature (+) < 3 minor features
B. 1 major B feature (+) ≥ 3 minor features
C. ≥ 5 minor features (any)

III. Indeterminate for CP
A. 3 to 4 minor features, no major features
B. major B feature alone or with <3 minor features
C. ≥ 5 minor features (any)

IV. Normal
≤ 2 minor features and no major features

Figure 4 (A-C): Contrast-EUS in a patient with mass forming chronic pancreatitis shows a mass in the head of pancreas with cystic component (arrow, A) with peripheral enhancement (arrow, B) and central nonenhancing component. Then the SR is calculated.\[^{21, 22, 25}\]

Figure 5 (A and B): EUS elastography in a patient with chronic pancreatitis shows heterogenous stiffness of the pancreas (A) with hard areas (arrow) and areas of intermediate stiffness (short arrow). In another patient with mass forming chronic pancreatitis (B), elastography shows that the mass is hard (blue areas). Also note the presence of a cyst (arrow)

Table 2 shows the SR of Rosemont categories.

As discussed above, CE-EUS, EUS elastography, and EUS FNA are the newer modalities which have improved the confidence in differentiating a focal pancreatic mass in CP from a malignant tumor.\[^{36}\]

Computed tomography

CT features of CP are shown in Table 3.\[^{35-38}\]

Calcifications are seen in the late stages of CP and hence detection of CP in early stages using CT is difficult [Figure 6A]. Sensitivity of CT in detecting late stages of CP is 60-95%.\[^{39}\]

Alcohol-induced pancreatitis and hereditary pancreatitis show calcifications in the gland at a relatively earlier stage than in other causes of pancreatitis like obstructive CP and cystic fibrosis-related CP.\[^{39}\]

Presence and number of parenchymal calcifications is an independent predictor of the degree of pancreatic fibrosis.\[^{40}\]

Multiphase protocol is now commonly used in the assessment of pancreas, which includes a precontrast scan which helps in excellent depiction of calcifications, a pancreatic phase which is the best phase to assess the arterial enhancement for surgical mapping and to study the arterial complications, followed by a venous phase which shows enhancement of the pancreatic parenchyma. This phase is best suited to
evaluate the parenchyma, pancreatic duct, focal lesions, and collections [Figure 6B].

Dilatation of the duct and parenchymal atrophy are less specific features than calcifications, as they can be seen in normal aging as well. The dilated duct could be smooth, irregular, or beaded [Figure 6C-E]. The main pancreatic duct may show intermittent areas of strictures and dilatation with pleomorphic ductal calculi [Figure 6F]. The calculi in hereditary pancreatitis, tropical pancreatitis, and in genetic mutation-related CP other than in cystic fibrosis are usually large (2-5 cm), in comparison to the ones in alcohol-related CP. MRI/MRCP has superseded CT in detection of pancreatic ductal abnormalities, however CT is still the preferred modality to assess the complications of CP.

Magnetic Resonance Imaging (MRI)

MRI/MRCP features of CP are shown in Table 4.

Normal pancreas appears diffusely hyperintense on T1-weighted images due to the presence of proteinaceous enzymes [Figure 7A]. Fat saturated sequence helps in suppressing the retroperitoneal fat and thus improves the contrast between the hyperintense pancreas and the fat-suppressed retroperitoneum. Recently, diffusion imaging has evolved in the assessment of pancreatic diseases. Normal pancreas shows no restriction of diffusion due to presence of free movement of the water molecules [Figure 7B]. Hence, the apparent diffusion coefficient (ADC) is high in normal pancreas. In cases of CP, there is restriction of diffusion of water molecules resulting in a drop in ADC [Figure 7C-E]. The limitations with MRI assessment of abdomen due to respiratory motions, peristalsis, and cardiac pulsations have been tackled effectively with the help of improved MRI techniques. Faster acquisition and improved signal-to-noise ratio has been achieved with the current techniques.

Addition of MRCP sequence to the routine pancreatic MRI has significantly improved the ductal assessment [Figure 8]. As MRCP is a noninvasive tool, it has preferred over ERCP for the diagnostic imaging of bile duct and pancreatic ducts.
S-MRCP
As MRI/MRCP fails to evaluate the exocrine insufficiency, Matos et al. proposed a technique called secretin-stimulated MRCP (S-MRCP). Secretin is a polypeptide amino-acid which is normally secreted by the S cells of the duodenal mucosa. This enzyme is responsible for the bicarbonate-rich secretions from the pancreas, into the duodenum. Prior to the procedure, the patient should be fasting for 4-6 h. Half hour prior to the study, a negative oral agent is administered to suppress the signals from the pre-existing bowel fluids. Pre-secretin images are first obtained. Secretin is injected intravenously following which a series of T2-weighted images are acquired every 30 s for 15 min. Normal main pancreatic duct shows dilatation which reaches a peak in about 2-5 min. Post-secretin dilatation of the main pancreatic duct should be at least 1 mm greater than the baseline images to suggest ductal compliance. Conventional MRCP fails to demonstrate the side branches. However, S-MRCP shows the dilated side branches in cases of CP. Depending upon the volume of fluid secreted into the duodenum, the exocrine function is assessed by three grades. Grade 1 is fluid restricted to the duodenal bulb. Grade 2 is fluid filling the first and second parts of the duodenum while grade 3 is fluid filling the third part of the duodenum as well.

