

# Minimally Invasive and Standard Surgical Therapy for Complications of Pancreatitis and for Benign Tumors of the Pancreas and Duodenal Papilla

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The treatment of severe pancreatitis and its complications is rapidly evolving because of increasing clinical application of effective, minimally invasive techniques. With ongoing innovations in therapeutic endoscopy, image-guided percutaneous techniques, and minimally invasive surgery, the long-standing traditional management algorithms have recently changed. A multidisciplinary approach is necessary for the treatment of complicated inflammatory diseases of the pancreas and benign periampullary tumors. Surgeons, gastroenterologists, and therapeutic radiologists combine expertise as members of a team to offer their patients improved outcomes and faster recovery.

The treatment of pancreaticobiliary disease requires comprehension of the developmental anatomy of the duodenum and pancreaticobiliary junction. As the hepatic diverticulum arises from the primitive foregut during the fourth week of gestation, the dorsal pancreatic primordium develops and later fuses with the ventral component. Continued growth results in formation of the normal liver, bile ducts, gallbladder, pancreaticobiliary junction (papilla), and duodenum (Fig. 1) [1]. This common origin from the primitive foregut creates the complex anatomy and shared blood supply that affect surgical approaches to the pancreas, bile ducts, and duodenum. Considerable anatomic variation in the pancreaticobiliary junction challenges surgeons and endoscopists alike (see Fig. 1). The potential for life-threatening complications due to perforation or leakage of proteolytic fluid

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Fig. 1. Pancreaticobiliary junction. (Courtesy of D. Chengelis, MD, Royal Oak, MI.)

from the pancreas into the retroperitoneum during invasive therapies remains a major concern.

## History

Surgeons traditionally treated periampullary tumors and the complications of pancreatitis. About 80 years after the development of the gastroscope by Mikulicz-Radecki in 1880, Hirschowitz performed the first flexible fiber optic gastroscopy, which significantly expanded access to the gastrointestinal organs [2]. After McCune performed the first diagnostic endoscopic retrograde cholangiopancreatography (ERCP) in 1968, Japanese and German innovators, including Oi, Kawai, Classen, and Demling, introduced endoscopic sphincterotomy using electric current, which permitted endoscopic therapy for pancreatic, biliary, and ampullary disease [2]. Advancement in endoscopic skills and formal training programs, in conjunction with the development of sophisticated endoscopes and accessories, permitted less invasive therapies for pancreaticobiliary diseases.

In 1963, Charles Dotter founded the discipline of “interventional radiology” and became the father of this important field [3]. After Dotter’s first femoral artery angioplasty in 1964, interventional radiologists moved from the vascular system to the treatment of hepatobiliary disease. Percutaneous and transluminal procedures are now important in the multidisciplinary treatment of obstructive jaundice and the complications of pancreatitis.

Although laparoscopy was first performed in 1901 by Oskarovich in St. Petersburg, Russia, minimally invasive surgery did not increase rapidly until 1988, following the initial reports of laparoscopic cholecystectomy by Mouret [4] in France and Reddick and Olson [5] in the United States. As a high-volume procedure throughout the world, laparoscopic cholecystectomy served to stimulate surgical innovation to expand the applications of

minimally invasive surgery. Extensive research and development of new devices allowed surgeons to extend minimally invasive surgery to virtually all organ systems. Minimally invasive treatment of pancreatic tumors and complicated pancreatitis has evolved slowly because of the complexity of the required procedures and the relative infrequency of the diseases. Centralization of complex pancreatic and hepatobiliary disease at tertiary care centers during the past decade has fostered the development of multidisciplinary therapies.

### **Acute pancreatitis and its complications**

In 1992, a group of 40 experts established a clinically based classification system for acute pancreatitis and associated complications, called the Atlanta classification [6]. The Atlanta classification is currently being updated to further clarify and standardize terminology to improve clinical management and to evaluate new therapy more objectively. The proposed revisions focus on distinctions between “clinical” and “image-based morphologic” manifestations of pancreatitis (MG Sarr, personal communication, 2007).

Minimally invasive and standard treatment of complications of acute pancreatitis, including peripancreatic fluid collections, pseudocysts, pancreatic abscess, and pancreatic necrosis, are reviewed in this article. Popular terms including phlegmon, infected pseudocyst, and hemorrhagic pancreatitis lack clear definition and are best avoided. New terms such as organized necrosis and central gland necrosis/disconnected duct syndrome are currently being debated, but a discussion of these terms is beyond the scope of this article [7].

#### *Acute peripancreatic fluid collection*

Acute fluid collections occur early in the course of acute pancreatitis and are located in, or near, the pancreas. Such collections lack a wall of granulation or fibrous tissue (Fig. 2) [6]. Acute collections occur in 30% to 57% of cases [6,8], and most of these resolve spontaneously [6]. Fluid collections can arise partly from inflammatory transudate or exudate [9], but most significant collections arise from pancreatic ductal disruption [9,10]. Collections detected by imaging studies during the initial 48 hours should be left alone in patients showing clinical improvement because they will frequently resolve [9,11]. Early percutaneous or endoscopic drainage is discouraged because of the risk for secondary infection of these sterile collections [9,11,12]. Patients who develop the systemic inflammatory response syndrome (SIRS) from pancreatitis, which manifests with fever, tachycardia, hypoxemia, and hypotension, can be indistinguishable from those who have sepsis. Walser and colleagues [12] recently compared clinical outcomes in a retrospective analysis of 15 patients undergoing diagnostic needle aspiration versus 22 patients undergoing early percutaneous catheter

