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Editorial and business offices
ACS-SRGS
633 N. Saint Clair St.
Chicago, IL 60611-3211
P 800-631-0033 or 312-202-5227
F 312-202-5009
srzs@facs.org | www.facs.org/publications/srgs

Managing editor:
Lynanne Feilen, lfeilen@facs.org

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Selected Readings in General Surgery (SRGS) is a topic oriented, in-depth review of the field of general surgery presented eight times annually as an educational offering of the Division of Education of the American College of Surgeons. The mission of the Division of Education is to improve the quality of surgical care through lifelong learning, based on educational programs and products designed to enhance the competence or performance of practicing surgeons, surgery residents, and members of the surgical team. The intent of the publication is to analyze relevant medical literature to give the surgeon the knowledge necessary to practice state-of-the-art surgery. To accomplish this goal, the editor selects 100–125 pertinent articles from the literature for each issue. Each article is reviewed and an overview is written that places the content of these articles in the perspective of the best, day-to-day, clinical practice. In addition to the overview, 12–18 full-text articles are reprinted in each issue.

The overview is compiled with the assistance of an 18-member, international board of editors who are experts in the various focus areas that comprise the specialty of surgery. In addition, the editorial board has representation and expertise in such important fields as medical evidence evaluation, surgical education, outcomes research, standard setting, and performance improvement. SRGS is a unique resource because the overview and selected full-text articles provide the reader with the most valuable and pertinent content illuminated with informed opinion and critique. Unnecessary material is eliminated. SRGS does not present itself as infallible and the editor-in-chief takes responsibility for the content that appears in each issue. The editor-in-chief and the editorial board recognize that there is no such thing as the "average" surgical patient, and that the information in the literature must be interpreted in the light of the clinical presentation of each individual patient.

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A pretest is mandatory to earn CME credit on the posttest. The pretest should be completed BEFORE reading the overview. Both tests must be completed online at www.facs.org/publications/srgs/cme.

1. All of the following are complications of choledochal cyst disease except which one?
   a) Cholangitis
   b) Cholangiocarcinoma
   c) Pancreatitis
   d) Pancreatic adenocarcinoma
   e) Biliary cirrhosis

2. Which of the following is the best therapy for Type 1 choledochal cyst?
   a) Irrigation of the cyst with 5-fluorouracil
   b) Resection of the extrahepatic biliary duct with hepaticojejunostomy
   c) Conformal radiation therapy
   d) Endoscopic retrograde cholangiopancreatography (ERCP) with papillotomy
   e) Anastomosis of the choledochal cyst to a Roux-en-Y loop of jejunum

3. Each of the following statements about gallbladder polyps is true except which one?
   a) All gallbladder polyps are premalignant
   b) Cholesterol polyps make up the majority of gallbladder polyps
   c) Inflammatory polyps account for 10% of gallbladder polyps
   d) The lowest risk of malignancy is seen in gallbladder polyps < 5 mm in diameter
   e) Gallbladder polyps are not caused by gallstone disease

4. Which of the following statements is true about gallbladder polyps?
   a) Most gallbladder cancers arise from gallbladder polyps
   b) Inflammatory polyps are the most common type of gallbladder polyp
   c) Malignancy risk rises for polyps more than 2 mm in diameter
   d) 85% of gallbladder polyps are non-neoplastic
   e) Gallbladder polyps are complications of gallstone disease

5. Which of the following statements is true about Caroli disease?
   a) The condition is characterized by isolated dilation of one intrahepatic duct
   b) The condition is a common cause of pancreatitis
   c) The condition is characterized by multiple intrahepatic cystic dilations of the bile ducts
   d) The condition is associated with gallstones
   e) A majority of patients develop pancreatic cancer

6. A 64-year-old male undergoes laparoscopic cholecystectomy for symptoms of gallstone disease. Histologic examination of the gallbladder discloses adenocarcinoma of the gallbladder that extends through the muscularis layer of the gallbladder. Which of the following is appropriate therapy?
   a) No further therapy is required
   b) Close followup with sequential ultrasound examinations
   c) External beam radiation to the gallbladder bed
   d) Right hepatic lobectomy
   e) Reoperation with resection of the hepatic gallbladder bed and local lymphadenectomy
7. Which of the following statements is true about cholangiocarcinoma?
   a) Cholangiocarcinoma associated with primary sclerosing cholangitis is uniformly fatal and treatment is contraindicated
   b) Intrahepatic cholangiocarcinoma will frequently require hepatic resection
   c) Distal duct cholangiocarcinoma is best treated with stenting of the duct
   d) The Klatskin tumor is the least common cholangiocarcinoma
   e) Hepatic transplantation is not an effective treatment for cholangiocarcinoma

8. A 56-year-old man presents with obstructive jaundice secondary to a hepatic hilar cholangiocarcinoma. Imaging suggests extension of the tumor into the right hepatic duct. The operation with the best chance of R0 resection (negative resection margins) is?
   a) Orthotopic liver transplantation
   b) Common bile duct resection with stenting of the right hepatic duct
   c) Excision of the tumor with right hepatic lobectomy
   d) Tumor debulking
   e) Stenting of the bile duct

9. Which of the following statements is true about primary sclerosing cholangitis
   a) Association with inflammatory bowel disease is common
   b) There is no evidence of a genetic component to primary sclerosing cholangitis
   c) The incidence of primary sclerosing cholangitis in the United States is 22/100,000
   d) Cholangiocarcinoma will develop in 80% of patients with primary sclerosing cholangitis
   e) Resection of the involved bile duct is contraindicated in patients with primary sclerosing cholangitis

10. Which of the following is not a complication of chronic pancreatitis?
    a) Pain
    b) Weight loss due to anorexia
    c) Weight loss due to malabsorption
    d) Cholangiocarcinoma
    e) Diabetes mellitus

11. All of the following are useful means of localization of pancreatic insulinoma except which one?
    a) ERCP
    b) Portal vein insulin assay with calcium injection into the pancreatic arteries
    c) CT imaging
    d) Intraoperative ultrasound
    e) Endoscopic ultrasound

12. Gastrinoma is diagnosed when which of the following circumstances are discovered?
    a) Hypergastrinemia and achlorhydria
    b) Hypergastrinemia and hyperglycemia
    c) Hypergastrinemia with hyperhidrosis
    d) Hypergastrinemia with a gastric pH < 2.1
    e) Hypergastrinemia with weight loss

13. A 50-year-old man has chronic pain due to chronic pancreatitis. A dense inflammatory mass has been located in the head of the pancreas and there is dilation of the pancreatic duct to the left of the mass. Which of the following statements is true about management of this patient?
    a) Pancreaticoduodenectomy is associated with pain control in more than 95% of patients
    b) Compared to duodenum-preserving, pancreatic head resection, pancreaticoduodenectomy is associated with superior quality of life
    c) Mortality is higher for the duodenum-preserving, pancreatic head resection compared to pancreaticoduodenectomy
    d) Pain control at five years postoperatively is better with duodenum-preserving, pancreatic head resection
    e) Pancreatic endocrine insufficiency is seen more often following duodenum-preserving, pancreatic head resection
14. Which of the following statements is true about endoscopic stenting for pain associated with pancreatic duct stricture?
   a) Pain relief is superior compared with operative management of pancreatic ductal obstruction
   b) Best long-term pain relief was associated with stent change “on demand”
   c) Pain relief at two years is observed in less than 20% of patients
   d) Endoscopic management of biliary obstruction is associated with complete long-term relief in all patients
   e) Once pain relief has occurred, there is no recurrence after stent removal

