

## Head mass in chronic pancreatitis: Inflammatory or malignant

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malignant mass. Advances in imaging technologies like endoscopic ultrasound in conjunction with techniques like fine needle aspiration, contrast enhancement and elastography as well as multidetector row CT, magnetic resonance imaging and positron emission tomography scanning have been shown to help in distinguishing inflammatory and malignant mass. Research is ongoing to develop molecular techniques to help characterise focal pancreatic mass lesions. This paper reviews the current status of imaging and molecular techniques in differentiating a benign mass lesion in chronic pancreatitis and from malignancy.

**Key words:** Chronic pancreatitis; Pseudotumour; Imaging; Endoscopic ultrasonography; Molecular tool

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**Core tip:** Evaluating head mass in chronic pancreatitis is clinically challenging. Advances in pancreatic imaging including endoscopic ultrasonography and molecular tools have been reviewed.

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### Abstract

Chronic pancreatitis increases the risk of developing pancreatic cancer. This often presents as a mass lesion in the head of pancreas. Mass lesion in the head of pancreas can also occur secondary to an inflammatory lesion. Recognising this is crucial to avoid unnecessary surgery. This is sometimes difficult as there is an overlap in clinical presentation and conventional computed tomography (CT) abdomen findings in inflammatory and

### INTRODUCTION

The risk of developing pancreatic cancer in patients with chronic pancreatitis is about fifteen times higher than in the average population<sup>[1]</sup>. A meta analysis has shown that 5% of the patients with chronic pancreatitis develop pancreatic cancer over a 20 year period<sup>[2]</sup>. About 70% of these tumours are located in the head

region of pancreas<sup>[3]</sup>. Patients with chronic pancreatitis also tend to develop inflammatory lesions in the head of pancreas which appears like tumour mass and is referred to as pseudotumour<sup>[4]</sup>. Confirming the diagnosis preoperatively is crucial because confusion may lead to either major pancreatic resection for benign disease or rejection of surgery for a potentially curable lesion.

Clinical features and biochemical parameters that suggest malignant mass in head of pancreas are older age, persistent jaundice, worsening abdominal pain, gastric outlet obstruction, significant weight loss and elevated CA 19:9 greater than 300 U/mL<sup>[5]</sup>. Conventional Imaging techniques like Ultrasound abdomen, CT and MRI provide useful information that helps in differentiating benign from malignant mass in head of pancreas<sup>[6]</sup>. Unfortunately, due to an overlap in clinical, biochemical and conventional imaging parameters, it is sometimes difficult to differentiate an inflammatory mass from cancer in head of pancreas<sup>[6]</sup>. This is supported by the fact that most large series of pancreatic resections for carcinoma head of pancreas show that 5%-10% of cases of inflammatory mass masquerade as pancreatic carcinoma<sup>[7,8]</sup>.

The advent of endoscopic ultrasound (EUS) has been a major development in assessment of pancreatic disease including mass lesions in the head of pancreas<sup>[9]</sup>. High frequency EUS probes in the stomach located close to the pancreas, provide detailed images with no intervening bowel gas<sup>[9]</sup>. In addition, fine needle aspiration (FNA) performed for obtaining tissue sample further helps in diagnosis. New EUS based techniques like Digital Image analysis, EUS Elastography and Contrast enhanced EUS have shown promise in better characterisation of pancreatic mass lesion. In this paper we review the role of EUS in assessing pancreatic head mass in chronic pancreatitis and also briefly look at other radiological and molecular tools available for evaluation of this entity.

## ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic ultrasonography has been found to be very useful in detecting small pancreatic mass lesions and has been shown to be better than other modalities for assessing vascular invasion and local spread<sup>[10,11]</sup>. EUS in association with other techniques like FNA or contrast enhancement has also been found to be useful in distinguishing benign from malignant pancreatic mass lesions. The data from studies evaluating the role of EUS in assessing pancreatic mass lesion has been summarised in Tables 1 and 2. Table 1 shows only studies which have included patients with background chronic pancreatitis. Most studies show that EUS alone is not capable of precisely differentiating between a pseudotumoral mass and carcinoma in the setting of chronic pancreatitis<sup>[12-14]</sup>. Presence of multilobularity, homogenous pattern, hyperechoic septa and Doppler signal within a lesion favour pseudotumour<sup>[12]</sup>. One

of the limitations with EUS is the subjective nature of image assessment and performance which varies depending on experience. As the architectural changes are better detected by computer based methods than naked eye, it is possible that digital image analysis (DIA) obtained during EUS can remove the error of subjective assessment. Two studies with adequate number of subjects have shown that digital image analysis has sensitivity and specificity of above 90% in differentiating malignant and benign pancreatic mass lesion<sup>[15,16]</sup>.