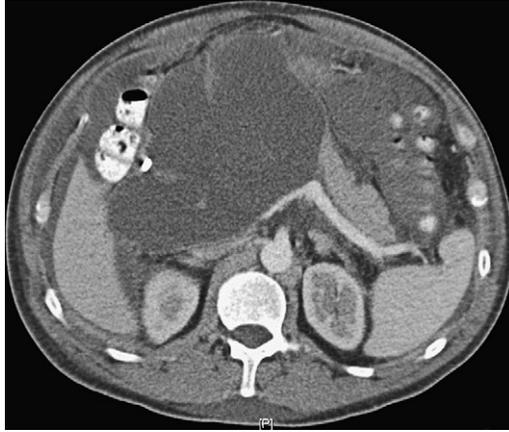


Fig. 2. Acute pancreatic fluid collection. Note the absence of an enhancing, well-defined wall.

drainage of sterile acute pancreatic fluid collections. The severity of the acute pancreatitis, as determined by the CT severity index and the early Ransom's criteria, was similar in the two groups. The investigators found no apparent benefit to routine catheter drainage; the hospital stay and mortality were similar in the two groups. About one half of the patients in the aspiration-only group ultimately required percutaneous drainage or surgery. Chronic catheter drainage resulted in positive cultures in 59%, as compared with only 20% in patients undergoing aspiration alone. Patients undergoing catheter drainage required more imaging studies and more frequent catheter manipulation or exchange. These investigators advocate aspiration alone or catheter removal when the fluid culture is negative at 48 hours, in patients who require sampling of acute pancreatic fluid collections.

Traverso and Kozarek [10] advocate an aggressive approach to acute fluid collections to reduce the risk for pancreatic pseudocyst or necrosis. For patients who have fluid collections and symptoms persisting beyond 1 week, ERCP is advocated to evaluate for pancreatic duct disruption. Two thirds of those evaluated had evidence of ductal disruption. Traverso and colleagues recommend aggressive treatment to stop ongoing egress of proteolytic pancreatic fluid that leads to further peripancreatic necrosis. Recommended measures include endoscopic placement of transampullary or transgastric catheters directly into the fluid collections or across the disrupted ductal segment to restore ductal continuity. Because of a high incidence of bacterial colonization, all collections which have undergone instrumentation require drainage. Acute fluid collections not amenable to endoscopic therapy may require percutaneous or surgical drainage. This aggressive approach for acute fluid collections rarely results in mature pseudocysts [10] or clinically significant peripancreatic necrosis [13].

### *Pancreatic pseudocyst*

A pancreatic pseudocyst is a collection of pancreatic juice surrounded by a wall of fibrous or granulation tissue. In contrast to acute fluid collections that represent inflammatory transudate, pseudocysts are believed to result from pancreatic ductal disruption with leakage of pancreatic fluid due to injury from acute pancreatitis, trauma, or ductal obstruction from chronic pancreatitis [6,9,10,13]. The inflammatory response at the periphery of the collection matures to form a fibrous wall, without an epithelial lining, leading to the term "pseudocyst." Acute peripancreatic fluid collections are generally not called pseudocysts unless they persist for 4 weeks, during which time the wall matures. According to the Atlanta classification, a chronic pseudocyst arises from chronic pancreatitis without an antecedent attack of acute pancreatitis. This terminology reflects the pseudocyst cause rather than its duration.

Pseudocysts occur more commonly with chronic than acute pancreatitis [14]. The incidence of pseudocysts is estimated at 15% to 40%, but the actual incidence is unknown because of inconsistent terminology and variable use of diagnostic studies [13,14]. Accurate diagnosis is essential in evaluating a cystic lesion of the pancreas because of the known malignant potential of mucinous cystic neoplasms. The frequent misrepresentation of incidental radiographic findings as "simple cysts" or "pseudocysts" can inappropriately imply benign behavior, even though more extensive diagnostic evaluation is required. The diagnosis of pseudocyst should be questioned in the absence of a clear clinical history of pancreatitis. Moreover, acute pancreatitis can occur as a manifestation of pancreatic neoplasia. A complete discussion of the evaluation of suspected cystic pancreatic neoplasms is beyond the scope of this article. The use of endoscopic ultrasound with aspiration, ERCP, MRI, or dedicated pancreatic protocol CT is often required.

Persistent symptoms or hyperamylasemia after acute pancreatitis occur in up to 76% of patients who have a pseudocyst [15], and such findings should prompt further investigation. Ultrasound and CT are highly sensitive for the detection of pseudocysts, with sensitivities of 75% to 90% and 90% to 100%, respectively [15].

Recently, the management of pancreatic pseudocysts has significantly changed because of a better understanding of their natural history. New algorithms incorporate recent advances in technology and in minimally invasive techniques. Bradley and colleagues [6] first analyzed the natural behavior of pancreatic pseudocysts in 1979 in 93 patients with pseudocysts followed expectantly. Major complications, including bleeding, rupture, or abscess, occurred in 46% of patients followed for more than 6 weeks, and in about 75% of those followed for more than 12 weeks [6,8]. These investigators, therefore, recommended surgical treatment of all pseudocysts that persist for more than 6 weeks. In contrast, Sarr and Vitas at the Mayo Clinic reported that only 9% of patients who had pseudocysts developed

complications [16]. Yeo supported the safety of nonoperative treatment of pseudocysts in a series from Johns Hopkins; many pseudocysts smaller than 6 cm in diameter resolved spontaneously [16]. In a recent review of 73 patients who had pseudocysts, 59% of patients experienced complications [17]. These dramatically different results were attributed to the 90% rate of acute biliary pancreatitis in this review [17], compared with the 75% rate of chronic pseudocysts from chronic pancreatitis in the earlier studies. These differences emphasize the importance of correct classification based on cause, and incorporation of pancreatic ductal anatomy in management algorithms. Therapy is aimed at relieving symptoms and preventing major complications. Observation is appropriate for patients who are asymptomatic or who show improvement in symptoms while remaining functional. Stability or decrease in cyst size on serial abdominal ultrasounds further supports a conservative approach. Pseudocysts larger than 6 cm in diameter resolve spontaneously in less than 30% of cases [15], whereas pseudocysts smaller than 4 cm in diameter almost always resolve without treatment [18].

