

Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

# Evaluation and Therapy of Pancreatic Cysts



Serge Sorser



Ali Siddiqui



Douglas G. Adler

**Pancreatic cysts are a common incidental finding as a result of increased use of diagnostic cross sectional imaging. They run the gamut from benign disease processes to pre-cancerous entities to frank malignant lesions. Much has been written in regards to the natural history of pancreatic cysts, their presentation, diagnostic evaluation, endoscopic and surgical intervention and surveillance. In this article, we aim to summarize the natural history/epidemiology of cysts, their evaluation, and future endeavors in the management of pancreatic cysts.**

## INTRODUCTION

The increased use of cross-sectional imaging in recent years has led to more incidental findings being noted.<sup>1</sup> The prevalence of pancreatic cysts has been documented to range from 2.6% to 13.5%.<sup>2,3</sup> The majority of these cysts are asymptomatic, but further work-up is often warranted once they are noted.<sup>4</sup>

Subsequent evaluation may be performed in the form of further imaging, but fluid acquisition/analysis helps delineate the nature of the cyst, its potential for

malignant transformation, possible need for surgical intervention and further surveillance. Endoscopic Ultrasound guided fine Needle Aspiration (EUS-FNA) plays a crucial role in cyst evaluation.<sup>5,6</sup> Multiple societal guidelines have been established to assist clinicians in directing the care of these patients, but the natural history and malignant potential of all cystic lesions is not entirely understood.<sup>7,8,9</sup> In this article, we aim to describe the common types of pancreatic cysts, their natural history, means of follow up, and possible modes of endoscopic and non-endoscopic intervention.

### Serous Cystadenoma (SCA)

SCA, previously known as a microcystic adenomas, are benign entities and the second most common cystic tumors of the pancreas, accounting for up to 30% of pancreatic cysts.<sup>10,11</sup> These tumors occur most commonly in the body and tail of the pancreas and are often seen

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Serge Sorser, MD,<sup>1</sup> Ali Siddiqui, MD<sup>2</sup> and Douglas G. Adler, MD, MD, FACG, AGAF, FASGE, Associate Professor of Medicine, Director of Therapeutic Endoscopy, Director, GI Fellowship Program, Gastroenterology and Hepatology<sup>3</sup> <sup>1</sup>Providence Hospital, Southfield Michigan <sup>2</sup>Jefferson University School of Medicine <sup>3</sup>University of Utah School of Medicine, Huntsman Cancer Center, Salt Lake City, UT

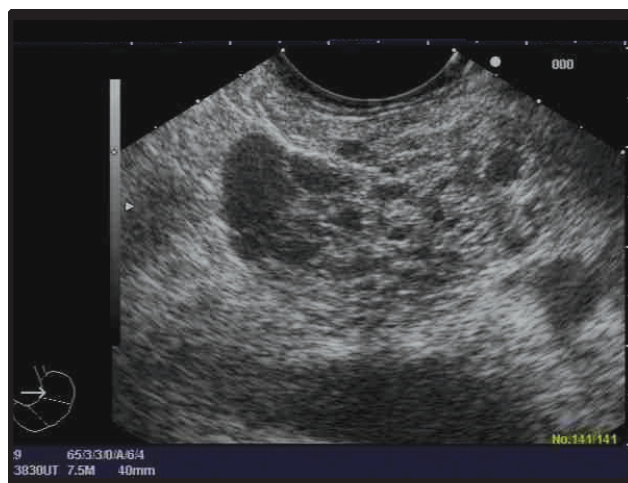
in middle-aged women, but can occur in both sexes and at any age.<sup>12,13</sup> Patients are commonly asymptomatic, but may present with abdominal pain and a palpable mass, depending on the size of the tumor.<sup>14</sup>

Cross sectional imaging may help make the diagnosis, as the tumor appears as a multi-septated cyst with so-called “honeycombing.”<sup>15</sup> A central, spiculated (“sunburst”) calcification may also be seen.<sup>16</sup> EUS FNA is commonly performed if the diagnosis of SCA is less than certain, but some advocate that if a lesion is classic for SCA, an EUS guided-FNA may not be needed.<sup>17,18</sup> (Figure 1) When fluid for analysis is obtained, it is often noted to be clear with cuboidal cells lining the cyst cavity, although acellular fluid is also commonly obtained.<sup>19</sup> A low cyst fluid CEA and bland cytology are frequently noted on fluid analysis.