15. A pancreatic pseudocyst in a patient with chronic pancreatitis is diagnosed by CT imaging. Ductal anatomy studies show that the duct is normal with no connection to the pseudocyst. Which anatomic type is this?
   a) Type IV
   b) Type IIB
   c) Type IA
   d) Type IB
   e) Type IIIB

16. A 66-year-old woman with a history of chronic pancreatitis, developing after several episodes of acute biliary pancreatitis, presents with a large pleural effusion. Thoracentesis discloses fluid with high amylase content. CT imaging shows a small pseudocyst at the junction of the neck and body of the pancreas. Which of the following is the best choice for therapy?
   a) Repeat thoracentesis
   b) Percutaneous tube drainage of the site of the pseudocyst
   c) Pancreatecoduodenectomy
   d) Tube thoracostomy, nutritional support, and possible octreotide therapy
   e) Open drainage of the pseudocyst

17. After three weeks of tube thoracostomy drainage, the patient described in the previous question has persistent drainage of 300–400 mL/day of fluid. Magnetic resonance imaging has localized the pancreatic ductal leak to the junction of the neck and body of the pancreas. Which is the next best step?
   a) Pancreatecoduodenectomy
   b) Open external drainage of the ductal leak
   c) ERCP with pancreatic ductal stenting
   d) Distal pancreatectomy with splenectomy
   e) Puestow procedure

18. Which of the following is associated with an increased risk of pancreatic cancer?
   a) Obesity
   b) Asian ancestry
   c) Hypertension
   d) Diabetes mellitus
   e) Cigarette smoking

19. Which of the following is associated with the best two-year survival for pancreatic adenocarcinoma located in the head of the pancreas with a diameter of 2.5 cm?
   a) Laparoscopic enucleation of the tumor
   b) Biliary bypass with gastrojejunostomy
   c) ERCP with stenting
   d) Pancreatecoduodenectomy with postoperative chemoradiation
   e) Pancreatecoduodenectomy

20. A 24-year-old woman has a solid tumor of the tail of the pancreas that is 4.5 cm in diameter. CT imaging discloses splenic vein thrombosis. There are gastric and esophageal varices visible on imaging. The best approach for management of this patient would be?
   a) TIPS procedure
   b) Laparoscopic enucleation of the mass
   c) Distal pancreatectomy with splenectomy
   d) Reconstruction of the portal vein using saphenous vein interposition graft
   e) Angiographic embolization of the splenic artery

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   This article is a clear and useful review of cystic diseases of the liver and biliary tract.


   This article is a complete review of surgical options for the management of Caroli’s disease and syndrome.


   This article is a valuable review of cystic neoplasia of the liver and biliary tract.


   Pilgrim and coauthors provide a valuable perspective on the use of imaging for the diagnosis of gallbladder cancer.


   This article reviews data supporting the usefulness of the Blumgart staging system for hilar cholangiocarcinoma.


   These data provide valuable guidance for clinicians wishing to estimate the probability of progression of main-duct IPMN.


   Data from a prominent European group of pancreatic surgeons suggests that contemporary treatment approaches to intraductal pancreatic mucinous neoplasms (IPMN) might underestimate the risk of malignant disease.


   This article presents data confirming the safety and effectiveness of enucleation for small pancreatic lesions with a low risk of malignancy.


   The authors provide data that support extended intraperitoneal exploration during laparoscopic staging procedures for pancreatic cancer.


   This article provides useful perspective on the management of lesions in the body and tail of the pancreas.


   Ollinger and coauthors provide a valuable longitudinal look at the progress of pancreas transplantation.
This issue of SRGS continues the discussion on diseases of the biliary tract and pancreas (see SRGS, Volume 40, No. 8). The overview opens with a review of choledochal cyst disease, an important congenital disorder involving the biliary tract. In following sections, a detailed review of neoplastic diseases (benign and malignant) of the biliary tract is presented. A discussion of the clinical manifestations, diagnosis, and management of chronic pancreatitis follows. The important complications of this debilitating disease are emphasized. The role of operative interventions to assist with the control of pain while maintaining endocrine function in chronic pancreatitis is a central component of this discussion. Following the discussion of chronic pancreatitis, a discussion of the diagnosis and management of benign and malignant tumors of the pancreas is presented. The overview concludes with the current status of pancreas transplantation for the treatment of diabetes mellitus.

We continue our practice of updating the content of each edition of SRGS with reviews of valuable, recent articles while retaining older articles that continue to be relevant. As with the first issue, I owe a debt of gratitude to Nicholas Zyromski, MD, FACS, for his assistance in selecting articles for inclusion in this two-issue series.
Choledochal cysts are congenital or acquired cystic dilations of the biliary tract. Kelly and Weber¹ in the *Journal of Gastrointestinal Surgery*, 2014, note that these lesions are seen in children and adults. The article is provided as a full-text reprint accompanying some formats of *SRGS*. They note that these lesions have traditionally been classified according to the system proposed by Todani² and Alonso-Lej.³ The classification system is depicted in Figure 1. A central anatomic and pathophysiologic feature of choledochal cyst disease is an abnormal pancreaticobiliary junction (APBJ). This is defined as a junction of the pancreatic duct and bile duct that is located within the duodenal wall more than 15 mm from the ampulla of Vater. This abnormality potentially allows entry of pancreatic secretions into the bile duct system and might contribute to the risk of developing malignancy within the choledochal cyst. This risk is the main reason that complete excision of the cyst with reconstruction of the biliary tract has traditionally been the recommended treatment for all types of choledochal cysts.

Recent data⁴,⁵ have confirmed that Type III choledochal cysts are acquired, rather than congenital, lesions; these cysts are actually biliary diverticula. They are not associated with APBJ and have essentially no risk for development of malignancy, but they are associated with sphincter of Oddi dysfunction. Most of the patients with Type III choledochal cysts are older male patients who have usually undergone a prior cholecystectomy. Clinical series have documented a high success rate of endoscopic sphincterotomy in managing symptoms resulting from this type of choledochal cyst and it has become the preferred approach, according to Kelly and Weber.¹

Additional data relevant to the management of Type III choledochal cyst are presented by Ziegler and Zyromski⁶ in *Annals of Surgery*, 2010. This report describes a single-center medical record review of patients with choledochal cyst disease. The authors open with a discussion of the Todani² classification system for choledochal cysts. They emphasize that there is evidence that Todani Type III choledochal cysts (choledochocele) may actually be duodenal/biliary diverticula. These cysts are lined with duodenal mucosa. These cysts represent fewer than 5% of reported choledochal cysts and the risk of malignancy seems to be much lower than in the other types of choledochal cysts. The report reviews medical record data on 28 patients with choledochocele. The authors note that this represents the largest reported experience in the Western literature. They found that patients with choledochocele were older, more likely to present with pancreatitis, and most likely to be treated using endoscopic techniques. Of interest is that sphincter of Oddi dysfunction was discovered in 38% of patients with choledochocele. Two patients had pancreatic neoplasia at the time of choledochocele diagnosis. No case of cholangiocarcinoma was discovered in a patient with choledochocele. The authors note that an anomalous biliary-pancreatic duct junction is encountered less often in patients with choledochocele. Only 11% of patients had operative management. Most of the patients reviewed were treated with endoscopic
papillotomy. The authors suggest, based on their data, that Type III choledochal cyst is not a choledochal cyst in the true sense of the definition.