Options for follow-up of pseudocysts include CT, MRI, percutaneous abdominal ultrasound, and endoscopic ultrasound. In most cases, CT imaging provides the most information, including cyst size, wall thickness, adjacent anatomy, concomitant cysts, and associated pancreatic necrosis. Percutaneous ultrasound has the benefit of low cost, wide availability, and lack of radiation exposure, but is limited by operator expertise, body habitus, and interference by overlying bowel gas [9]. For cysts that are well seen on the initial study, ultrasound represents an ideal choice for follow-up examination. Clinical progress and symptomatology largely determine the frequency of follow-up examination. Endoscopic ultrasound is generally reserved for the investigation of potential cystic neoplasms, whereas ERCP is used to determine ductal integrity and for therapy.

Treatment options for symptomatic, enlarging, or complicated pseudocysts include percutaneous, endoscopic, and surgical approaches, including laparoscopy (see Fig. 2). Treatment is individualized according to the patient's condition, cyst anatomy, and available expertise. Minimally invasive approaches are favored whenever possible.

Cysts with extremely thick walls are usually best treated by conventional surgery, but may be suitable for endoscopic transgastric drainage with placement of temporary internal stents. The viscosity of the cyst contents often determines the success of endoscopic or percutaneous therapies. For cysts containing thick debris from extensive retroperitoneal necrosis during the acute pancreatitis, a widely patent cyst-enteric anastomosis may be required. Differentiation between acute and chronic pseudocysts, and the anatomy and integrity of the pancreatic duct, must be considered in treatment selection.

In patients who have chronic pancreatitis with pancreatic calcifications and ductal abnormalities, the rate of spontaneous resolution is only 0%

to 9% [18]. Although less invasive than ERCP, MR cholangiopancreatography is useful in defining the ductal anatomy but it lacks sensitivity for detection of ductal disruption or communication with pseudocysts. ERCP provides greater sensitivity and permits therapeutic intervention. Several authorities advocate routine investigation of the pancreatic duct in all patients who have pancreatic fluid collections and pseudocysts [10,13,19]. D'Edigio and Nealon have established classification systems of pancreatic ductal anatomy to help select the appropriate therapy [14,19].

### **Percutaneous drainage**

Percutaneous drainage of pancreatic pseudocysts has become increasingly popular because of the increasing availability of interventional radiologists and the increasing popularity of minimally invasive treatment. Simple aspiration has a failure rate of up to 70% [15]. Interpretation of early data regarding percutaneous intervention is difficult because of inconsistent terminology and variable follow-up. Acute pancreatic fluid collections, acute and chronic pseudocysts, pancreatic abscesses, and infected pseudocysts were often lumped together [16]. A large database review by Morton and colleagues demonstrated higher mortality and increased length of stay for patients treated by percutaneous drainage, compared with those treated with surgical drainage. Better results occurred in patients who underwent ERCP during their evaluation, resulting in more appropriate selection of therapeutic techniques [16]. Other series have shown successful pseudocyst resolution in 60% to 90% with percutaneous drainage [20], with complication rates of 7% to 20% [15,20]. Careful patient selection is imperative for success. Percutaneous drainage is most successful in treating acute pancreatic pseudocysts that are homogeneous and unassociated with significant pancreatic necrosis or debris. External catheter drainage is used successfully as a temporizing measure in septic patients or in those who have acute symptoms from a thin-walled acute collection. High failure rates occur in patients who have a cyst–pancreatic duct communication or in patients who have chronic pancreatitis associated with a ductal stricture [20]. Chronic pancreatic fistulas occur in a significant percentage of patients who have ductal disruption when drained externally, but up to 70% of them close spontaneously [20].

### **Endoscopic treatment**

Endoscopic drainage of pancreatic pseudocysts is becoming an increasingly popular first-line therapy when the endoscopic expertise is available. Methods include transmural and transpapillary approaches. Transmural drainage can be used when the pseudocyst directly abuts the duodenum or posterior gastric wall (Fig. 3). Like traditional surgery, successful

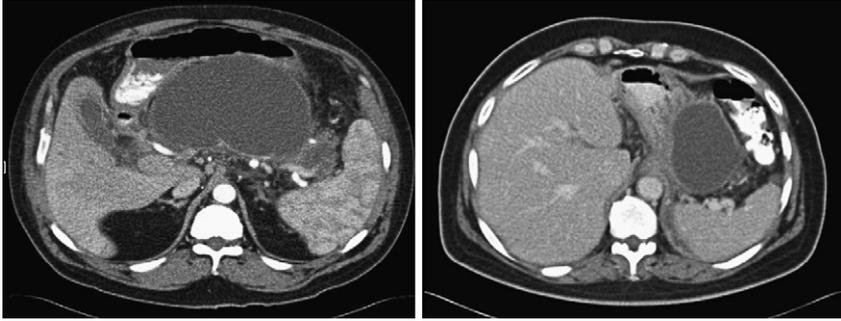


Fig. 3. Mature pseudocysts, with well-developed walls. The pseudocyst on the left is amenable to endoscopic drainage with direct apposition to posterior gastric wall. The pseudocyst on the right demonstrates a thicker wall and a position that requires Roux-en-Y surgical drainage.

