REVIEW

The Role of Endoscopy in the Management of Cystic Pancreatic Lesions

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ABSTRACT

Pancreatic cystic lesions may be due to pseudocysts and related inflammatory fluid collections, simple cysts, cystic tumours such as serous cystadenoma, mucinous cystic neoplasm and intraductal papillary mucinous neoplasm, as well as solid tumours with areas of cystic degeneration. The main diagnostic challenge is to distinguish premalignant and malignant cystic lesions from benign cystic lesions. Cross-sectional imaging using computer tomography and magnetic resonance imaging/ magnetic resonance cholangiopancreatography provides the initial morphological characterization. Endoscopic ultrasound (EUS) is an important tool when diagnostic doubts persist and is crucial in the assessment of invasive malignancy. EUS-guided fine needle aspiration and cyst fluid analysis has been shown to be cost-effective for risk stratifying the malignant potential of cystic tumours and the need for surgical resection. In the management of symptomatic pseudocysts and related fluid collections, endoscopic drainage has been established as the preferred technique, with efficacy similar to surgery but lower costs and morbidity.

Keywords: endosonography, pancreas, pseudocysts, tumours

INTRODUCTION

Pancreatic cystic lesions present a diagnostic and therapeutic challenge. Commonly these lesions are pseudocysts and related inflammatory collections that arise as a consequence of acute or chronic pancreatitis, post pancreatic surgery and trauma. Therapeutic drainage is required for symptomatic collections and endotherapy has emerged as the technique of choice. Asymptomatic pancreatic cystic lesions are increasingly being detected incidentally by computer tomography (CT) and magnetic resonance imaging (MRI), with reported prevalence rates of 1–2%[1]. The main challenge is to differentiate premalignant/malignant and benign cystic lesions. CT or MRI/magnetic resonance cholangiopancreatography (MRCP) provides the initial morphological characterisation. The presence of symptoms and obvious malignancy will mandate resection in surgical candidates. When symptoms are absent, or patients are borderline candidates for surgery, endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration (EUSFNA) are important diagnostic tools that have been shown to be cost-effective for risk stratifying the malignant potential of cystic tumours. In this review, the utility of EUS and EUSFNA in the evaluation of suspected pancreatic cystic tumours and the evidence base for endoscopic drainage of pseudocysts and other fluid collections will be examined.

THE NATURE AND CLASSIFICATION OF PANCREATIC CYSTIC LESIONS

Broadly pancreatic cystic lesions may be classified as neoplastic and non-neoplastic. The former includes mucinous cystic tumours such as mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN), serous cystic tumours such as serous cystadenoma (SCN) and serous cystadenocarcinoma, solid pseudopapillary tumour (SPPT), lymphoepithelial cyst as well as cystic variants of solid neoplasms like cystic ductal adenocarcinoma and cystic neuroendocrine tumour. Non-neoplastic lesions include inflammatory collections like pseudocysts, congenital or simple cysts and cysts related to infections such as hydatid cysts. Clinical features

Table 1. Features of Commoner Pancreatic Cystic Lesions.