The limitations of conventional B mode EUS can be overcome by performing FNA which gives a tissue diagnosis. FNA is relatively safe as it does not traverse peritoneal cavity and avoids seeding of peritoneum. Unfortunately, FNA which has a sensitivity of above 90% in detecting pancreatic malignancy in pancreas with normal parenchyma, underperforms in the presence of chronic pancreatitis with sensitivity dropping to below 75%<sup>[12,17-19]</sup>. Vardarajulu and colleagues reported that in the 300 EUS FNA performed for pancreatic mass lesions, sensitivity was 91.3% in pancreas with normal parenchyma but only 73.9% when chronic pancreatitis was present<sup>[17]</sup>. Other studies have shown even poorer performance. In a study from Romania on 72 patients with Chronic Pancreatitis (17 had Pancreatic Carcinoma), EUS FNA had a sensitivity of only 50%<sup>[18]</sup>. Similarly, in another report from Germany on 13 patients with Chronic Pancreatitis and carcinoma, EUS FNA was able to detect carcinoma in only 7 of them<sup>[19]</sup>. Making more number of passes during FNA or repeating FNA may improve the yield<sup>[17,20]</sup>.

Using molecular tools to detect mutation in tissue sample may be a useful adjunct to improve diagnostic yield<sup>[21-23]</sup>. Khalid *et al*<sup>[21]</sup>, studied microsatellite markers and mutation in *K-ras* gene on EUS-FNA samples from patients with benign and malignant pancreatic masses. The mean fractional mutation rate was higher in pancreatic malignancy and use of molecular tool improved the diagnostic performance of FNA<sup>[21]</sup>. In another study from Czech Republic which included 101 subjects, mutations in *K-ras* and allelic loss in tumour suppressor genes were determined on EUS-FNA specimen<sup>[22]</sup>. Detection of mutation in *k-ras* gene, allelic loss of *p16* and *DPC4* gene improved the sensitivity of cancer detection to 100%<sup>[22]</sup>. A large prospective multicenter study which only looked at *k-ras* mutations in addition to cytopathology on FNA samples, found that assessing for *k-ras* mutation improved the diagnostic sensitivity for malignancy to 88% which was only marginally better than cytopathology alone (83%)<sup>[24]</sup>. However, absence of *K-ras* mutation was a strong indicator of benign lesion<sup>[24]</sup>. This study also highlights the importance of studying multiple markers rather than single one. Other studies have shown that absence of *k-ras* mutation in FNA samples from patients with chronic pancreatitis and mass lesion strongly suggest a benign lesion<sup>[24,25]</sup>. Data from the above studies suggest that molecular tests can play a significant role in diagnosing

**Table 1 Endoscopic ultrasound in evaluating pancreatic mass lesions in patients with chronic pancreatitis**

Ref.	Study subjects	Procedure	Outcome <sup>1</sup>
Fritscher-Ravens <i>et al</i> <sup>[19]</sup>	74 patients with focal pancreatic lesions and chronic pancreatitis	EUS FNA	Sn-54%
Vardarajulu <i>et al</i> <sup>[17]</sup>	75 patients with CP and focal pancreatic mass lesion	EUS FNA	Sn-73.9% Sp-100%
Iordache <i>et al</i> <sup>[18]</sup>	CP-55 CP and PC-17	EUS FNA	Sn-50% Sp-73.7%
Hocke <i>et al</i> <sup>[13]</sup>	86 patients with CP and pancreatic lesion	EUS CE-EUS	Sn-73.2% Sp-83.3% Sn-91.1% Sp-93.3%

<sup>1</sup>Differentiating malignant and non-malignant pancreatic lesion. Sn: Sensitivity; Sp: Specificity; CP: Chronic pancreatitis; PC: Pancreatic cancer; CE: Contrast enhanced; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

pancreatic cancer in FNA samples and one should assess for k-ras mutations along with loss of tumour suppressor genes to improve yield.