treatment requires a mature cyst wall, at least 6 weeks in development. Endoscopic ultrasound may help in selecting the optimal point for transmural cyst puncture. After creating a communication with the pseudocyst through the gastric or duodenal wall by electrocautery, one or more pigtail catheters are introduced. Although multiple series report encouraging rates of success, the individual series are generally small. Long-term successful drainage has been reported in more than 90% of cases [15,16,20]. Complications including bleeding, infection, and perforation occur in 4% to 8%, with a mortality of approximately 1% [15,16,20]. Seventeen percent of patients required additional procedures, including surgical drainage [16]. Endoscopic transgastric drainage is less successful for cysts involving the pancreatic tail, compared with cysts in the pancreatic head or proximal body. Increased rates of infection, and failure rates as high as 50%, are reported when pseudocysts are associated with pancreatic necrosis and internal debris. Small-caliber pigtail catheters frequently occlude and require replacement [20].

Transpapillary drainage is an effective option in the 40% to 70% of pseudocysts that do not directly communicate with pancreatic ducts [16,20]. When pancreatic ductal disruption and cyst communication is demonstrated by ERCP, accessible strictures are dilated and stents are placed either across the point of disruption or directly into the pseudocyst cavity. Drainage is usually maintained for 1 to 3 months. Avoiding penetration of the gastric or duodenal wall decreases the risk for bleeding or free perforation. The transpapillary technique is not limited by the thickness of the cyst wall and does not require direct approximation of the pseudocyst wall to the stomach or duodenum. Like any stent or catheter-based drainage, the fluid in the cyst must be thin and lack significant necrotic debris. Although the reported series include only 12 to 33 patients, the overall success rate is greater than 80% [16,20]. Complications include pancreatitis in 5% and bleeding in 1% [20]. About 12% of patients develop infection from stent

occlusion, but this infection can often be treated successfully with stent replacement.

### **Operative drainage**

The need for surgery has been reduced by the development of effective percutaneous techniques and the use of large-caliber drains. Internal drainage refers to the creation of a direct communication between the pseudocyst and the adjacent hollow viscera, such as the stomach (cyst-gastrostomy), duodenum (cyst-duodenostomy), or jejunum (cyst-jejunostomy). Cyst excision, which may include distal pancreatectomy, is performed only for lesions in the pancreatic tail when a suspicion of cystic neoplasm remains following the diagnostic evaluation [15]. Surgical approaches include open traditional techniques and innovative laparoscopic methods.

Operative internal drainage is still considered the most effective and reliable treatment. Pseudocysts best suited for traditional or laparoscopic operative intervention have ductal disruption associated with chronic pancreatitis and underlying pancreatic duct abnormalities. Pseudocysts containing thick necrotic debris as indicated by ultrasound or CT, or those associated with extensive peripancreatic necrosis, are best treated by cyst-enteric anastomosis. Pseudocyst walls should be biopsied during the surgery to exclude a potentially malignant mucinous cystic neoplasm.

Indications for laparoscopic drainage of pseudocysts are identical to those for open traditional surgery. They can be performed by surgeons with advanced laparoscopic skills. The results of the laparoscopic techniques appear similar to those of open surgery, but no randomized trials have been reported and the results are based only on small groups of patients ( $n = 10$  to 29). Complications include bleeding and infection in 5% to 6%, recurrence in 3% to 4%, and death in 1.1%; these rates are comparable to the open approach [16]. Benefits of laparoscopy include decreased wound infection and dehiscence, less postoperative pain, and an earlier return to work and full activity. These benefits have not been shown directly for laparoscopic pancreatic pseudocyst treatment because of small patient numbers, but they can be reasonably extrapolated from other minimally invasive procedures. Combined laparoscopic and endoscopic intraluminal procedures are being developed.

### **Pancreatic abscess**

Pancreatic abscess is defined in the Atlanta classification as a circumscribed intra-abdominal collection of pus in, or near, the pancreas, which arises as a consequence of pancreatitis or pancreatic trauma. Pancreatic abscesses contain little or no pancreatic necrosis. They are a rare complication of pancreatitis, with an approximate incidence of 2% [21]. The term "pancreatic abscess" was previously used interchangeably with infected

pancreatic necrosis, leading to confusion in the literature regarding therapy. Pancreatic abscesses can occur when pancreatic pseudocysts become infected through instrumentation or hematogenous routes. The term “infected pancreatic pseudocyst” is no longer part of the accepted Atlanta nomenclature but some authorities continue to use the term to differentiate the conditions that are described below [7]. Pancreatic abscess is thought to arise from pancreatic necrosis that has undergone autolysis and liquefaction weeks after an episode of acute pancreatitis [9,21].

Clinical features of a pancreatic abscess include new onset or worsening malaise, fever, abdominal pain, tachycardia, leukocytosis, and sepsis. Such features in a patient who has a history of recent pancreatitis should prompt immediate investigation and imaging. CT scanning is the modality of choice because of better sensitivity than ultrasound (75% versus 35%) and because it can simultaneously evaluate the entire abdomen for other fluid collections [22]. The presence of a rim-enhancing fluid collection in this setting supports the diagnosis. The diagnosis is confirmed by percutaneous aspiration of fluid for culture and Gram stain to exclude a sterile systemic inflammatory response.

Pancreatic abscess generally does not resolve without adequate external drainage. Traditional treatment includes intravenous antibiotic therapy, surgical debridement, and the placement of closed suction drains. More recently, treatment has been effectively accomplished by percutaneous drainage in well-selected patients [21]. Excluding patients who have secondarily infected pancreatic pseudocysts, the success of percutaneous drainage is diminished in an abscess [22]. Abscesses that contain solid debris or are associated with significant retroperitoneal necrosis are best treated by traditional surgical or laparoscopic techniques. Secondarily infected pancreatic pseudocysts or unilocular abscesses occurring several weeks after pancreatic necrosis (allowing time to liquefy) can be drained percutaneously with success rates as high as 86% [21,23].