	Pseudocysts	**IPMN**	**MCN**	**SCN**	**SPPT**
Demographic and clinical features	No gender predisposition. Prior history of pancreatitis or pancreatic surgery	Age range: 60 – 80 years. Male:female ratio: 1 – 2:1. Frequency: 21 – 35% of cystic tumours. Presentation: asymptomatic or history of pancreatitis or pain.	Age range: 30 – 50 years. Male:female ratio: 1:9. Frequency: 10 – 45% of cystic tumours. Presentation: asymptomatic or may present with pain or abdominal mass.	Age range: 60 – 80 years. Male:female ratio: 1:3 – 4. Frequency :18 – 39% of cystic tumours. Presentation: asymptomatic or may present with pain or abdominal mass.	Age range: 20 – 40 years. Male:female ratio: 1: 10. Frequency: <10 – 27% of cystic tumours. Presentation: asymptomatic but may present with abdominal discomfort.
Location and morphology	Location evenly distributed. Unilocular or multilocular macrocysts	Location: more frequently located at head. Appear as dilated main pancreatic duct or side branches; may appear as septated cyst; "fish mouth" papilla seen in main duct IPMN.	Location: more frequently located at body and tail. Appear as unilocular macrocyst with smooth contour.	Location: more frequently located at body and tail. Appear as microcysts.	Location: evenly distributed. Appear as large encapsulated solid/ cystic mass.
Risk of malignancy	No	Premalignant; malignancy rate in resected main duct IPMN: 40 – 70%; malignancy rate in branch IPMN: 0 – 5% with malignant transformation rate of 1 – 2%/ yr.	Premalignant; malignancy rates in resected MCN range from 6 – 27%.	Untreated, indolent growth usually; malignant forms very rare.	Premalignant
Features suggestive of malignant transformation	—	Dilation of the main pancreatic duct over 10mm; the presence of mural nodules; size >3 cm for branch IPMN.	Size >2cm; cyst wall irregularity and thickening; intracystic solid regions; adjacent solid mass; cyst wall calcification.	—	—
Need for surgery	Endoscopic drainage is the first line treatment for symptomatic collections.	Resection of main duct and mixed IPMN in surgical candidates is recommended. In branch IPMN, the risk of malignancy is lower, and surveillance can be considered; resection needed in symptomatic lesions, lesion > 3cm and lesions with mural nodules.	Resection of MCN in surgical candidates is recommended.	Surgery only if symptomatic.	Surgery is recommended.

will provide a clue to the nature of pancreatic cystic lesions and cross-sectional imaging alone may suffice in making a diagnosis to guide the treatment decision. A summary of the key clinical and morphological features of the more common pancreatic cystic lesions is shown in Table 1[2,3,4,5].

THE ROLE OF ENDOSCOPY IN THE EVALUATION OF PANCREATIC CYSTIC LESIONS

Endoscopic retrograde cholangiopancreatography (ERCP) has limited value in the evaluation of pancreatic cystic lesions, whether there is duct communication or not. CT, MRI and more recently EUS has replaced ERCP for this purpose. In the case of main duct IPMN, inspection of the ampulla of Vater may reveal the highly specific finding of mucus extruding from a patulous pancreatic orifice (so-called "fish mouth papilla"). "Fish mouth papilla", although pathognomonic, is uncommon. The focus of the review will be on EUS, which has emerged as the main diagnostic tool.

EUS Assessment of Pancreatic Cyst Morphology

Some characteristic morphological details may be evident on CT or MRI (Fig. 1). However, cross-sectional imaging alone may not provide sufficient diagnostic certainty to guide the treatment strategy. EUS allows excellent visualisation of pancreatic morphology. When the echoendoscope is inserted into the duodenal or gastric lumen, the ultrasonic transducer lies just adjacent to the pancreas and allows a detailed examination with resolution superior to CT and MRI[6]. The key morphological details of the commonly seen cystic tumours will be described briefly[3,4].

1. IPMN: (a) presence of dilated main pancreatic duct or side branches; (b) may appear as a septated cyst; (c) an absence of EUS features of chronic pancreatitis with pancreatic duct calculi, which is another differential for a dilated pancreatic duct; however, main duct IPMN may develop some parenchymal features of chronic pancreatitis due to mucin obstruction.

2. MCN: (a) macrocystic, occasionally septated; (b) presence of peripheral calcifications.

3. SCN: (a) characteristically microcystic with a "honeycomb" appearance; (b) rarely macrocystic component may be present; (c) central scarring is characteristic.