Kelly and Weber¹ and Zeigler and Zyromski² note that the symptoms of choledochal cyst have traditionally included right-sided abdominal pain, jaundice, and a right upper quadrant mass. This triad is present in a relatively small proportion of patients with choledochal cyst and is more commonly observed in children. Data reported in these articles suggest that 85% of children have at least two components of the triad. This proportion drops to 25% in adult patients.

Diagnosis of choledochal cysts may be possible before birth using ultrasound. Because complications such as pancreatitis and cholangitis are more common in children, antenatal diagnosis may permit surgical therapy before complications ensue. Data relevant to this approach are presented in an article by Diao and coauthors³ in the Journal of Pediatric Surgery, 2012. The authors report outcomes from a randomized, prospective clinical trial involving 36 patients in whom diagnosis of choledochal cyst was made using prenatal ultrasonography. The neonates were divided into two groups; one group (n=16) underwent cyst excision and biliary reconstruction during the first month after birth; the remaining patients were assigned to undergo operation more than one month after birth. The authors report no instances of mortality or postoperative bile leak in either group. The group operated on at more than one month after birth had more severe degrees of liver fibrosis and normalization of liver chemistries took significantly longer compared with the group operated on early. Patients who had diagnosis of choledochal cyst at the 4–5 month gestational age had more severe liver fibrosis than patients diagnosed later in pregnancy. The authors hypothesize that biliary stasis exists in these patients and the longer interval between diagnosis and therapy is associated with increasing liver damage. The authors conclude that early operation is feasible, safe, and may avoid progression of liver fibrosis in neonates with choledochal cyst disease.

Approximately 20% of patients with choledochal cyst disease are adults; choledochal cyst disease is frequently diagnosed when imaging is done for nonspecific abdominal symptoms. Symptoms in adults often overlap with symptoms observed in patients with other abdominal conditions and include upper abdominal pain, nausea, and pancreatitis. Jaundice and cholangitis can also be seen in adult patients with choledochal cyst disease. In symptomatic patients, ultrasound and magnetic resonance imaging (MRI) are the best means of confirming the diagnosis. The presence of cystic dilations with nodularity in the cyst wall suggests an increased risk of malignancy, according to Kelly and Weber¹.

As choledochal cyst disease has been increasingly recognized in adults, data on the frequency of and risk factors for complications have become important for efficient clinical decision-making. An article that reviews data on complications and outcomes of management of choledochal cyst is by Saluja and coauthors⁴ in the American Surgeon, 2012. The article reports data from a prospectively maintained database including 120 adults and 12 children. All patients in this group had Type 1 (93 patients) or Type IVA (27 patients) choledochal cysts. The most common complication encountered was intracystic stone formation in 49% of patients. Cholangitis and pancreatitis were encountered in 32% and 10% of patients, respectively. Malignant disease was seen in 3% of patients and all were carcinomas of the gallbladder.

Additional data on the clinical manifestations, complications, and operative management of patients with choledochal cyst disease are presented in an article by Gong and coauthors⁵ in the American Surgeon, 2012. The authors present a retrospective review of medical records in 222 patients seen over an eight-year interval. The most common types of cysts encountered were Type I and Type IV cysts. The authors attempted complete cyst excision with biliary reconstruction in all patients. Surgical procedures included cyst excision, anatomic hepatic resection, and pancreatoduodenectomy. Malignant disease was present in 24 patients and included tumors of the gallbladder as well as cholangiocarcinoma; in these patients complete cyst and tumor excision was not possible in approximately half of the patients because of the extent of intrahepatic and extrahepatic tumor spread. For cystic disease with extensive hepatic involvement, orthotopic liver transplantation is recommended. Postoperative complications were encountered in 11 patients with anastomotic stricture being the most common reason for reoperation. The authors concluded that the diagnosis of choledochal cyst
disease is increasing in adults and surgical excision of the cyst with biliary reconstruction is the most commonly recommended operative procedure.

As noted earlier, the preferred treatment of choledochal cyst is complete excision with biliary tract reconstruction. Hepatic resection and orthotopic liver transplantation are potential therapeutic avenues when multiple intrahepatic cysts (especially Caroli disease) are present. This topic is discussed in an article by Ulrich and coauthors\(^\text{10}\) in *Annals of Surgery*, 2008. The report describes a retrospective, single-center medical record review of 40 patients with multiple intrahepatic cysts and recurrent episodes of cholangitis. Involvement of the left hepatic lobe was the most common presentation. Thirty-three patients underwent formal hepatic resection and four patients had orthotopic liver transplantation. Three patients had cyst excision and biliary-enteric anastomosis. Overall five-year survival was 97.5% and no deaths were from liver or biliary disease in a follow-up interval of nearly seven years. The authors stress that most of the patients with multiple intrahepatic cysts had involvement of only one hepatic lobe, suggesting that liver resection would be appropriate for these patients.

A clear description of the operative management of Type I choledochal cyst is the focus of an article by Ammori and Mulholland\(^\text{11}\) in *Journal of Gastrointestinal Surgery*, 2009. The authors describe an open approach to this condition via a right subcostal incision that is extended as necessary. The extrahepatic bile duct is dissected from the bifurcation of the hepatic ducts down to the point where the bile duct and the main pancreatic duct are joined. The authors stress that all of the involved bile duct tissue must be removed. Fibrosis of the tissue with adherence of the cyst wall to the portal vein and/or hepatic artery may make total excision challenging. Ammori and Mulholland suggest that the posterior cyst wall can be left if the mucosa of the cystic dilatation is completely excised. The hepaticojejunostomy is constructed at or near the hepatic hilum. The hepatic hilar plate may need to be dissected and opened to permit an anastomosis of sufficient size (usually at least 2 cm in diameter). Once the area of the hilar plate is opened, an extension of the opening in the bile duct can be accomplished by opening the left hepatic duct in the area of the hilar plate. A 50-cm Roux-en-Y jejunal limb is constructed and a jejunal-to-hepatic duct anastomosis is constructed. The authors describe a two-layer anastomosis using an outer layer of silk sutures and an inner layer of absorbable suture.

Recently, laparoscopic excision of choledochal cysts has been reported and this approach is the focus of an article by Jang and coauthors\(^\text{12}\) in *Surgical Endoscopy*, 2013. The authors report a retrospective case series including 83 patients; laparoscopic cyst excision and biliary reconstruction were attempted in all patients. Conversion to an open operation was necessary in three patients because of difficult anatomy or intraoperative hemorrhage. There were no perioperative deaths and the most common significant postoperative complication was bile leak (7%); anastomotic stricture, pancreatic fistula, and intestinal obstruction were diagnosed in one patient each. Long-term complications included anastomotic stricture in three patients. The authors include data from a nationwide survey conducted in Korea that confirmed a diagnosis of malignancy in 10% of patients presenting with choledochal cyst. The most common site of malignancy was the gallbladder. The authors concluded that laparoscopic excision of choledochal cyst was feasible and safe. When concomitant liver resection was necessary, it could be carried out laparoscopically as well.