### **Pancreatic necrosis**

Pancreatic necrosis is defined as diffuse or focal areas of nonviable pancreatic parenchyma, typically associated with peripancreatic fat necrosis. Pancreatic necrosis develops in up to 15% to 20% of acute pancreatitis [9]. About 40% of pancreatic necroses become infected, leading to a mortality of 20% to 56% [9,23].

Pancreatic necrosis occurs early in the course of acute pancreatitis; it usually presents within 96 hours of disease onset [9]. It is usually accompanied by a significant SIRS that can mimic sepsis. However, infection is rarely present at this early stage [24]. Infection of the necrotic pancreas more commonly occurs 2 to 3 weeks after the onset of pancreatitis. Translocation of gram-negative organisms from the gastrointestinal tract is believed to be responsible for most infections. With increasing administration of

prophylactic antibiotics, gram-positive bacteria and fungal infections are increasingly encountered, linked to hematogenous spread [24].

Pancreatic necrosis is suspected in patients who have severe pancreatitis, multiple organ failure, hemodynamic instability, tachycardia, abdominal pain, and fever. Ecchymosis of the flanks or periumbilical region is rarely seen. Neither the severity of the abdominal pain nor the level of hyperamylasemia correlates with the severity of the pancreatic necrosis [9].

Contrast-enhanced CT scan is the diagnostic modality of choice for severe pancreatitis. "Nonenhancement" describes pancreatic parenchyma measuring less than 50 Hounsfield units of density affecting more than 3 cm or 30% of the gland. Contrast-enhanced CT is more than 90% accurate in detecting necrosis, but can overestimate the extent, especially when the peripancreatic fluid is extensive (Fig. 4). Although usually accurate, nonenhancement of the pancreas on CT does not always signify necrosis [25]. Correlation with clinical progress and hemodynamic parameters is important. C-reactive protein is commonly used as an indicator of pancreatic necrosis. Progressive rise in the C-reactive protein level to more than 120 to 150 mg/dL is highly indicative of pancreatic necrosis, with an accuracy of 85% [5,24]. Other useful markers include polymorphonuclear elastase, interleukin-6, phospholipase A2 type II, and urinary trypsinogen activator peptide.

Differentiation between infected and sterile pancreatic necrosis is important when imaging studies demonstrate lesion nonenhancement. Infected necrosis typically occurs several weeks after the onset of pancreatitis, with clinical findings of fever, tachycardia, abdominal distension, and leukocytosis. CT findings of gas in the retroperitoneum or a well-circumscribed, dense, rim-enhancing fluid collection with sparse debris (pancreatic abscess) indicate an infection (Fig. 5). Often, patients who have mild-to-moderate clinical deterioration demonstrate only CT evidence of necrosis and peripancreatic fluid, which causes difficulty in distinguishing sepsis from the SIRS. Fine needle aspiration (FNA) with culture and Gram stain is the



Fig. 4. Pancreatic necrosis with nonenhancement of the pancreatic head.



Fig. 5. Infected pancreatic necrosis with peripancreatic gas.

test of choice for diagnosing infection. When performed with CT or ultrasound guidance, FNA has a sensitivity of 88% and a specificity of 90% [26]. Secondary infection from a FNA is rare.

Traverso and colleagues have emphasized the value of early ERCP with transpapillary or percutaneous drainage of peripancreatic fluid if ductal disruption is detected. These therapies prevent continued egress of digestive enzymes, lessen the degree of necrosis, reduce the need for necrosectomy, and lower the mortality [25,27].

### *Sterile necrosis*

The management of severe pancreatitis with necrosis has recently changed. Early aggressive surgical debridement used to be advocated for significant necrosis, to prevent the inflammatory cascade [26]. However, premature surgery may accelerate the inflammatory cascade [9]. Early surgery results in a 65% mortality in patients who have severe pancreatitis [14,26]. In patients who have sterile pancreatic necrosis, surgical debridement has a mortality of 11%, compared with a mortality of only 2.3% in patients managed conservatively [28]. Although most studies are retrospective, one randomized, prospective trial demonstrated increased mortality with early surgical intervention [26,29]. A recent systematic review concluded that avoiding necrosectomy for at least 30 days after hospital admission resulted in significantly less mortality, compared with early intervention (8% versus 45% to 75%) [23]. Risks of early surgery include contamination of the sterile field and bleeding from an acutely inflamed retroperitoneum. Unnecessary debridement of inflamed, but viable, tissue can increase the risk for long-term pancreatic endocrine and exocrine dysfunction [9,30]. Clinicians are regularly challenged to differentiate patients who have sterile necrosis

from those who have infection, to select and time the surgery appropriately. The International Association of Pancreatology guidelines state: "Patients with sterile pancreatic necrosis (FNA-negative) should be managed conservatively and only undergo intervention in selected cases. Early surgery within 14 days after onset of disease is not recommended in patients with necrotizing pancreatitis unless there are specific indications" [30]. Patients who have progressive multisystem organ failure despite maximal ICU therapy may require early surgical intervention, but this practice is controversial [23,26,30–32]. Early surgery is clearly indicated for early complications, such as significant hemorrhage or bowel perforation. Necrosectomy can be performed by advanced laparoscopic techniques as well with favorable results, but the case series reported are small [33].