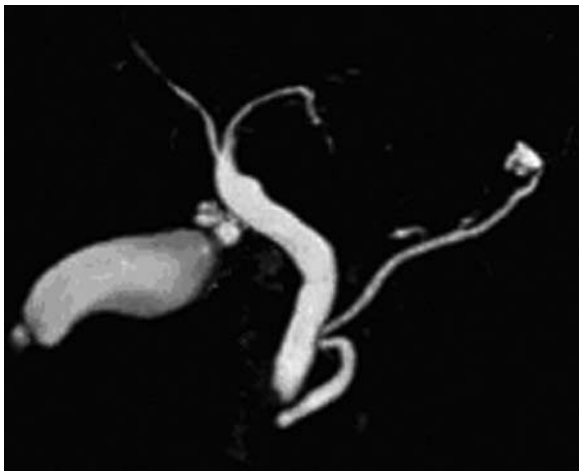

Fig. 1. MRCP showing branch type intraductal papillary mucinous neoplasm.

4. SPPT: solid and cystic components present.

5. Pancreatic carcinoma with cystic degeneration: primarily a solid mass with cystic spaces.

In a small subcentimetre cystic lesion, the possibility of malignancy or malignant transformation is minimal. In this context, interval cross-sectional imaging at 1 year for surveillance may suffice. Another alternative would be to perform EUS to better characterise the morphology and if it is unremarkable, then repeat cross-sectional imaging in a year to ensure that the lesion does not increase in size. For larger lesions, it would be prudent to further characterise the lesion using EUS in order to identify patients with mucinous lesions which have malignant potential or which may already have undergone malignant transformation and hence would require surgical resection. Features of early malignancy in mucinous lesions include intramural nodules and small adjacent masses. Some lesions such as SCN (Figs. 2 and 3, overleaf) have a characteristic appearance on EUS. The etiology of a macrocystic unilocular lesion may however be unclear. In this context, EUSFNA with cytological evaluation and fluid analysis will be crucial.

EUSFNA and Cyst Fluid Analysis

EUSFNA of pancreatic cystic lesions under real time Doppler ultrasound guidance can be performed easily and the cyst fluid aspirated for cytological evaluation and biochemical analysis. Any adjacent solid mass or regional lymph node can also be

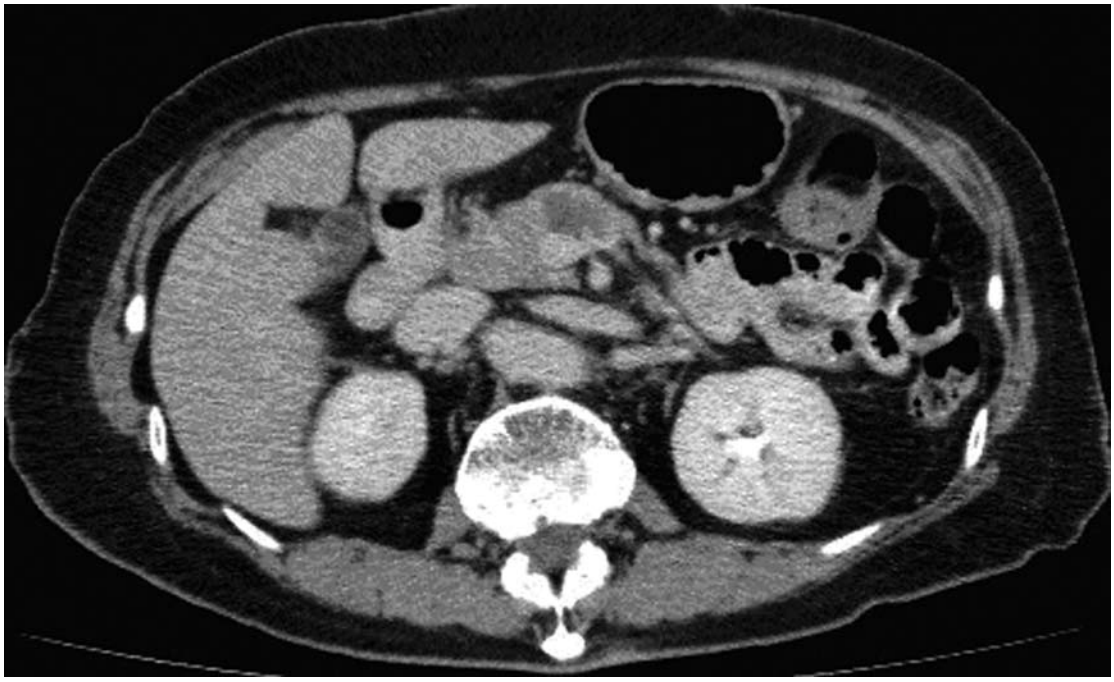

Fig. 2. A serous cystadenoma appeared as a non-descript cystic lesion on CT.