**Editorial comment:** On the basis of the articles reviewed, it is obvious that choledochal cyst is an unusual cause of abdominal symptoms. Although most cases are seen in children, the diagnosis is increasing in frequency in adults. There are more complications of choledochal cyst disease encountered in adults, including pancreatitis, cholangitis, and intracystic and intrahepatic stone formation as well as development of malignancy. This finding emphasizes the need for accurate diagnosis and prompt operative care. Open or laparoscopic excision of the cyst with biliary reconstruction is the preferred operative intervention. Available data confirm that Type III choledochal cyst is a distinct entity that does not carry the risk of complications or malignancy observed in the other cyst types. Most of these are managed endoscopically with sphincterotomy because sphincter of Oddi dysfunction is common in Type III cysts.
Benign and malignant biliary cysts

Kelly and Weber\(^1\) provide a clear review of the spectrum of hepatic cystic conditions. Additional discussion of hepatic cystic disease was presented in SRGS, Volume 38, Number 5. In this section of the overview we review data pertinent to the diagnosis and management on biliary cystic conditions, including congenital disorders (Caroli disease and syndrome or Type V choledochal cyst) as well as biliary cystic neoplasms. Kelly and Weber note that Caroli disease and syndrome comprise the most common congenital forms of biliary cystic disease.

An article that provides data on outcomes of surgical management of Caroli disease and syndrome is by Mabrut and coauthors\(^1\) in *Annals of Surgery*, 2013. This article is also provided as a full-text reprint accompanying some formats of SRGS. The authors note that Caroli disease and syndrome presents clinically with signs of biliary obstruction. Cholangitis, intrahepatic biliary stone formation, and cholangiocarcinoma are all complications of these conditions. The authors define Caroli disease as congenital biliary cystic disease isolated to the liver; Caroli syndrome is defined as congenital biliary cystic disease occurring in association with congenital renal cysts. The authors stress that definitive diagnosis of Caroli disease and syndrome is difficult since there are no pathognomonic histologic criteria for diagnosis. The most common clinical sign on imaging is the “central dot sign” which represents contrast enhancement within the vessels supplying the cystic tissue. This sign is, unfortunately, not present in all patients.

Mabrut and colleagues note that the critical issues in determining the management strategy include the risk of developing cholangiocarcinoma, the presence of symptoms, the extent of liver involvement, the severity of septic complications, and the severity of associated renal disease. Unilobar disease is treated with anatomic liver resection. The authors emphasize that management of bilobar disease is challenging and that there is insufficient data in the literature to support a single management strategy. The authors present outcomes data from a study organized by the French Surgical Association. The study was designed to evaluate outcomes of liver resection for unilobar disease and liver transplantation for bilobar involvement. The study group consisted of 155 patients; surgery was performed in 148 patients over a 33-year interval. Elective operation for cure was carried out in 139 patients (111 anatomic liver resections and 28 liver transplants). There was no operative mortality following liver resection and complications occurred in 15% of patients. Perioperative mortality for liver transplant was 10% and complications occurred in slightly more than 39% of patients. Eight patients had cholangiocarcinoma at the time of definitive operation and the one-year survival in these patients was 33%. Overall five-year survival for all patients was 88% and quality of life in surviving patients was excellent.

The authors emphasize that surgical management of patients with Caroli disease and syndrome, who are acceptable operative risks, should be the preferred strategy, with anatomic liver resection or liver transplant chosen based on the extent of involvement. Septic complications are treated aggressively with biliary drainage and elective operation is planned once sepsis is cleared. Discussion presented in the review by Kelly and Weber\(^1\) agrees with this approach.

Kelly and Weber note that other biliary cystic neoplasms include cystadenomas, cystadenocarcinomas, and intraductal papillary mucinous neoplasms of biliary origin (IPMN-B). These lesions comprise less than 1% of bile duct tumors. Cystadenocarcinomas include two variants, one with ovarian stroma and one without; tumors with ovarian stroma are more aggressive. Many of these lesions are asymptomatic and clinical presentations can include nonspecific signs and symptoms or more severe presentations with jaundice and cholangitis. Surgical treatment is recommended for suspected biliary cystadenoma because of the risk of developing malignancy; suspected cystadenocarcinoma is also an indication for operation. Imaging with ultrasound, CT, and MRI help to confirm the diagnosis. Cross-sectional imaging most often shows multilocular cystic lesions. Cholangiography is useful since cystadenomas and cystadenocarcinomas do not usually connect to the main biliary tract unless fistulas have developed; this finding raises suspicion for malignant degeneration. If there is a connection from the cystic lesion to the main biliary tract, this suggests IPMN-B. Kelly and Weber note that serum and cyst fluid levels of tumor markers such as CA 19-9 have not been consistently helpful in establishing a diagnosis.

Additional data on using tumor markers to establish a diagnosis in patients with biliary cystic neoplasms are presented by Fuks and coauthors\(^5\) in the *British Journal*.
of Surgery, 2014. The authors sampled cyst fluid from intrahepatic cysts in 118 patients. Mucinous cystic lesions (cystadenoma in 19, cystadenocarcinoma in 4 and IPMN-B in 4) were present in 27 patients. The authors found that cyst fluid levels of CEA and CA 19-9 were not accurate for establishing a diagnosis. Levels of tumor-associated glycoprotein, in contrast, identified mucinous lesions with a near 100% accuracy.

Kelly and Weber recommend complete resection for suspected cystadenomas; recurrence rates are very low with this approach, but are unacceptably high if partial resection with drainage is the treatment approach. IPMN-B and suspected cystadenocarcinomas are treated with anatomic liver resection. Because of the risk of recurrence following anatomic resections of cystadenocarcinoma, long-term surveillance with imaging is recommended.

Risk factors for malignancy in patients with hepatic cystic lesions are reported by Wang and coauthors in Digestive and Liver Disease, 2012. The authors report outcomes in 30 patients. In this relatively small group (understandable because of the rarity of these lesions) older age, male gender, and shorter duration of symptoms were all strongly suggestive of malignant disease.

Another informative review article is by Soares and coauthors in the Journal of the American College of Surgeons, 2014. This article is included as a full-text reprint accompanying some formats of SRGS. The authors provide an extensive review of imaging for the diagnosis of biliary cystadenocarcinoma. Most available data support the fact that multiloculated cystic lesions with mural nodules, bile duct dilation, and intracystic debris are at increased risk for the diagnosis of cystadenocarcinoma. The authors recommend surgical excision using open or laparoscopic anatomic resection for lesions isolated to one lobe. Centrally located lesions are more likely to require enucleation. The authors review data confirming that the presence of ovarian stroma is predictive of shorter survival after resection. Recommendations contained in this review are supported by data reported in a multi-institutional study by Arnaoutakis and coauthors in Annals of Surgery, 2014.

Gallbladder tumors, cholangiocarcinoma, and sclerosing cholangitis

A variety of benign and malignant neoplastic diseases affect the biliary tract and pancreas. Several of these present unique and interesting challenges for general surgeons. Included among these challenges are determining the relationship between gallbladder polyps and malignant disease of the gallbladder and management of cholangiocarcinoma.

Gallbladder polyps

The first article discussed in this section is by Donald and coauthors in the American Surgeon, 2013. The authors report a retrospective analysis of 2,416 patients who underwent cholecystectomy in a single institution over a nine-year interval. Gallbladder polyps were the reason for cholecystectomy in 27 patients and gallbladder cancer was diagnosed in 20 patients. Among the patients with gallbladder polyps, dysplasia or cancer was not diagnosed in any polyp less than 2 cm in diameter. Cancer was diagnosed only in polyps that were more than or equal to 3 cm in diameter. The authors noted that patients with gallbladder cancer were more likely to be symptomatic (abdominal pain and/or mass) compared with patients who had polyps. They recommend that cholecystectomy be done for patients with gallbladder polyps if the patient is symptomatic or if the polyp is larger than 2 cm in diameter. Asymptomatic patients with small polyps could be managed with ultrasound surveillance to detect and document polyp growth.