Prophylactic antibiotics in sterile necrosis remain controversial. Several randomized trials did not provide conclusive evidence in support of their use [28,31], but subgroup analysis revealed that the use of imipenem reduces the rate of subsequent infection in the setting of sterile necrosis (10.6% versus 36.4%) [28]. The effect of prophylactic antibiotics on mortality is unclear [28,31]. However, antibiotics are frequently used for severe sterile necrosis because of studies showing trends toward improvement. Liberal use of antibiotics has changed the causative microorganisms to include more fungi and gram-positive species.

### *Infected pancreatic necrosis*

Infected pancreatic necrosis constitutes an absolute indication for prompt intervention. Treatment options include (1) operative necrosectomy by traditional open or laparoscopic approaches; (2) percutaneous drainage, including drain tract necrosectomy; and (3) endoscopic necrosectomy. Open operative drainage remains the definitive, standard approach to debriding necrotic retroperitoneal tissue. Methods include (1) open necrosectomy with abdominal closure and placement of large-bore drains for lavage, (2) open necrosectomy with open packing of the abdomen and re-exploration for irrigation and dressing change, and (3) open necrosectomy with abdominal closure and planned re-exploration. Although no randomized trials have compared the various alternatives, open packing is now generally avoided despite its efficacy because of the risk for fistula and bleeding [28,34]. The efficacy of closure with drainage is increased by using large-bore (24–28 F) catheters and implementing frequent catheter exchanges by radiographic guidance to avoid drain occlusion, as advocated by Traverso [25,27]. Necrosectomy is also advocated for failure to thrive and persistent pain after three weeks in patients with more than 50% of gland necrosis [32].

Critically ill patients who have accessible fluid collections can benefit from interim percutaneous drainage to permit semiselective surgical debridement after patient stabilization [25]. Small case series of patients who had infected necrosis managed successfully with percutaneous drainage have

been reported, with success rates of 47% to 100% [25]. This approach requires large-bore catheters and meticulous catheter care. Frequent pancreatic imaging and catheter exchanges are required by skilled radiologists.

Percutaneous endoscopic necrosectomy requires insertion of a catheter under CT guidance into the necrotic retroperitoneal collection. The drain tract is subsequently dilated to 28 to 30 F under general anesthesia to allow piecemeal necrosectomy at multiple endoscopic sessions. Small case series, of 6 to 24 patients, report a 62.5% to 80% success rate, with acceptable mortality [25].

Peroral transgastric endoscopic methods similar to the techniques for pseudocyst drainage have been described. They are used only for walled-off necrosis adjacent to the gastric or duodenal wall, occurring 3 to 4 weeks after presentation. An endoscopic posterior gastrotomy is created with cautery. Following balloon dilatation, two 10 F drains are positioned into the retroperitoneum. An additional nasobiliary drain can be placed within the necrotic cavity, for irrigation. Retrieval baskets and balloons can be used to remove necrotic debris. Success rates of 72% to 81% have been reported [35]. Advantages over open surgery include avoidance of a major abdominal wound and avoidance of the risks for a postoperative incisional hernia and external fistulae. This technique requires advanced endoscopic expertise and repeated endoscopic procedures. The likelihood of success is limited if extensive solid necrotic debris is present. Concurrent percutaneous drainage is required in 25% of patients [35]. With improving technology and expertise, this endoscopic technique may become more widely applied. Successful noninterventional management of infected pancreatic necrosis has been reported in stable patients, but is not currently recommended [36].

## **Hemorrhage**

Significant retroperitoneal bleeding from acute pancreatitis is uncommon. It usually results from secondary splenic artery pseudoaneurysm, rather than diffuse "hemorrhagic pancreatitis." Pseudoaneurysm formation is related to peripancreatic inflammation and enzymatic digestion of the vascular wall. Clinical manifestations range from a subtle decline in hemoglobin to massive hemorrhage and shock. The diagnosis requires a high index of suspicion. It is diagnosed by arterial phase-contrast CT or angiography. Surgical treatment is associated with a mortality ranging from 28% to 56% [9]. Angiographic embolization is the therapeutic procedure of choice when permitted by the patient's condition and the available expertise.

## **Therapy for pancreatic and ampullary lesions with benign or uncertain behavior**

Traditional open surgical resection remains the standard for proved or suspected malignancy of the duodenum, ampulla, pancreas, and bile ducts.

Despite the morbidity of pancreaticoduodenectomy (Whipple procedure) and traditional distal pancreatectomy, adherence to sound oncologic principles is paramount for treatment with curative intent. Although minimally invasive techniques including endoscopic, percutaneous, and laparoscopic approaches are attractive, surgical compromise with inadequate margins of resection or inadequate lymphadenectomy is unacceptable. However, several benign or low-grade malignant lesions of the pancreas and periampullary duodenum permit safe application of less invasive techniques. These lesions and the less invasive therapies are now considered.