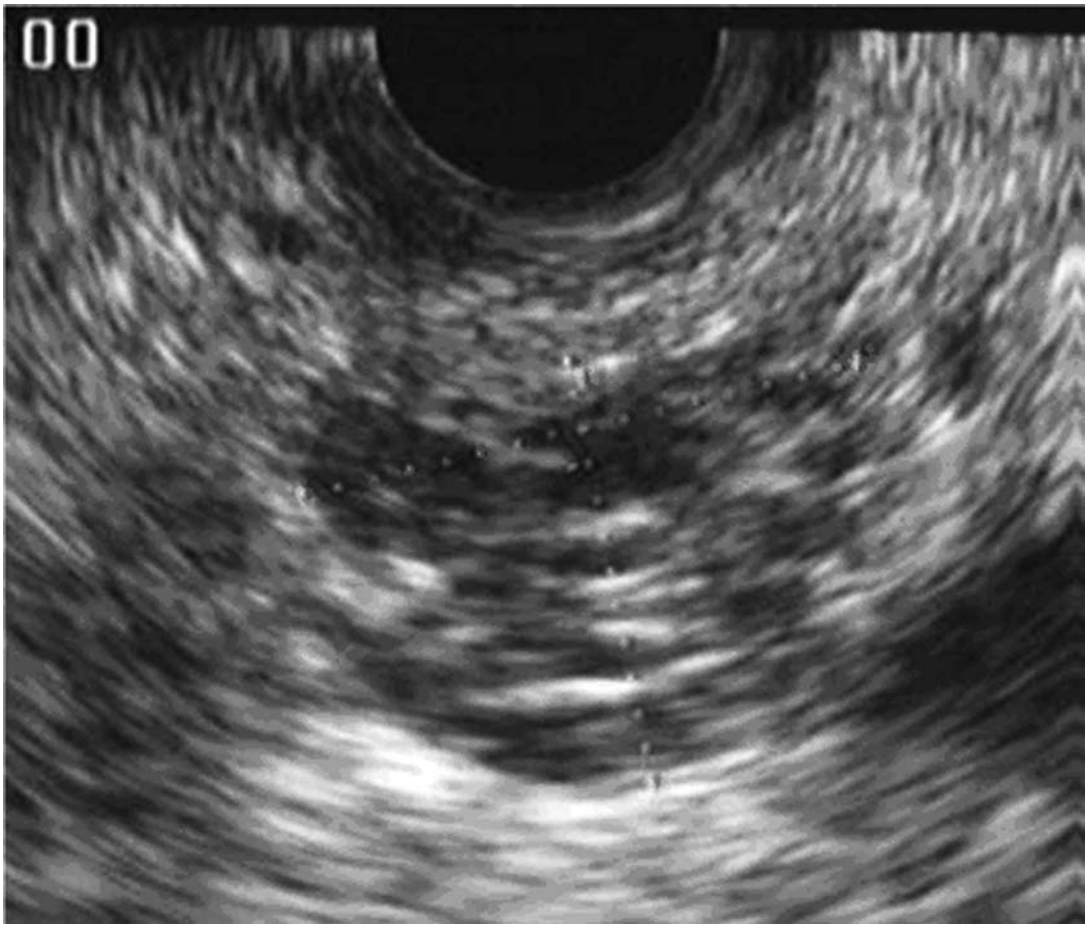

Fig. 3: Characteristic microcystic features of serous cystadenoma seen with EUS.