Due to the benign nature of SCA, no surveillance is generally felt to be warranted. SCA have a low rate of malignant transformation, quoted as less than 3%.<sup>20</sup> Surgical intervention is not indicated for serous cystadenomas, unless they are symptomatic. However, recent literature recommends consideration of surgical intervention if the patient has symptoms that can be attributed to the lesion and if the cyst in aggregate is greater than 4 cm.<sup>21,22</sup> It should be stated that many lesions that are, in fact, SCAs do not have all of the classic findings of these lesions and it can sometimes be hard to distinguish SCA from other, more ominous lesions.

## Mucinous Cystic Neoplasm (MCN)

MCNs are the most common type of pancreatic cysts. They constitute up to one half of all known cystic lesions of the pancreas. They range in size from 5 to 35 cm and are predominantly found in females.<sup>23,24</sup> The age of onset is usually in the fifth or sixth decade of life and the tumor tends to localize in the body or tail of the pancreas.<sup>25, 26, 27</sup> These cysts are defined strictly by the presence of ovarian type stroma within the tumor.<sup>28,29</sup> On cross sectional imaging, no communication with the main pancreatic duct is typically noted. On fluid analysis, thick and mucoid material is typically found, with a low amylase and an elevated cyst fluid CEA level.<sup>30,31</sup> Histologically, these cysts are mostly benign. An adenoma was noted in 72% of the cases, borderline neoplasm in 10.5%, carcinoma in situ in 5.5% and invasive cancer in 12% of patients in a series of 163 patients.<sup>32</sup> Given that malignant transformation may occur via K-ras and p53 mutations, surgical resection



**Figure 1. EUS image of a pancreatic serous cystadenoma. Note the innumerable small cysts.**

*(Image courtesy Douglas Adler, MD)*

should be considered for MCNs in patients who are suitable operative candidates.<sup>33,34,35,36</sup> The cysts are typically unifocal and when the lesion is resected and is noted to be non-invasive, no surveillance is typically required although in practice many patients undergo post-treatment imaging periodically.<sup>8</sup>

## Pancreatic Pseudocysts

Pancreatic pseudocysts are most commonly a complication of acute or chronic pancreatitis, although they can also occur following trauma to the pancreas. Pseudocysts are rich in amylase and are not lined by an epithelium.<sup>37</sup> The underlying etiology is multifactorial, but ultimately leads to ductal disruption and an increase in pancreatic ductal pressure.<sup>38</sup> Patients tend to present with ongoing abdominal pain and anorexia weeks after their initial presentation, with rare complications such as jaundice or sepsis also noted.<sup>39</sup> Jaundice can result from extrinsic compression of the bile ducts, and sepsis from secondary infection of the cyst itself can be seen. Large cysts frequently compress the stomach and/or duodenum and can cause gastric outlet obstruction. Pseudocysts are usually distinguished from other pancreatic fluid collections by the lack of significant solid debris (as is more commonly seen in walled off pancreatic necrosis (WOPN)). The diagnosis of a pseudocyst is made by cross-sectional imaging. CT scans will, in general, underestimate the amount of solid debris within a lesion.<sup>40</sup> Other modes of evaluation, including MRI or EUS may be considered.<sup>41</sup> MRI and EUS will give a more accurate assessment of the amount

of solid debris with in a pancreatic fluid collection.

Numerous studies have been published regarding cyst fluid analysis to help distinguish pseudocysts from mucinous cystic neoplasms.<sup>42,43,44</sup> In general, pancreatic pseudocysts will have a high cyst fluid amylase with a low cyst fluid CEA. Pancreatic cyst fluid is often laden with debris and macrophages and often has a “dirty” chocolate brown color. Endoscopic, surgical and interventional radiology approaches may be offered for treatment/drainage of the cysts.<sup>45</sup>