### **Ampullary adenoma**

Villous and tubulovillous adenomas represent the most common periampullary tumors. The adenoma-to-carcinoma sequence for these lesions is well supported: in one study, 55% of patients showed residual adenoma within a resected periampullary carcinoma [37]. Although pancreaticoduodenectomy remains the standard for invasive periampullary carcinoma, with nearly one half of all resected patients surviving for 5 years [38], local surgical resection or endoscopic snare offers a less invasive alternative therapy for patients who have benign disease. Despite extensive preoperative evaluation by endoscopic ultrasound and biopsy, predictors of malignancy remain unreliable. Heidecke and colleagues [39] reported 32 patients undergoing resection of benign adenomas, with low-grade dysplasia in 34% and high-grade dysplasia in 66%. Invasive carcinoma was found in 27% and 29%, respectively, findings consistent with previously reported false-negative biopsy rates of 17% to 40%. Sauvanet and colleagues [40], in a study of 26 patients in France, demonstrated a 20% false-negative rate for the detection of malignancy despite the use of endoscopic ultrasound and even endoscopic sphincterotomy and forceps biopsy of ampullary adenomas. In a series of 30 patients treated with open local excision of ampullary adenomas, Meneghetti and colleagues [41] found all patients who had high-grade dysplasia demonstrated on a preoperative biopsy had invasive carcinoma when the entire lesion was examined pathologically by permanent section. Because of the limitations of frozen section analysis, Meneghetti advocates pancreaticoduodenectomy for all suitable patients who have high-grade dysplasia. Recent studies report that identification of p53 and Ki-67 markers or Kirsten-ras (K-ras) mutations in ampullary malignancy may help select patients who require more radical resection [42,43]. Norton [44] have reported successful application of thermal ablation for periampullary adenomas using Nd-YAG laser and subsequent argon beam coupled with regular endoscopic surveillance. Despite the investigators' success in local control of adenomas, ablative therapy has not been proved to reduce the incidence of malignancy in high-risk patients, such as those with familial adenomatous polyposis (FAP) syndrome. Because of the high rate of occult malignancy in periampullary villous tumors, ablative therapy, such as laser or argon beam

fulguration with the destruction of pathologic material, is reserved only for patients who are poor surgical candidates.

Options for local resection include open approaches by duodenotomy and surgical sphincteroplasty of bile and pancreatic ducts or endoscopic snare techniques. The appropriate therapy depends on careful assessment of the lesion anatomy, the patient risk factors for surgery, and the local endoscopic and surgical expertise. Endoscopic ultrasound to evaluate tumor extension into the biliary and pancreatic ducts is valuable but is limited by the presence of indwelling biliary stents in obstructed patients [29]. Quirk and colleagues [45] noted a 42% cost reduction for local excision compared with pancreaticoduodenectomy when endoscopic ultrasound identified patients acceptable for local excision.

### *Endoscopic excision*

Endoscopic excision of ampullary adenomas can be considered for lesions smaller than 3 cm in diameter with no evidence of pancreatic or biliary ductal extension by endoscopic ultrasound. In a series of 103 patients treated with endoscopic resection at four institutions, the treatment was successful in 80% [46]. The 20% failure rate was predominantly due to local recurrence, which was significantly higher in patients who had lesions larger than 3 cm in diameter and those who had a genetic predisposition to adenomas. Special considerations for patients who have FAP are discussed later. Technical adjuncts, such as submucosal epinephrine injection, routine use of pancreatic duct stents, and supplemental thermal ablation, may improve the initial and long-term outcomes [42,47]. Complications of endoscopic papillectomy occur in about 25%. They include pancreatitis, bleeding, cholangitis, papillary stenosis, and perforation [46]. Given the significant risk for local recurrence and the malignant potential of the lesions, a follow-up endoscopic examination at least every 6 months is recommended. With an average time for recurrence for benign and malignant tumors of 3.5 years (range 1–6.8 years), the appropriate duration of surveillance is unknown as yet [41]. The American Society for Gastrointestinal Endoscopy has promulgated guidelines for the endoscopic management of duodenal adenomas [47].

### *Local surgical excision*

Halstead performed the first transduodenal resection of carcinoma of the ampulla in 1899, more than 30 years before Whipple's earliest pancreaticoduodenectomy [48]. Although endoscopic snare techniques permit removal of mucosal lesions or papillectomy, true ampullectomy requires concomitant sphincteroplasty or reanastomosis of the bile and pancreatic duct to the duodenal wall (Fig. 6). Advantages of surgical ampullectomy over endoscopic removal include the ability to extend the resection into the distal pancreatic and bile ducts with less risk for perforation or leakage, and the opportunity for sampling regional lymph nodes. Although some authorities

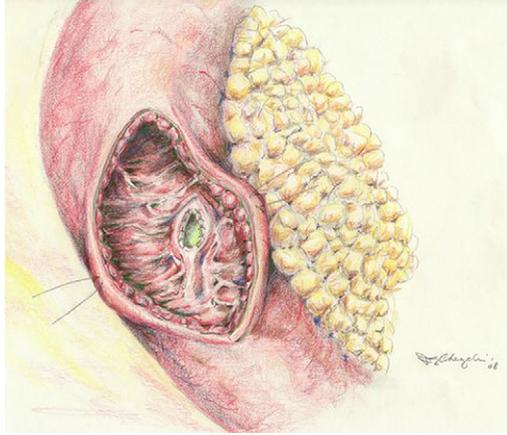


Fig. 6. Sphincteroplasty or reanastomosis of the bile and pancreatic duct to the duodenal wall. (Courtesy of D. Chengelis, MD, Royal Oak, MI.)

advocate local resection for pathologic tumor stage Tis (carcinoma-in-situ) and T1 invasive carcinoma (confined to the ampulla without invasion of duodenal wall or pancreas), regional lymph node involvement occurs in 6% to 10% of cases [48]. With 5-year survival rates of about 84% following pancreaticoduodenectomy for stage I disease, the decision to proceed to radical resection needs to be considered. Meneghetti and colleagues [41] reported recurrence of benign adenoma in 3 of 23 patients (13%) treated by ampullectomy, with an average time to recurrence of 3.2 years. Six patients in this series underwent ampullectomy as definitive therapy for adenocarcinoma, with two recurrences (33%), despite negative margins at the initial resection [41]. In a series of 32 patients, recurrence rates after local excision for benign villous tumors of the duodenum were 32% at 5 years and 43% at 10 years [49]. Complications from surgery are generally minor. They include pancreatitis, cholangitis and, rarely, duodenal fistula.