Recent advances in EUS based technology like EUS Elastography, Contrast Enhanced EUS and computer software in interpreting images have shown promise in better characterisation of pancreatic mass lesions<sup>[26-28]</sup>. EUS elastography measures tissue stiffness<sup>[26,29]</sup>. The stiffness in malignant tumour is different from benign lesion or normal tissue and this is represented as different colour regions on the conventional real time EUS images. Usually blue colour indicates hard tissue, red suggests soft tissue and green represents tissue with intermediate stiffness. To remove subjective error, tissue strain can be quantitatively measured by software to provide strain ratios which are different for benign and malignant lesions<sup>[29,30]</sup>. The results of earlier studies with EUS elastography were disappointing showing low sensitivity and specificity<sup>[31,32]</sup>. This was probably due to fibrous architecture in both tumour and chronic pancreatitis<sup>[31]</sup>. Subsequent studies after the introduction of quantitative assessment methods including measurement of strain ratio have shown better outcomes (sensitivity > 90%)<sup>[30,33-35]</sup>. In a study measuring strain ratio during EUS elastography, ratio was 1.68 for normal pancreas, 3.38 for inflammatory mass and a very high ratio of 18.12 for pancreatic adenocarcinoma<sup>[30]</sup>.

Contrast enhanced (CE) EUS makes use of injected contrast to assess vascularity of lesion and low mechanical index technique enables this to be done in real time without problem of artefacts<sup>[36]</sup>. Arterial phase lasts for about 30 s and venous phase for the next 90 s<sup>[37]</sup>. Pancreatic tumours are hypovascular with delayed contrast uptake and usually lack venous structure<sup>[13,38,39]</sup>. A time intensity curve can be generated using image software and the peak characteristics can give a clue to the underlying diagnosis. Results from most studies using

CE EUS have been encouraging with sensitivity and specificity greater than 90%<sup>[13,14,38,40,41]</sup>. Seicean *et al*<sup>[38]</sup> measured the contrast uptake ratio index during CE EUS and found it to be significantly lower in pancreatic cancer than in mass forming chronic pancreatitis. A cut-off ratio of 0.17 had good discriminatory value<sup>[38]</sup>. The contrast enhancement and elastography techniques can also be used in combination. In a study using combination of above techniques, the positive predictive value was 96.7% in evaluating pseudotumour of chronic pancreatitis and pancreatic cancer<sup>[41]</sup>. The results of elastography, CE EUS and digital image analysis are encouraging but are affected by equipment characteristics and type of contrast used. Development of consensus guidelines and uniformity in performing these procedures will make it easier to integrate their use in clinical practice.

## OTHER IMAGING MODALITIES

### Computed tomography

Computed tomography (CT) was considered to be the gold standard for pancreatic parenchymal imaging. Conventional CT however has difficulty in differentiating between inflammatory and neoplastic masses as well as detecting lesions < 2 cm in diameter as small tumours are sometimes isoattenuated to background pancreatic parenchyma. Recent developments including 64 slice multidetector row CT (MDCT) have shown promise in evaluating pancreatic mass lesion<sup>[42,43]</sup>. During triple phase pancreatic protocol CT, normal pancreas shows early washout (first phase) while there is delayed washout in chronic pancreatitis<sup>[44]</sup>. On the other hand pancreatic cancer shows an increasing pattern without washout<sup>[44]</sup>. This can be quantitatively assessed using time attenuation curve and Yamada *et al*<sup>[44]</sup> have shown this technique to have 90.4% accuracy in differentiating pancreatic cancer from chronic pancreatitis. Lu *et al*<sup>[45]</sup> evaluated 15 patients with pancreatic pseudotumor and 64 patients with pancreatic cancer and quantitative hemodynamic information obtained using time density curve was useful in distinguishing the two conditions.