Symptoms from pseudocysts that require treatment include pain, infection, hemorrhage into the cyst, and compression of the stomach, bowel, and/or bile duct. Many symptomatic pancreatic pseudocysts can be treated endoscopically with transampullary drainage via pancreatic duct stent placement. In some patients the cyst decompresses through the pancreatic duct via the stent, while in other patients the pancreatic stent simply relieves pressure on the pancreatic duct; this stops the backfilling of the cyst, allowing it to resolve over time.<sup>46</sup> A recent paper by Lin et al. showed that transpapillary drainage may be an adequate approach in up to 79.5% of patients.<sup>47</sup>

If transmural drainage is desired, technique usually involves puncturing the stomach or the duodenum to gain access to the cyst via EUS under fluoroscopic guidance, delineating the cyst cavity, dilating the tract and placing multiple plastic double pigtail stents or single metal stents.<sup>48,49,50,51</sup> (Figure 2) Some patients warrant both transmural and transampullary drainage simultaneously.<sup>52</sup> Surgical management involves creation of a cyst-enterostomy in the most dependent part of the cyst cavity.<sup>53,54</sup> The percutaneous approach involves finding the most appropriate window (transperitoneal, retroperitoneal, transgastric, transduodenal or transhepatic) and placement of a Percutaneous External Drain.<sup>55,56</sup> Percutaneous approaches are the least invasive and can be favored in patients who are poor candidates for other interventions, although they result in external drainage and there is a risk of chronic cutaneous fistula development.

### Walled-off Pancreatic Necrosis (WOPN)

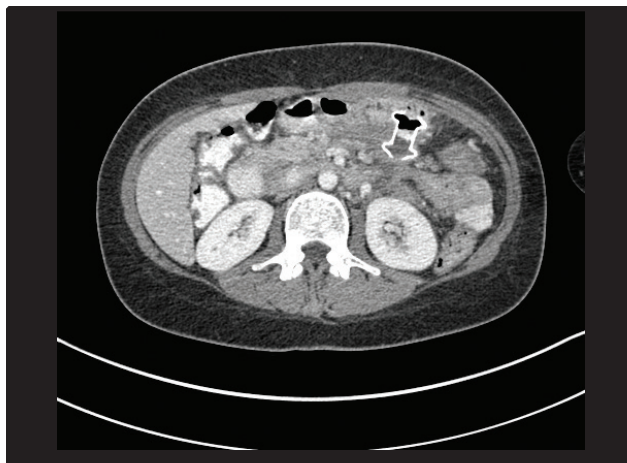
WOPN, a complication of necrotizing pancreatitis, is defined as a collection of fluid and solid components that tends to develop 3 to 6 weeks after an episode of pancreatitis, although some patients can develop an immature form of this lesion in a shorter timeframe.<sup>57</sup> WOPN is seen in 1 to 9% of cases of acute pancreatitis



**Figure 2a. Pancreatic Pseudocyst seen on CT scan.**  
(Image courtesy Douglas Adler, MD)



**Figure 2b. EUS image of same pseudocyst immediately before placement of transmural stent.**  
(Image courtesy Douglas Adler, MD)



**Figure 2c. Same cyst following EUS-guided placement of a transmural stent. The stent was removed 4 weeks after placement.** (Image courtesy Douglas Adler, MD)



and occurs most commonly after biliary pancreatitis.<sup>58</sup>

Patients typically present with ongoing abdominal pain as well as fever and leukocytosis.<sup>59</sup> Fever and leukocytosis can be present even in the absence of infection. The diagnosis of WOPN is typically made on cross-sectional imaging by visualizing a non-enhancing pancreatic fluid collection, which may contain solid and liquid debris, correlated with the age of the fluid collection and the presence of a surrounding capsule.<sup>60</sup> Indications for intervention include clinical suspicion of, or documented, infected necrotizing pancreatitis with clinical deterioration, gastric outlet, intestinal, or biliary obstruction due to mass effect of walled-off necrosis or persistent symptoms in patients with walled-off necrosis without signs of infection.<sup>61</sup>

While many therapeutic modalities for WOPN exist, not all infected pancreatic necrosis requires intervention. Multiple case series have reported good clinical outcome in patients treated conservatively with a prolonged course of antibiotics and supportive care.<sup>62,63</sup> This was later supported by a meta-analysis of eight studies, including 324 patients, which noted that conservative management without necrosectomy is a successful approach in 64% of patients.<sup>64</sup>