### Radical pancreaticoduodenectomy

First performed by Kausch in 1912 and popularized in the United States by Whipple in 1933, pancreaticoduodenectomy remains the standard for potentially curative treatment of malignant ampullary tumors. Despite common perceptions of severe morbidity, high operative mortality, and postoperative disability, surgical outcomes of Whipple procedures have dramatically improved during the past 2 decades. Rosemurgy and colleagues [50] reported a clear trend in Florida of increasing numbers of pancreatectomies performed by a smaller cohort of surgeons. In-hospital mortality was inversely proportional to the frequency with which surgeons performed the procedure. In a national observational study by McPhee and colleagues [51], patients undergoing pancreaticoduodenectomy at institutions

performing more than 18 procedures per year experienced an in-hospital mortality of 2.7%, compared with 11.1% at institutions performing fewer than 5 procedures per year. Winter and colleagues [52] review of 1423 pancreaticoduodenectomies for cancer performed at Johns Hopkins Hospital over 36 years demonstrated a decline in operative mortality from 30% in the 1970s to 1% in the current decade.

### *Ampullary adenoma in familial adenomatous polyposis*

Ampullary and duodenal adenomas in patients who have FAP warrant special consideration. Patients who have this autosomal dominant disorder have mutations in the adenomatous polyposis coli gene located on chromosome 5q21 [53,54]. With modern surveillance and early total proctocolectomy, inevitable death from metastatic colon cancer is usually avoided. Arvanitis and colleagues [55] reported that desmoid tumors and periampullary malignancy were responsible for most of the deaths in patients who had FAP and who underwent prophylactic colectomy. Although endoscopic or limited surgical resection of the ampulla clearly has a role, the known field defect in FAP warrants consideration of radical treatment, including pancreaticoduodenectomy. In patients who have FAP, the relative risk for periampullary or duodenal cancer is estimated at 200 to 300 times that of the general population. Careful surveillance and aggressive therapy for upper gastrointestinal polyps is warranted because of an estimated 5% lifetime risk for duodenal cancer in FAP patients, with an average age of cancer diagnosis of 52 years [56]. Surveillance has been recommended to begin at age 20 and to be repeated at regular intervals, based on the Spigelman and colleagues [57] classification of duodenal involvement. Pharmacologic approaches, such as use of cyclooxygenase II (COX II) inhibitors, have shown limited success in the treatment of foregut disease.

The known genetic field defect and younger age of onset of disease justifies an aggressive therapeutic approach for duodenal and ampullary polyps in patients who have FAP. In Farnell's [49] series of open surgical ampullectomy, recurrence rates at 5 and 10 years were significantly higher in FAP patients than in patients who had sporadic occurrence (60% versus 32% at 5 years and 73% versus 42% at 10 years, respectively). In patients who had recurrent adenoma, 4 of 17 (23%) had invasive adenocarcinoma at the time of recurrence [49,54]. Further supporting the field risk in patients who have FAP, Murakami and colleagues [58] reported the development of duodenal cancer involving the proximal duodenal cuff in a 40-year-old patient following pylorus-preserving pancreaticoduodenectomy.

### **Nonepithelial ampullary tumors**

Ampullary carcinoid tumors, or well-differentiated neuroendocrine tumors, are rare causes of pancreatitis or obstructive jaundice. Arising

from cells of the amine precursor uptake and decarboxylase system, these neuroendocrine tumors can potentially secrete polypeptide hormones but rarely produce the carcinoid syndrome. Fewer than 3% of patients who have ampullary carcinoid have symptoms of flushing, diarrhea, and asthma [59]. Extrapolating from the observed biologic behavior of carcinoids elsewhere in the gastrointestinal tract, treatment decisions are generally based on tumor size, mitotic activity, and histologic evidence of angioinvasion. Immune reactivity to proliferating nuclear cell antigen and Ki-6 are associated with more aggressive tumor behavior and more frequent metastasis [60].

Because of the rarity of ampullary carcinoid, definitive management guidelines have not been established. Although pancreaticoduodenectomy with lymphadenectomy is usually performed for lesions larger than 2 cm in diameter or with aggressive-appearing histology, ampullectomy can provide a viable alternative. In a review of 105 cases, Hartel and colleagues [61] found that the size of the tumor has not been shown to correlate with prognosis and that the tumor mitotic activity may not correlate with metastatic potential. Although local excision achieves a 90% rate of long-term survival for well-differentiated tumors [62], the safety of local pancreaticoduodenectomy, using standard oncologic principles, should not be compromised when biologic risk is uncertain. Gangliolytic paraganglioma of the ampulla of Vater represents another rare neuroendocrine tumor. In a review of 21 cases of ampullary paraganglioma, 7 (33%) of resected paragangliomas had lymph node metastasis or subsequent distant metastases. Despite the small number of analyzed cases, the investigators advocated pancreaticoduodenectomy for most patients.

### *Minimally invasive pancreatic resection*

Innovation, advancement of technical skills, and development of sophisticated laparoscopic instruments have allowed surgeons to offer laparoscopic pancreatic resection as a safe alternative to traditional pancreatic surgery. Improved performance of body imaging has led to increasing detection of pancreatic cystic neoplasms, endocrine tumors, and other lesions with malignant potential. Currently, patients affected by these benign or low-grade malignant lesions are often candidates for laparoscopic pancreatic resection by enucleation [63], central pancreatectomy [64], distal pancreatectomy, or even pancreaticoduodenectomy [65]. Although these minimally invasive therapies emphasize patient comfort, decreased hospital stay, and more rapid return to normal activity, adherence to sound principles of oncologic surgery remains paramount.

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