aspirated. Typically a size 22 or 19 gauge needle is used for cyst aspiration. In order to minimise the risk of secondary cyst infection, a prophylactic antibiotic with gram negative cover, such as ciprofloxacin is administered, and continued for a further 3 days after EUSFNA. One should also limit EUSFNA to a single puncture, and attempt to completely drain the cystic lesion. In terms of cytological evaluation, the accuracy for diagnosing various cystic lesions by EUS-FNA range from 54–97%; malignancy within a cystic neoplasm can be identified by cytology with 83% to almost 100% specificity, but the reported sensitivities vary from 25–88%[3]. The yield of cytology with aspiration is generally low unless solid lesions are present. In this light, a special FNA needle adapted to perform brush cytology may potentially increase the cytological yield[7]. Analyses of fluid amylase, CEA and CA19-9 have been used to distinguish mucinous cystic lesions from non-mucinous lesions. Despite limitations of variable sensitivity and specificity, depending on value cut-offs, they do serve as an important adjunct in diagnostic evaluation. In a large prospective study with surgical correlation, a CEA cut-off of 192ng/mL differentiated mucinous from non-mucinous tumors with a sensitivity of 75% and a specificity of 84%[8]. A pooled analysis of 12 studies with 450 patients revealed the following: (1) cysts with an amylase concentration <250U/L were SCN, MCN, or mucinous adenocarcinoma (sensitivity 44%, specificity 98%) and, thus, virtually excluded pseudocysts; (2) CEA <5ng/mL suggested SCN or pseudocyst (sensitivity 50%, specificity 95%); (3) CEA >800ng/mL strongly suggested MCN or mucinous adenocarcinoma (sensitivity 48%, specificity 98%); (4) CA19-9 <37U/mL strongly suggested pseudocyst or SCN (sensitivity 19%, specificity 98%)[9]. EUSFNA has been associated with complications such as pancreatitis (2–3%), intra-cystic haemorrhage (<1%) and infection (<1%)[3]. Hence the decision to perform EUSFNA should be guided by how this would impact on management strategy.

Clinical Application of EUS and EUSFNA in Evaluation of Cystic Tumours

Clearly EUS and EUSFNA would not be required in all instances. The possibility of malignant transformation of a sub-centimetre cystic lesion is low hence a repeat cross-sectional imaging with CT or MRI within a year may suffice. Surgical resection would be indicated for all symptomatic cystic tumours, if the patient is a surgical candidate. The main value of EUS and EUSFNA resides in stratifying the potential for malignancy for indeterminate cystic lesions in surgical candidates, and in assessing the presence of malignant transformation of mucinous cystic tumours (Table 1) and hence need for surgery in borderline surgical candidates. In addition, it complements CT in the assessment of surgical resectability in cystic malignancies. A recent decision analysis explored the cost-effectiveness of 3 different strategies for managing solitary, asymptomatic pancreatic cystic neoplasm in a Markov model.

1. Strategy I: the natural history of the lesion was followed without any specific intervention.

2. Strategy II: an aggressive surgical approach was considered in that all patients were considered for resection.

3. Strategy III: an initial EUSFNA with cyst fluid analysis was performed for risk stratification, and patients with mucinous cysts were considered for resection.

In the baseline analysis, strategy III yielded the highest quality-adjusted life years with an acceptable incremental cost-effectiveness ratio. In a Monte Carlo analysis, the relative risk of patients developing unresectable pancreatic cancer was decreased in strategy III compared to the other strategies. It was concluded that for asymptomatic patients with incidental solitary pancreatic cystic neoplasm, a blanket policy of surgical resection for all patients cannot be justified. Risk stratification of malignant potential by EUSFNA and cyst fluid analysis was the most cost-effective management strategy[10].

Role of EUS-guided Cyst Ablation

Quite apart from the established clinical application of EUS in the process of diagnostic evaluation, there is ongoing interest and research into the possibility of EUS-guided injections of cystic tumours as a form of ablative therapy. It is of particular relevance in patients who are poor surgical candidates, or do not wish to undertake pancreatectomy, despite a potentially premalignant disease. EUS-guided ethanol lavage[11,12], and EUS-guided ethanol lavage with paclitaxel injection[13] have been studied and initial results are encouraging. Larger series and more long term data are required to establish the effectiveness and safety of this approach.