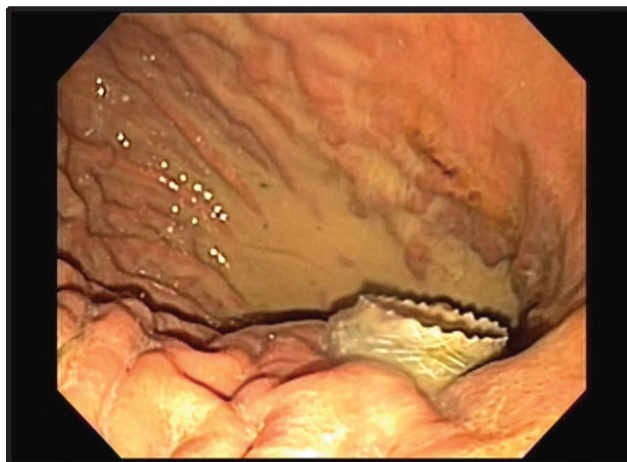
In patients who are deemed candidates for intervention, multiple treatment modalities are available. In stable patients, therapy should be delayed a suitable amount of time (usually 4 weeks or more) to allow liquefaction of the contents and the development of a fibrous wall around the necrosis.<sup>65</sup> This timeframe also allows the fibrous wall to adhere to the stomach or duodenum if endoscopic approaches are to be undertaken.

Multiple endoscopic drainage methods are available for patients with WOPN. One option is endoscopic transmural drainage, in which one or more transmural tracts are created with EUS guidance between the necrotic cavity and the GI lumen. These tracts can be flushed with saline or a mixture of saline and hydrogen peroxide via endoscopic means or via a nasocystic catheter. The tracts can be held open via plastic or metal stents per physician preference.<sup>66</sup> In the combined percutaneous/endoscopic techniques, a large caliber percutaneous catheter can be used for irrigation of a cavity that has been accessed endoscopically to provide multiple routes for irrigation and drainage.<sup>67</sup>

Recently, the use of dedicated, covered, transmural self-expanding metal stents has been described, in which a short, barbell shaped metal stent is deployed



**Figure 3a. EUS image of Walled-off Pancreatic Necrosis (WOPN) showing copious solid debris.**  
(Image courtesy Douglas Adler, MD)



**Figure 3b. Endoscopic image of the stomach of the same patient after transmural stent placement. Note necrotic contents in stomach.**  
(Image courtesy Douglas Adler, MD)

and apposes the pancreatic cyst to the gastric cavity.<sup>68</sup> (Figure 3) The use of fully covered esophageal and biliary stents has also been noted for these purposes.<sup>69</sup> A tailored endoscopic approach has also been proposed, which is based on size and extent of the walled-off necrosis and stepwise response to intervention.<sup>70</sup>

Patients undergoing necrosectomy by any route constitute a high risk population; procedure related complications are as high as 25%. These complications include bleeding, sepsis and perforation and the procedure has an overall success rate of 82-93%.<sup>71,72</sup> It should be noted that some patients will fail endoscopic approaches and still require a traditional surgical necrosectomy and/or percutaneous drains.

The radiologic approach has been noted to be safe and feasible. This technique is minimally invasive and has an overall success rate of 33-56% in resolving the WOPN.<sup>73,74</sup> Complications of the percutaneous approach include internal and external pancreatic fistulas, with an overall mortality rate of 17.4%.<sup>75</sup>

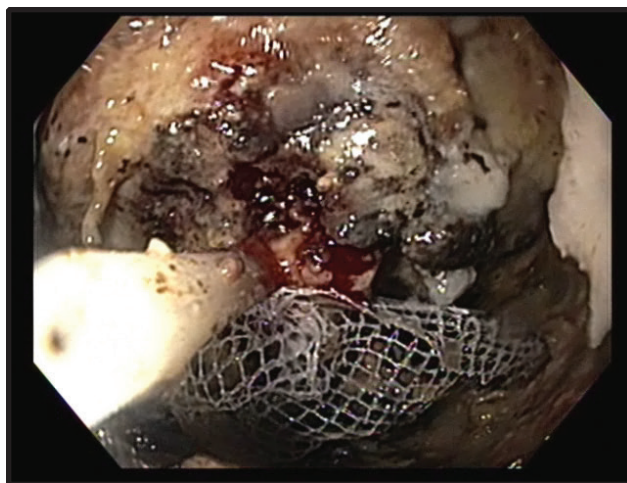
Surgical approaches to patients with WOPN are well described and are now often performed through minimally invasive/laparoscopic techniques, although some patients still require an open necrosectomy. With the laparoscopic approach, a transgastric endolumenal cystogastrostomy is created.<sup>76</sup> Common adverse events include pancreatic fistulae (28.6%), debris recollection (10.7%) and wound infection (10.7%).<sup>77</sup>