Additional perspective on the clinical problem of gallbladder polyps is found in a detailed review by Gal- lahian and Conway in Gastroenterology Clinics of North America, 2010. The review begins by discussing the two large categories of gallbladder polyps, neoplastic and non-neoplastic. The authors note that cholesterol polyps are the most common of the non-neoplastic polyps. Adenomyo-
matosis of the gallbladder is also a non-neoplastic variety of gallbladder polyps. The lesion is found mostly in the fundus of the gallbladder and these lesions can grow to a relatively large size. Together, cholesterol polyps and adenomyomatosis account for 85% of gallbladder polyps. Inflammatory polyps are also non-neoplastic and account for 10% of gallbladder polyps. Adenomas and adenocarcinomas account for 4% of gallbladder polyps. Available data cited by Gallahan and Conway suggest, but do not confirm, a progression of adenoma to adenocarcinoma. Several varieties of neoplastic polyps make up the remaining 1% of gallbladder polyps. Gallahan and Conway note that abdominal ultrasound is the most common means of confirming the presence of gallbladder polyps. Polyp size is generally thought to be associated with the probability of a neoplastic polyp. A diameter of 10 mm has been suggested as a cutoff for suspicion of increased malignancy risk. Several reports cited by the authors note that a significant number of gallbladder polyps confirmed to be neoplastic are less than 10 mm in diameter. In contrast to previous reports, the authors suggest that polyps more than 6 mm in diameter are a consideration for increased cancer risk and should be subjected to surveillance ultrasound, with cholecystectomy performed if growth is confirmed. They review several reports that support the use of endoscopic ultrasound to improve the accuracy of diagnosing the presence of polypoid lesions, and their size. Although endoscopic ultrasound cannot, by itself, predict malignant potential, it is likely that endoscopic ultrasound can assist in the diagnosis of polyps that are suspicious because they are more than 6 mm in diameter. Several other articles deal with the relationship of polyp size to the risk of malignancy. The first article is by Ito and coauthors in the Journal of the American College of Surgeons, 2009. The article presents data from a retrospective medical record review of 417 patients seen over an 11-year interval in a single institution. The patients underwent abdominal ultrasonography for evaluation of abdominal symptoms or during the diagnostic workup of another disease. Only 23% of the patients underwent evaluation for symptoms suggestive of gallbladder disease. Nearly 95% of the patients had polypoid lesions less than 10 mm in diameter. One hundred forty-three patients were followed with sequential ultrasonography; growth of the polyp was observed in 6% of these patients. Eighty patients underwent cholecystectomy. Pseudopolyps or no polyps were found in 90% of these patients. Neoplastic polyps were present in 10% of patients and only one of these was an in situ malignancy in a polyp that was 14 mm in diameter. The authors conclude that small gallbladder polyps (less than 10 mm in diameter) can be safely followed with sequential ultrasound examinations; patients at risk for gallbladder cancer development will exhibit growth of the polypoid lesion. In this series, gallbladder polyps were not associated with increased risk of gallstone disease.

Additional data confirming the safety of a “wait and see” attitude in patients with small gallbladder polyps are found in an article by Colecchia and coauthors in the American Journal of Gastroenterology, 2009. This report describes a prospective case control study of 63 patients who had gallbladder polyps discovered on abdominal ultrasound examination. Matched groups of 30 patients, each with gallstones and normal gallbladders, were used for comparison purposes. Nearly two-thirds of the patients were asymptomatic on enrollment and the majority of patients with gallbladder polyps were men. No polyp growth was seen on follow-up ultrasound examinations. Studies of bile from patients with gallbladder polyps showed elevated cholesterol saturation. Although a few patients developed gallstones while under observation, none was symptomatic. The authors conclude that patients having small gallbladder polyps are at minimal risk for the development of any gallbladder disease and at particularly low risk for development of gallbladder cancer. Risk of developing gallstones in this group of patients was the same as for the general population.

A retrospective case review of patients undergoing cholecystectomy for gallbladder polyps is by Zielinski and coauthors in the Journal of Gastrointestinal Surgery, 2009. This report describes a series of 130 patients seen at a single institution over an 11-year period. All patients in this study underwent cholecystectomy and had histopathologic examination of excised tissue. Multivariate analysis was done to assess factors that were associated with gallbladder malignancy. Seven patients had associated primary sclerosing cholangitis (discussed later in the overview) that carries an increased risk of biliary tract malignancy. Twelve patients had neoplastic polyps discovered on histologic analysis. Four of these were benign lesions confirmed by pathology.
and eight were dysplastic or malignant. Two patients with dysplasia or malignancy had polyps less than 10 mm in diameter. No polyp with dysplasia or malignancy was less than 6 mm in diameter. Other factors associated with dysplasia or malignancy were the presence of vascularity and signs of invasion of surrounding tissue on ultrasound. Based on these data, the authors suggest that the lower limit for observation of gallbladder polyps with sequential ultrasound should be 6 mm rather than 10 mm.

Additional perspective on the relationship between gallbladder polyps and gallbladder cancer is presented in an article by Pilgrim and coauthors in the *Journal of the American College of Surgeons*, 2013. This article is provided as a full-text reprint accompanying some formats of SRGS. The authors emphasize the fact that the overwhelming majority of gallbladder cancers do not arise from gallbladder polyps. Because of this, an approach that emphasizes cholecystectomy for most patients who have imaging evidence of gallbladder polyps is not based on sound reasoning. Data presented by these authors strongly suggest that polyps of less than 6 mm in diameter do not require cholecystectomy or imaging followup, and that surveillance should be used only for polyps documented on sequential imaging studies to be more than 10 mm in diameter. Pilgrim and coauthors agree with Donald and coauthors that cholecystectomy is indicated for symptomatic patients, for patients with documented polyp growth, and for polyps that are more than 2 cm in diameter at initial diagnosis.

**Editorial comment:** Although the data presented in these studies are interesting, guidance for the clinician remains a challenge. The report by Zielinski describes a population of patients who underwent cholecystectomy and, interestingly, 36 of 130 polyps diagnosed on imaging were not present when the cholecystectomy specimen was examined. The articles by Ito and Colecchia describe patients evaluated by ultrasonography for a variety of complaints including gallbladder symptoms. These patient groups are not strictly comparable. It is possible that the group described by Zielinski was at higher risk because of the clinical decision made to undertake cholecystectomy. For patients who underwent cholecystectomy in the articles reviewed, the false positive rate for gallbladder polyp diagnosis approached 25%. These data suggest that abdominal ultrasound may “overcall” gallbladder polyps. From the data available, it seems appropriate that the ultrasonographic examination should carefully seek signs of vascularity and invasion. The use of endoscopic ultrasonography may complement abdominal ultrasound in selected patients. Patients with gallbladder polyp diameters ≤ 6 mm in diameter could acceptably be carefully followed for polyp growth using sequential ultrasound examinations with a low clinical threshold for cholecystectomy. I agree with Gallahan and Conway who suggest that patients with gallbladder polyps and symptoms consistent with gallbladder disease should probably undergo cholecystectomy. Cholecystectomy also seems indicated for patients with polyps more than 10 mm in diameter.