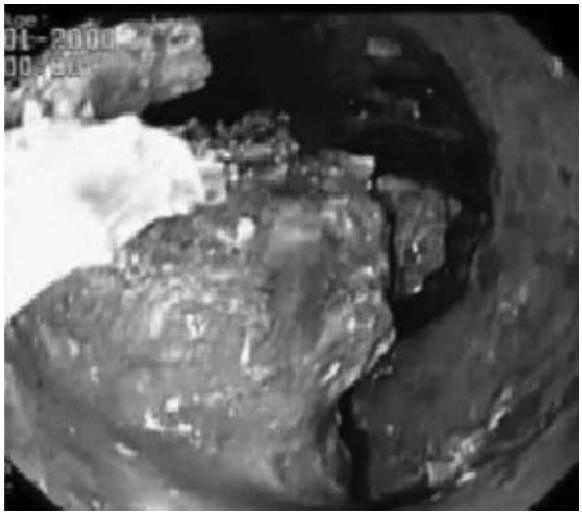

Fig. 4: Endoscopic necrosectomy in a patient with infected walled off necrosis.

ROLE OF ENDOSCOPY IN MANAGEMENT OF PSEUDOCYSTS

Endoscopic transmural drainage, especially with endoscopic ultrasound (EUS)-guidance, is now regarded as the technique of choice for the management of symptomatic pancreatic fluid collections, due to a lower morbidity compared to surgery and percutaneous methods, and similar efficacy as surgery[14,15]. Surgery remains important in the overall strategy and will have to be considered in the event of complications from endoscopic drainage such as perforation, when collections are not accessible endoscopically or inadequately drained, especially when there are a lot of solid debris within the cavity, as well as in the context of anatomical abnormalities that need surgical correction, as such the disconnected pancreatic duct syndrome. EUS-guided drainage has clearly been shown to be superior to non-EUS guided transenteric drainage, being able to drain fluid collections without endoscopic luminal bulging[16,17]. In the management of uncomplicated symptomatic pseudocysts, EUS-guided drainage has also been shown to be equivalent to surgical cyst-gastrostomy in terms of clinical efficacy but with lower costs and shorter length of hospital stays[18]. Nonetheless, despite the excellent results of endoscopic drainage, there are important patient and clinical factors that must be considered and addressed, in order to optimise the clinical outcome of endoscopic treatment, and to recognise its limitations, so as to facilitate timely surgical interventions.

The first consideration is the nature of the fluid collections. Endoscopic drainage of pseudocysts has excellent results, with success rates exceeding 90%[14]. However, in the case of infected pancreatic fluid collections with significant solid debris, inserting transmural drains alone is inadequate because the solid debris needs to be physically removed. Transmural drainage alone for infected walled off necrosis had a success rate as low as 25%[19]. An aggressive endoscopic strategy, including endoscopic transmural necrosectomy (Fig. 4), is feasible and important for clinical success[15,20–23]. With such an aggressive approach, the success rate was higher at 81%[22] to 93%[23]. One must, however, be cognizant of the potential limitations and risks of such a technique. This strategy is not feasible if there is minimal liquefaction of the pancreatic necrosis. In addition, if the collection is large and endoscopic access is limited, surgical debridement should be performed when feasible.

The second consideration is the presence or absence of underlying pancreatic duct abnormalities that if untreated, would predispose to recurrent fluid collections[24]. These abnormalities include disconnected pancreatic duct syndrome, pancreatic duct fistulas, strictures and stones and should be treated by ERCP, with surgery reserved as a salvage treatment procedure.

CONCLUSION

Endoscopy has a pivotal role in the management of pancreatic cystic lesions. From a diagnostic viewpoint, EUS and EUSFNA have been shown to be important and cost-effective for risk stratifying the malignant potential of cystic tumours. From a therapeutic perspective, endoscopic drainage is now the preferred technique for treatment of symptomatic pancreatic pseudocysts and related fluid collections, with efficacy similar to surgery but lower costs and morbidity.

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