While each individual approach has its advantages and disadvantages, a combined/multidisciplinary approach may be needed. A 2012 study by Gluck et al. showed that dual modality (endoscopic and percutaneous) drainage reduced length of stay, number of radiological procedures and number of ERCPs with a durable long-term outcome (100/103 patients did not require surgery at two years).<sup>78,79</sup> A multidisciplinary approach should be undertaken and the treatment modalities selected should rely on individual center expertise, but also depend on the anatomical position, the ratio of solid to fluid components within the collection, and the degree of systemic organ dysfunction.<sup>80,81</sup>

### Intraductal Papillary Mucinous Neoplasm (IPMN)

IPMNs are mucin producing lesions of the exocrine pancreas. They account for up to one third of pancreatic cysts, but are felt to be responsible for only one percent of pancreatic cancers.<sup>82</sup> They may be subcategorized in terms of their ductal involvement: main duct (16-30%), side branch (40-65%) or mixed type (15-23%).<sup>83,84</sup> Most IPMN are solitary and are located in the pancreatic head, but 20-40% may be multifocal.<sup>85</sup> Histologically, the tumors are graded as having low-grade dysplasia, intermediate grade dysplasia and high-grade dysplasia. IPMN are also sub-classified into four different types: gastric, intestinal, pancreaticobiliary and oncocytic. This classification is descriptive and indicative of different pathways of differentiation and progression to carcinoma.<sup>58,86</sup>

While IPMN are usually incidentally found on imaging, diagnostic evaluation with EUS is commonly undertaken for a more detailed evaluation and for cyst fluid aspiration and analysis.<sup>87</sup> (Figure 4)



**Figure 3c. Direct endoscopic necrosectomy of debris in the WOPN cavity using an endoscopic net after transmural stent placement.**

*(Image courtesy Douglas Adler, MD)*

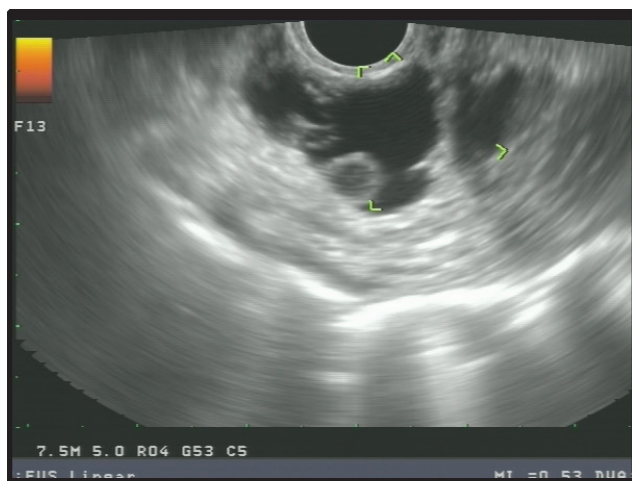
The cyst content may be analyzed in a number of ways, including mucin stain and viscosity, and cyst fluid CEA level, although all of these tests can be limited when attempting to identify malignancy.<sup>88,89</sup> DNA studies of cyst fluid are also available but are not in widespread use. IPMN may be malignant at presentation, but they carry a better prognosis than pancreatic adenocarcinoma in this setting.<sup>90</sup> Worrisome features of IPMN lesions include size greater than 3 cm, presence of mural nodules, dilation and/or involvement of the main pancreatic duct and cyst location (main duct versus side branch).<sup>91</sup> Surgical intervention includes pancreaticoduodenectomy, distal pancreatectomy, total pancreatectomy, segmental resection, enucleations and duodenum preserving resections.<sup>92,93,94</sup> For patients who are not surgical candidates, endoscopic ablation of the cyst cavity with ethanol has been described but can only be considered experimental at this time.<sup>95,96,97</sup> Surveillance strategies after definitive therapy are guided by the Sendai Criteria, and are based on clean surgical margins, extent of dysplasia and whether known cystic lesions remain in the pancreas.<sup>8</sup>