### Magnetic resonance imaging

Magnetic resonance imaging (MRI) has traditionally been considered less sensitive than CT scan for assessing pancreatic mass lesions. T1 weighted images have similar features in both chronic pancreatitis and pancreatic cancer but T2 weighted images show different signal intensity pattern in inflammatory and neoplastic tissue<sup>[46]</sup>. Assessment of pancreatic ductal structures can sometimes provide a clue as pancreatic cancers may lack pancreatic ductal structures while a pseudotumour may contain dilated side branches<sup>[47]</sup>. Recent advances in techniques and technology have been effective in distinguishing between inflammatory and malignant mass of pancreas<sup>[42,43,48,49]</sup>. (1) Diffusion weighted MRI: Huang *et al*<sup>[50]</sup> studied 37 patients

**Table 2** Data from other studies on role of endoscopic ultrasound in evaluating pancreatic mass lesions

Ref.	Study subjects	Procedure	Outcome <sup>1</sup>
Ardengh <i>et al</i> <sup>[12]</sup>	69 patients with pancreatic head mass	EUS	Sn-63.63% Sp-75.86%
		EUS FNA	Sn-72.7% Sp-100%
Das <i>et al</i> <sup>[16]</sup>	Normal-22	EUS, Digital image analysis	Sn-93%
	CP-12		Sp-92%
Zhu <i>et al</i> <sup>[15]</sup>	PC-22	EUS, Digital image analysis	Sn-96.25%
	CP-262		Sp-93.38%
Hirsche <i>et al</i> <sup>[32]</sup>	70 patients with focal pancreatic lesion	EUS	Sn-41%
		Elastography	Sp-53%
Giovannini <i>et al</i> <sup>[33]</sup>	121 patients with pancreatic mass lesion	EUS	Sn-92.3%
		EUS Elastography	Sp-68.9%
Iglesias-Garcia <i>et al</i> <sup>[35]</sup>	78 patients with malignant pancreatic tumour	EUS Elastography	Sn-100%
	42 patients with inflammatory pancreatic mass		Sp-80%
Iglesias-Garcia <i>et al</i> <sup>[30]</sup>	86 patients with pancreatic mass	Quantitative EUS Elastography	Sn-100%
	(27 of them had inflammatory mass)		Sp-92.9%
Seicean <i>et al</i> <sup>[38]</sup>	30 patients with pancreatic lesion	CE harmonic-EUS	Sn-80%
	(12 had pseudotumour)		Sp-91.7%
Saftoui <i>et al</i> <sup>[41]</sup>	Focal pancreatic mass lesion	CE + elastography during EUS	Sn-75.85
	(21 had pseudotumour)		Sp-95.2%
Saftoui <i>et al</i> <sup>[34]</sup>	258 patients with focal pancreatic mass	Quantitative EUS Elastography	Sn-93.4%
		EUS	Sp-66%
Hocke <i>et al</i> <sup>[14]</sup>	Focal CP-39	EUS	Sn-61.5%
		EUS elastography	Sp-73.7%
Gheona <i>et al</i> <sup>[40]</sup>	PC-19	CELM-EUS	Sn-33.4%
		CEHMI-EUS	Sp-94.7%
Gheona <i>et al</i> <sup>[40]</sup>	PC-32	Quantitative CE-EUS	Sn-76.9%
	Pseudotumoural pancreatitis-19		Sp-84.2%
			Sn-89.5%
			Sp-84.2%
			Sn-93.7%
			Sp-89.4%

<sup>1</sup>Differentiating malignant and non-malignant pancreatic lesion. Sn: Sensitivity; Sp: Specificity; CP: Chronic pancreatitis; PC: Pancreatic cancer; CE: Contrast enhanced; CELMI: Contrast enhanced low mechanical index; CEHMI: Contrast enhanced high mechanical index; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

with pancreatic cancer and 14 patients with mass forming chronic pancreatitis using diffusion weighted MRI imaging with quantification techniques and showed that this technique can differentiate mass forming chronic pancreatitis from pancreatic cancer; (2) Gadolinium (Gd) enhanced 3D- Gradient echo: Kim *et al*<sup>[51]</sup> studied 22 patients with pancreatic mass (pancreatic cancer: 14; chronic pancreatitis: 8) using Gd enhanced 3D-GE and found that this technique differentiated pancreatic cancer from inflammatory mass with a sensitivity and specificity of 93% (13/14) and 75% (6/8), respectively; (3) Time signal intensity curve obtained during contrast enhanced MRI is another technique that helps in differentiating between malignant and inflammatory lesions<sup>[50]</sup>; and (4) Magnetic resonance spectroscopy: Focal pancreatitis has lower lipid content compared to cancer due to difference in fibrous tissue content in the two conditions. This can be detected by magnetic resonance spectroscopy and helps distinguish inflammatory mass from cancer<sup>[52]</sup>.