**Cancer of the gallbladder**

The first article reviewed in this section of the overview is by Butte and coauthors in *Annals of Surgical Oncology*, 2013. The report presents data on the use of tumor marker frequencies to explain the regional differences in the incidence of gallbladder cancer. Tissue samples from cholecystectomy specimens were obtained from one center in Chile, one in Japan, and one in the United States. The authors assayed tissue samples for cell cycle regulatory, angiogenesis-related, and p13k protein levels. Distinct differences were found in expression of these proteins when centers were compared. Lower levels of protein expression were observed in samples from the center in Japan. Of interest is that survival in patients with less extensive gallbladder cancers was longer in Japanese patients compared to the other centers. The authors conclude that these findings suggest regional differences in the pathogenesis of gallbladder cancer.

Additional data about the epidemiology of gallbladder cancer is found in a report by Mastoroki and coauthors in *Hepato-Gastroenterology*, 2010. This article notes that gallbladder cancers are frequently discovered at an advanced stage due to the vague and nonspecific nature of the clinical symptoms. Only about half the patients discovered to have the disease are candidates for treat-
ment. Surgical excision of the tumor along with a wedge of adjacent liver and surrounding lymph nodes remains the only effective treatment. Although gallbladder cancers are usually found in patients with cholelithiasis, a causal link between gallstones and gallbladder cancer has not been discovered.

Evidence supporting a causal link between gallstones and gallbladder cancer is presented in an article by Jain and coauthors in *Annals of Surgery*, 2014. The authors reviewed tissue from excised gallbladders in 350 patients seen over a four-year interval. They examined tissue for preneoplastic changes and loss of heterozygosity in eight genetic loci. Preneoplastic changes in gallbladder tissue were found alone, or in combination, in 14% of patients. Loss of heterozygosity was common in tissue with preneoplastic changes. Examination of normal gallbladder tissue disclosed no preneoplastic changes or loss of heterozygosity. The authors concluded that this evidence supports a causal link between gallstones and gallbladder cancer.

Findings on imaging usually suggest the diagnosis of gallbladder cancer. Controversial areas of the preoperative evaluation include the use of imaging, such as PET scanning and staging procedures like laparoscopy. Challenges in the diagnostic evaluation of patients with gallbladder cancer are discussed in the article by Pilgrim and coauthors (cited in earlier discussion). The authors review data indicating that CT imaging is best suited to identify gallbladder thickening (the most common imaging evidence of gallbladder cancer) as well as enlarged regional nodes that would suggest the presence of metastatic disease. They note that gallbladder wall thickening of 10 mm or more is a strong indicator of the presence of gallbladder cancer. Multiphase imaging with timed images following intravenous contrast injection can show portal vein enhancement that permits the interpretation of enhancement patterns in the gallbladder wall. They note that a thick one-layer enhancement of the gallbladder wall or strong enhancement of the inner layer of the gallbladder wall, with weak enhancement of the outer layer, are the two findings that most strongly suggest the presence of gallbladder cancer. They emphasize that this makes intuitive sense because gallbladder cancer arises from the mucosa of the gallbladder while cholecystitis is a condition causing edema of the serosal layer of the gallbladder wall.

Enhancement patterns on MRI can be used to support the diagnosis of gallbladder cancer as well. Endoscopic ultrasound has the advantage of being able to direct fine-needle biopsy of the suspicious area of the gallbladder wall. Differentiation of gallbladder cancer from xanthogranulomatous cholecystitis and adenomyomatosis may be possible using MRI, according to data cited in the article. The authors conclude that when imaging (possibly combined with needle biopsy) can confirm the presence of established gallbladder cancer, efforts to exclude the presence of metastatic disease in lymph nodes and distant organs are indicated. They close the article by noting that evidence is currently insufficient to support a role for PET imaging in the evaluation of patients with gallbladder cancer. Available data suggest that PET imaging may, however, be useful for establishing the presence of metastatic disease.

A prospective study of PET imaging in patients with suspected gallbladder cancer is by Ramos-Font and coauthors in the *Journal of Surgical Oncology*, 2014. The authors report data on 49 patients. Gallbladder cancer was confirmed in 34 patients. PET imaging had 96% accuracy for confirming the primary lesion and 86% accuracy for detecting nodal metastasis. Accuracy for detecting distant metastatic disease was 96%. The authors concluded that PET imaging was valuable for diagnosis and staging of gallbladder cancer.

A review article on the topic of gallbladder cancer and cholangiocarcinoma is by Sicklick and Choti in *Seminars in Oncology*, 2005. This review article focuses on management controversies for these two diseases. The authors open the discussion by emphasizing the fact that both of these tumors are uncommon, but gallbladder cancer is the most common cancer of the biliary tract. Gallbladder cancer, for example, has an incidence in the United States of 1.7/100,000 and the majority of tumors are in women. Eighty percent of gallbladder cancers are adenocarcinomas. Approximately 10% of the tumors encountered are discovered incidentally during histopathologic examinations of excised gallbladders. The authors discuss controversial aspects of the preoperative evaluation, and intraoperative management of patients with gallbladder cancer. Factors that bear on the determination of operative risk include an assessment of liver reserve.
Patients who have cirrhosis or in whom extended tumor resection would not leave sufficient functioning liver are not candidates for surgical resection. Patients with severe associated comorbid conditions would, as well, be at excessive risk for liver resection. Tumor characteristics that preclude resection include invasion of the common hepatic artery and/or main portal vein. Lymph-node metastases outside the area of gallbladder and hepatic hilum and distant metastases preclude resection.

Sicklick and Choti emphasize that patients with lymph-node metastases and distant metastatic disease often have low volumes of tumor, which may not be visible on cross-sectional imaging using CT or MRI. PET scanning is potentially useful, therefore, for identification of tumor outside of the area of resection. Staging laparoscopy could potentially identify lymph-node metastases and foci of distant metastasis within the peritoneal cavity. Available data cited by the authors indicate that staging laparoscopy has an accuracy of 50% overall in identifying patients who are not resectable. When patients are stratified, according to CT imaging characteristics that suggest the presence of larger primary lesions (T2 or T3), accuracy of staging laparoscopy improves. Laparoscopy is more effective in patients who have not had cholecystectomy.

The authors next consider characteristics of the primary tumor that guide decision-making on the choice of resection. Tumors identified at histopathologic examination of excised gallbladders do not require additional treatment if the tumor is in situ or if the tumor is staged T1 with invasion no deeper than the lamina propria-muscularis layer of the gallbladder. Five-year survival rates exceed 90% for patients with early-stage disease.

Debate continues about management of certain gallbladder cancers discovered on histopathologic examination of an excised gallbladder. An article focusing on the topic of incidentally discovered gallbladder cancer is by Misra and Guleria29 in the Journal of Surgical Oncology, 2006. These authors agree that incidentally discovered gallbladder cancers that do not extend beyond the lamina propria could be effectively treated with cholecystectomy alone. They stress that where suspicion of gallbladder cancer exists, based on preoperative imaging, open cholecystectomy with wedge resection of the liver and hilar/superior pancreatic lymphadenectomy is the preferred procedure. If the tumor discovered in an excised gallbladder following laparoscopic cholecystectomy is stage T1b, indicating extension of the tumor into the gallbladder muscularis, these authors favor reoperation with wedge resection of the liver and lymphadenectomy. All laparoscopic trocar sites are excised. They cite data to indicate that treatment of T1b tumors by cholecystectomy alone has been associated with five-year survivals of only 68%. Locoregional recurrence was present at two to three years of followup in more than 50% of patients treated with cholecystectomy alone for stage T1b tumors. By contrast, 10-year survival was 87% in a report of 12 patients treated with cholecystectomy plus wedge resection of the liver and lymphadenectomy for T1b cancers of the gallbladder. The authors caution that the case numbers reported are small. They recommend consideration of cholecystectomy plus wedge resection and lymphadenectomy for patients with T1b or more advanced tumors. Additional data cited in the review by Mastoraki and coauthors25 support these recommendations.