### Rare Pancreatic Cystic Lesions

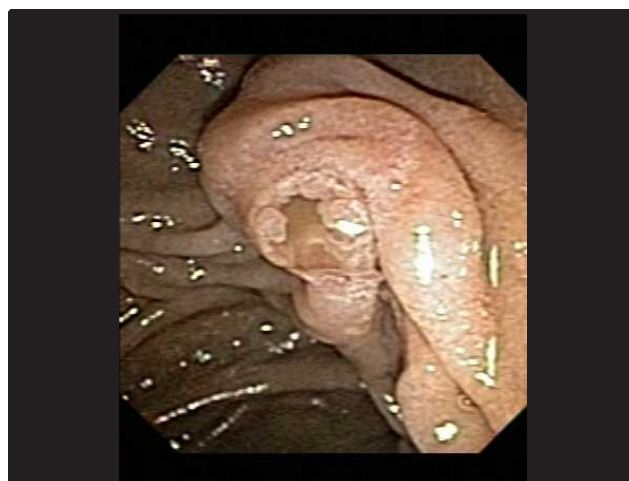
There are a number of relatively rare cystic lesions of the pancreas or solid lesions with cystic degeneration or solid lesions with cystic components that are also worthy of brief discussion.

Cystic lymphangioma of the pancreas arise





**Figure 4a. EUS image of an Intraductal Papillary Mucinous Neoplasm (IPMN) showing a pancreatic cystic lesion with a mural nodule.**  
(Image courtesy Douglas Adler, MD)



**Figure 4b. Endoscopic image of the ampulla in the same patient as Figure 4a, showing a "fish mouth" appearance with copious mucous being extruded, consistent with main pancreatic duct involvement.**  
(Image courtesy Douglas Adler, MD)

from lymphatic vessels, and this is thought to be developmental aberrancies. They account for 0.2% of all pancreatic cysts and are most often noted incidentally.<sup>98</sup> These tumors are benign, but may be locally invasive, and are more commonly found in women.<sup>99</sup> Symptomatic lymphangioma patients usually present with epigastric pain and a palpable mass although they can be asymptomatic as well.<sup>100</sup> Review of histology yields interconnecting cysts separated by septa, lined by epithelial cells, and contain serous, serosanguineous, or chylous fluid (elevated triglyceride level).<sup>101</sup> Given their benign nature, no further work-up is needed and lesions can be resected based on symptoms as needed.<sup>102</sup>

Lymphoepithelial cysts are also benign cystic entities, most commonly seen in men and also typically discovered incidentally.<sup>103</sup> The diagnosis is made by EUS/FNA showing abundant anucleated squamous cells, multinucleated giant cells, mature lymphocytes in a background of keratinaceous debris and a lack of neoplastic cells.<sup>104</sup> Surgery is not recommended in most patients unless they are symptomatic.<sup>105</sup>

Other rare cystic tumors include cystic degeneration of ductal adenocarcinoma<sup>106</sup> and solid pseudo-papillary tumors of the pancreas<sup>107,108</sup> and other mesenchymal origin cysts.<sup>109</sup>

## CONCLUSION

Cystic lesions of the pancreas are more commonly encountered with increased use of cross sectional imaging for evaluation of gastrointestinal and other symptoms. These lesions have a wide range of presenting symptoms, while most are asymptomatic. EUS/FNA plays a key role in the diagnostic work-up, and offers prognostic value, with surveillance recommendations made based on the cyst size and fluid characteristics. Depending on the type of cyst, endoscopic, radiologic and/or surgical modalities may be employed in treating the underlying pathology. No definitive guidelines exist for surveillance of all the known cyst types, and a tailored approach is recommended in many cases. In the future, genetic profiles and tumor markers may play a role in improving treatment strategies. ■

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