### Positron emission tomography

The sensitivity of FDG-positron emission tomography (PET) for differentiating pancreatic cancer from chronic pancreatitis is more than that of CT or MRI<sup>[53]</sup>. Singer and colleagues have shown that pancreatic cancer causes focal tracer enhancement while chronic pancreatitis causes diffuse enhancement<sup>[54]</sup>. This feature had 86.4% sensitivity and 78.9% specificity in distinguishing cancer from benign mass in their study on 41 patients. PET-CT detects unsuspected metastasis to liver, lung and bone which aids in discriminating between inflammatory mass and cancer. The sensitivity of PET is superior to CT in detecting lesions less than 2 cm in diameter, but CT scanning is superior to PET for diagnosing cancers larger than 4 cm in diameter because of lower metabolic rates in larger tumors<sup>[55]</sup>.

### Molecular techniques

Advances in molecular techniques and tools like microarray, nuclear magnetic resonance and mass

spectrometry have enabled detection of a large number of molecules rapidly. At cellular level genetic information gets transcribed into mRNA which gets translated into proteins and subsequently metabolised. Alteration of genes at cellular level in neoplastic cells leads to changes in protein and metabolites and this can be detected using "omics" technology<sup>[56-58]</sup>. Genomics aims at detecting genes, proteomics at detecting set of expressed proteins and metabolomics the metabolic profile. While molecular techniques can detect a large array of products, filtering out the specific markers useful for diagnosing different conditions remains a challenge. A proteomics based study from United States, aimed to identify the plasma protein profile in subjects with chronic pancreatitis, pancreatic cancer and non-pancreatic disease controls<sup>[59]</sup>. They identified more than 1300 proteins and found that a composite marker of TIMP1 and ICAM1 performed better than CA19-9 in differentiating pancreatic cancer from rest of the group. They also suggested that a protein called AZGP1 could serve as a biomarker for chronic pancreatitis<sup>[59]</sup>. Paulo *et al*<sup>[60]</sup> studied expressed proteins in chronic pancreatitis, pancreatic cancer and autoimmune pancreatitis and found a range of differentially expressed proteins in the three different groups. Using liquid chromatography with tandem mass spectrometry, they found that 29 proteins were exclusively expressed in chronic pancreatitis and 53 protein in pancreatic cancer<sup>[60]</sup>. These tests were conducted on tissue samples and hence can serve as an adjunct to histology but require validation in larger cohort.

Zhang *et al*<sup>[61]</sup> used NMR based metabolomics strategy to distinguish pancreatic cancer from chronic pancreatitis and healthy individuals and found the results promising. Patients with pancreatic cancer had a number of abnormalities in amino acid and lipid metabolism including elevated levels of N-acetyl glycoprotein and dimethylamine and reduced levels of citrate, alanine, glutamine. In another metabolomics based study done employing gas chromatography mass spectrometry on subjects with chronic pancreatitis, pancreatic cancer and healthy volunteers, Kobayashi and colleagues were able to develop a model which performed reasonably well in differentiating PC from CP. Other studies have shown, Ca 242, M2 pyruvate kinase, PBF-4, PNA binding glycoprotein, nTert, MMP-2, Synuclein-gamma, and neopterin to be useful biomarkers in differentiating pancreatic cancer from chronic pancreatitis<sup>[59,62,63]</sup>. A study from Germany has shown that micro RNA abundance measured in tissue and blood performs well in distinguishing chronic pancreatitis and pancreatic cancer<sup>[64]</sup>. Overall, molecular tools appear promising but are not yet ready for clinical application.

## CONCLUSION

There have been a number of developments in imaging

and molecular technologies to aid in differentiating benign from malignant mass lesion in patients with chronic pancreatitis. While some like EUS-FNA and advanced CT/MRI techniques are already in clinical use, technologies like CE EUS, EUS elastography and digital image analysis require development of standardised protocol, consensus and operator training facilities before they can be inducted into regular clinical usage. The molecular techniques are still in the early stage of development. Continued research and development is required to help in the correct diagnosis of this challenging condition.

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