Patients with T2 and T3 lesions are candidates for extended hepatic resection if operative risk is acceptable. Improvements in outcomes of hepatic resection (see discussion in SRGS, Volume 38, Numbers 4 and 5, for information about techniques of hepatic resection) have improved outlooks for patients with gallbladder cancer. The operation for gallbladder cancer includes resection of the gallbladder and adjacent liver to include all gross tumor tissue. A hepatic hilar lymphadenectomy and superior pancreatic lymphadenectomy are included in the procedure. For more advanced lesions, resection of segments IV and V of the liver or an extended right hepatic lobectomy may be required to achieve negative tumor margins. The authors emphasize the continuing debate over the routine use of anatomic resection of segments IV and V and resection of the common bile duct despite the presence of negative margins of resection after en bloc resection of the gallbladder bed and a negative cystic duct margin. They stress that high-quality data do not support routine use of this more extensive resectional approach.

An article presenting data on the use of extended hepatic resection combined with pancreatoduodenectomy for advanced gallbladder cancer is by Sakamoto and coauthors30 in Surgery, 2013. The authors report outcomes data for five patients with advanced gallbladder cancer who underwent extended hemihepatectomy and pan-
creatoduodenectomy for gallbladder cancer. One patient died and pancreatic fistula developed in 95% of patients. Five-year survival for patients with gallbladder cancer was zero and median survival was nine months. The authors concluded that the benefit of extended resection with pancreatoduodenectomy could not be confirmed for patients with gallbladder cancer.

Recent data from the United States cited by Mastoraki and coauthors support the use of common bile duct resection only if the cystic duct margin is positive at the time of cholecystectomy and wedge resection of the liver. Data comparing outcomes of surgical treatment of gallbladder cancer at three different centers located in different areas of the world is the topic of a report by Butte and coauthors in the Journal of the American College of Surgeons, 2011. The data reported disclose that incidentally discovered tumors were more common in the centers located in the United States and Chile compared to the participating center in Asia. These data confirm the relation of long-term survival and resection of the primary tumor to achieve negative margins. Lymphadenectomy to detect lymph-node metastases is important because lymph-node negative patients have a distinct survival advantage. Patients with negative surgical margins and negative lymph nodes had equivalent survival rates (median more than two years) in all three centers.

The data from this international analysis also does not support the use of common bile duct resection unless the cystic duct margin is positive. The available data confirm that cholecystectomy alone is indicated for patients with superficial tumors confined to the lamina propria of the gallbladder. When the tumor is stage T1b, T2, or T3, wedge excision of the gallbladder bed until negative margins are acquired is associated with the best outcomes. Lymphadenectomy, as described above, is included. Extended resection may be indicated when negative margins cannot be achieved with resection of the adjacent gallbladder bed.

The increasing use of laparoscopy for surgical treatment of gallbladder cancer has prompted consideration of port site resection to prevent port site recurrences and perhaps improve survival in this patient group. This issue is examined by Maker and coauthors in Annals of Surgical Oncology, 2012. The authors report data on 113 patients who had gallbladder cancer discovered on histologic examination of an excised gallbladder. All patients were referred for laparoscopic resection of the adjacent liver. Port-site metastasis was observed in 19% of patients. Absence of port-site metastasis was associated with extended median survival but did not increase five-year survival rates. Port-site resection was not associated with improved survival rates and the authors concluded that mandatory port-site resection was not necessary.

An article examining the potential benefit of adjuvant radiation therapy in patients undergoing surgical treatment of gallbladder cancer is by Hyder and coauthors in Surgery, 2014. The authors extracted data from the SEER national database and matched patients who received adjuvant external beam radiotherapy with patients who did not receive radiation using propensity scores to adjust for confounding variables. Data from 899 patients who received radiation therapy were compared with outcomes for 4,112 patients who did not receive radiation. The analysis showed that adjuvant radiation improved short-term survival but the benefit dissipated over time so that there was no improvement in five-year survival rates.

**Cholangiocarcinoma**

Discussion relevant to the management of cholangiocarcinoma can be found in the final issue of a three-part series on liver diseases (SRGS, Volume 38, Number 5). For completeness and consistency, a portion of the discussion in that issue of SRGS is reproduced here. An overview of cholangiocarcinoma is by Gatto and coauthors in Digestive and Liver Disease, 2010. The authors note that cholangiocarcinoma is the cause of 3% of cancer-related deaths in the United States. Worldwide, the highest rates of death from cholangiocarcinoma are recorded in India, Asia, and parts of South America. The lowest rates of death are observed on Australia. Death rates are reported separately for the two main variants of cholangiocarcinoma. Extrahepatic cholangiocarcinoma incidence in the United States is .82/100,000 and for intrahepatic cholangiocarcinoma, the incidence is .95/100,000. Gatto and colleagues note that the incidence of intrahepatic cholangiocarcinoma in the United States has increased by 165%, while the incidence of extrahepatic cholangiocarcinomas has decreased 14% over the past decade. Similar changes in incidence have been confirmed in Western Europe.
Risk factors for development of cholangiocarcinoma have been identified, but these are present in less than 30% of patients presenting with these tumors. The risk factors include primary sclerosing cholangitis, infestation with liver fluke, hepatitis C infection, exposure to thorium dioxide (Thorotrast), and Caroli’s disease.

Additional discussion on general aspects of cholangiocarcinoma is presented in an article by Patel35 in Nature Reviews Gastroenterology and Hepatology, 2011. Patel notes that there are two basic phenotypes of cholangiocarcinoma. The extrahepatic phenotype includes the classic Klatskin36 tumor that is usually located in the hepatic hilum. The perihilar cholangiocarcinoma subtype is the most common type of cholangiocarcinoma. Additional subtypes of extrahepatic cholangiocarcinoma include tumors located in the distal common bile duct and ampulla of Vater; the distal extrahepatic subtypes are the second most common types of cholangiocarcinomas. These tumors tend to spread proximally and distally along the duct; nodal and extraportal spread is frequently present at the time of diagnosis. Intrahepatic cholangiocarcinoma is the least common subtype of cholangiocarcinoma and this phenotype usually presents as a liver mass. Clinical evaluation proceeds as for other primary tumors of the liver. Intrahepatic cholangiocarcinomas grow radially; nodal and extraportal metastases are usually present at the time of diagnosis. Cure of intrahepatic and extrahepatic cholangiocarcinomas is possible only with complete (R0) surgical resection of the tumor. Both phenotypes are resistant to radiation therapy and chemotherapy although data are available suggesting that treatment with 5-fluorouracil and gemcitabine has improved outcomes in patients with R1 and R2 resections.