Grade 1 and 2 suggest exocrine insufficiency. This quantification also correlates well with the fecal elastase 1 value. Thus S-MRCP helps in morphological and functional assessment of the pancreas. Studies have also evaluated the pancreatic exocrine function using diffusion weighted imaging with S-MRCP. As secretin injection increases the exocrine secretion and promotes diffusion of water, ADC is expected to rise in normal pancreas. However in cases of CP, there is delay in the peak of ADC beyond 10 min of secretin injection. Hence, ADC peak time after secretin stimulus can be used as a marker for pancreatic exocrine insufficiency in cases of CP.

ERCP which was once considered as the gold standard test for CP is seldom used for diagnosis of CP at present. MRCP is now preferred for diagnosis of CP. Agreement of 83–100% for ductal dilatation [Figure 9A], 70–92% for identification of strictures [Figure 9B], and 92–100% for identification of filling defects [Figure 9C] has been revealed on comparison of MRCP and ERCP.

18-F-flouro-deoxy-glucose positron emission tomography (FDG PET): In order to obtain both biochemical and
structural information, FDG-PET with CT and more recently with MRI has been used to assess focal pancreatic lesions.\[^{60}\] The standardized uptake value (SUV) of FDG is significantly greater in malignant masses of the pancreas compared with focal pancreatic masses in CP. SUV >4 is usually seen in a pancreatic carcinoma [Figure 10A and 10B], SUV of 3-4 is more commonly seen in cases of focal pancreatic masses in CP and SUV <3 is seen in healthy individuals [Figure 11C and D].\[^{61,62}\] However, focal lesions in autoimmune pancreatitis (AIP) have high SUV and there is no significant difference compared with pancreatic carcinoma.\[^{63}\] Nodular FDG uptake is more common in pancreatic carcinomas as compared with AIP (95% versus 23.1%). AIP commonly shows longitudinal FDG uptake (69.2% of AIP versus 2.5% of pancreatic carcinoma cases).\[^{60,63}\] Several studies have shown the sensitivity and specificity of FDG-PET to be between 81 and 100% and 65 and 100%, respectively, for diagnosing carcinoma in cases of focal pancreatic masses.\[^{64}\]  

**Special varieties of CP**

Few special varieties of CP are autoimmune pancreatitis and groove or paraduodenal CP.

**Autoimmune pancreatitis (AIP)**

It is a rare type of CP accounting for about 2-6% of all cases of CP.\[^{65,66}\] It is commonly seen in association with IgG4-related disease and other autoimmune conditions like primary
biliary cirrhosis, primary sclerosing cholangitis, Sjogren’s syndrome, etc. CT shows diffuse smooth hypodense enlargement of the gland with enhancement in the delayed phase [Figure 11A]. MRI shows reduced T1 signals and mildly raised T2 signals, with delayed post-gadolinium enhancement. Capsule like rim of decreased intensity is a relatively specific finding [Figure 11B and 11C]. AIP is commonly diffuse in nature and rarely focal/multifocal. Important differentials are lymphomas, metastasis, and other infiltrative disorders. Simultaneous involvement of other systems favors a diagnosis of AIP [Figure 11D]. Focal pattern is much less common and is difficult to differentiate from ductal adenocarcinomas [Figure 12].

**Groove pancreatitis**

In groove/paraduodenal pancreatitis, there is focal inflammation in the pancreaticoduodenal groove with or without involvement of the head of pancreas. Obstruction of the accessory pancreatic duct is suspected to be the etiology of this entity. There can be ill-defined fat stranding to frank fibrotic soft tissue within the groove showing delayed post-contrast enhancement [Figure 13]. Associated medial duodenal wall thickening and cystic foci near the minor papilla may be seen [Figure 14]. MRI shows hypointensity on T1-weighted and mild hyperintensity on T2-weighted images, with delayed enhancement. Cystic lesions in the groove are better appreciated on T2-weighted images. EUS and EUS elastography are also useful in depicting changes of groove pancreatitis [Figure 15].

**Adenocarcinoma in CP**

There is an increased risk of adenocarcinomas in cases of CP, however this risk is much higher with hereditary and tropic pancreatitis as compared with alcohol related CP. CP can present as a focal mass in about 30% cases. Differentiation from pancreatic ductal adenocarcinoma is quite challenging. Double duct sign may be seen in both the conditions. Presence of calcifications and ductal calculi are more commonly associated with CP. The mild enhancement during the arterial and a persistent enhancement during the pancreatic phase are relatively specific but not sensitive for distinguishing mass forming CP from adenocarcinomas. One of the important signs differentiating focal CP from ductal adenocarcinoma is the duct penetrating sign seen on MRCP. Here, a smoothly stenotic duct is seen to penetrate the mass with no cutoff as commonly appreciated in an adenocarcinoma. Duct penetrating sign has a sensitivity and a specificity of 85% and 96%, respectively.

**Summary of diagnostic tests**

Sensitivities of the diagnostic tests for CP in descending order are ERCP (82%), EUS (81%), MRCP (78%), MDCT (75%), and ultrasound (67%). Specificities for the diagnosis of CP are MRCP (96%), ERCP (94%), MDCT (91%), and EUS (90%). MRI, MDCT, EUS, and ERCP were found to have high diagnostic accuracy. Among them, the latter two had the highest scores. However, due to the invasive nature of these tests, MDCT and MRCP are preferred over these tests. MDCT and MRCP are the first line investigation in CP. ERCP is generally used only when therapeutic interventions are planned. ERCP for diagnostic purpose has been substituted by EUS, MDCT, and MRCP.

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**Conflicts of interest**

There are no conflicts of interest.
References