Gatto and coauthors34 discuss the origin cells of cholangiocarcinoma. They cite data that the primitive form of cholangiocarcinoma, which contains elements of hepatocellular carcinoma, may arise from stem cells from periductal glands and biliary ductules. The data cited indicate that genetic markers of these stem cells can be recovered from tissue samples taken from these tumors. For most cholangiocarcinomas, the cell of origin is the cholangiocyte. Available data cited by Gatto and colleagues indicate that chronic inflammation plays a central role in carcinogenesis for these tumors. Inflammation increases cholangiocyte turnover. Furthermore, by-products of inflammation produced by the breakdown of nitric oxide can cause DNA mismatch repair abnormalities in cholangiocytes. Additional factors that contribute to DNA mismatch repair include proinflammatory cytokines such as interleukin-8. COX-2 metabolites, dopamine, and estrogen are also involved in the carcinogenesis process. Other inflammatory mediators that can contribute to cholangiocarcinoma carcinogenesis include cytidine deaminase and germinal center nuclear protein.

Cholangiocarcinomas are classified according to anatomic location as intrahepatic, hilar, and distal bile duct tumors. The authors note that intrahepatic cholangiocarcinomas are treated according to principles established for other hepatic tumors. Distal bile duct tumors are managed according to principles defined for pancreatic tumors. Because hilar cholangiocarcinoma (Klatskin tumor) is a relatively unique variant and is the most commonly encountered type of cholangiocarcinoma, the discussion focuses on this variant. The coauthors note that cholangiocarcinoma is uncommon; in contrast to gallbladder cancer, and the majority of patients encountered are male. Patient factors that influence the choice of operative treatment are similar to those described in the foregoing discussion and primarily relate to general operative risk and the function of the liver, especially the portion that might remain after resection. The authors stress that a critical feature of the preoperative evaluation is to determine the extent of bile duct involvement and the extent of involvement of the hepatic artery and portal vein. A thorough search for metastatic lesions is required because
even a single metastatic focus in the liver represents a contraindication to resection. The extent of soft tissue and vascular involvement can be assessed using cross-sectional CT imaging. Magnetic resonance cholangiopancreatography is a useful means of determining the extent of bile duct involvement.

A staging system for hilar cholangiocarcinoma that would accurately predict suitability of a given tumor for complete curative resection would have value for planning operative interventions. Such a staging system is the focus of an article by Matsuo and coauthors in the *Journal of the American College of Surgeons*, 2012. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The article describes the staging processes and outcomes in 380 patients with hilar cholangiocarcinoma treated at a single institution over an 18-year interval. Tumors were staged using imaging with ultrasound, CT, and MR procedures. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography were not used for diagnosis alone but were valuable to place biliary stents to assist in the management of cholangitis. Patient characteristics that indicated inoperability included presence of cirrhosis and/or other significant comorbid conditions. Tumor characteristics indicating inoperability included extensive involvement of intrahepatic ducts and the portal venous system along with presence of extrahepatic metastatic disease.

The three-tier staging system is defined according to tumor involvement of the portal venous system with concurrent atrophy of the section of the liver perfused by the involved portal vein as well as unilateral and bilateral involvement of intrahepatic bile ducts. The staging system is reproduced as Figure 2. The data analysis showed that resectability was 64% for T1 tumors; the frequency of resectability decreased with increasing tumor stage. For T3 tumors, resection was possible in slightly more than 1% of patients. A complete (R0) resection was possible in 44% of the total cohort of patients (76% of the 120 patients resected with curative intent). The authors emphasize that a concomitant hepatic resection was a significant contributor to achieving an R0 resection and was associated with improved survival. When an R0 resection was possible, five-year disease-specific survival was 43%. The authors concluded that the staging system was useful for predicting resectability in patients with hilar cholangiocarcinoma but the system was less useful for predicting survival.

Data from a European center confirming the value of extended hepatectomy and vascular resection are presented in a report by van Gulik and coauthors in the *European Journal of Surgical Oncology*, 2010. This report provides a long-term, single-center experience involving three eras. The authors note that extended hepatectomy and en bloc resection of involved portions of hepatic artery or portal vein characterized their practice in the...
most recent era. They stress the importance of a multi-disciplinary team consisting of surgeons, radiologists, gastroenterologists, and pathologists in the provision of optimum management for patients with cholangiocarcinoma. The preoperative evaluation includes careful imaging and biliary drainage of the segment of the liver that will remain following resection. Surgical exploration with supraduodenal bile duct resection and heptectomy, with caudate lobe resection on the side of the liver suspected to be involved, represent important components of the surgical procedure. Portal lymphadenectomy is included and careful documentation of margin status is obtained. Resection of the hepatic artery or portal vein is added if these structures are involved. The authors report data from 99 patients followed over the three eras. They noted a significant increase in R0 resections accompanying the adoption of heptectomy and vascular resection. Operative mortality and morbidity was the same (10% and 68%) in all three eras. In the third era, actuarial five-year survival increased to 33%. The authors note that further advances and improvements in survival will require development of effective adjuvant treatments.

Additional perspective on the use of extended, multiorgan resection for cholangiocarcinoma is by Sakamoto and coauthors. The authors report a retrospective medical record review of 14 patients with distal bile duct cholangiocarcinoma seen over a 21-year interval. Extended resection including hemihepatectomy and pancreatoduodenectomy were performed in these patients. Complete resection with negative radial margin was achieved in all patients and final pathology indicated T1 or T2 tumor stage. The disease-specific five-year survival for this group of patients was good, at 44%. Perioperative morbidity was high with 95% of patients developing pancreatic fistula. Median hospital length of stay was more than 1.5 months. The authors conclude that carefully selected patients with extensive distal bile duct cholangiocarcinoma benefit from extended, multiorgan resection. These results are noteworthy, but this is, fortunately, a rare variant of cholangiocarcinoma. Because the patients were treated over more than two decades, it is difficult to draw generalizable conclusions from these data.

The incidence of intrahepatic cholangiocarcinoma is increasing. An analysis of current trends in management and outcomes of treatment is by Amini and coauthors in the Journal of Surgical Oncology, 2014. The authors emphasize the facts that even though the incidence of intrahepatic cholangiocarcinoma is increasing and this tumor is the second most common hepatic malignancy, the number of patients seen in tertiary referral centers is small and the majority of patients are unresectable at the time of diagnosis. Overall five-year survival rates are low (10%–40%) even when tumors are resectable. The authors examined data from a national database to analyze population-based trends in diagnosis and management of this tumor type. They learned that the proportion of poorly differentiated tumors increased over time. Survival after surgical resection approached 45% at five years and equivalent five-year survivals were achieved with surgery plus intraoperative radiation for patients with evidence of advanced disease and/or nodal metastasis discovered at operation. The authors concluded that the frequency of liver-directed interventions increased for patients with intrahepatic cholangiocarcinoma over time and that surgical resection with or without intraoperative radiation therapy offered the best opportunity for long-term survival.

Additional information relevant to intrahepatic cholangiocarcinoma is found in a review by Poultsides and coauthors in Surgical Clinics of North America, 2010. The authors open with a discussion of data about the increasing incidence of intrahepatic cholangiocarcinoma. They note that there has been a 165% increase in the incidence of intrahepatic cholangiocarcinoma in the United States during the past 30 years. Reasons for the increasing incidence include improved detection of tumors and an increase in some of the risk factors for cholangiocarcinoma including hepatitis C and nonalcoholic steatohepatitis. The authors agree that the cell of origin of cholangiocarcinoma is the cholangiocyte. They note that hilar cholangiocarcinomas and distal bile duct cholangiocarcinomas present clinically with symptoms and signs of biliary obstruction. Intrahepatic cholangiocarcinoma presents clinically as a liver mass. Frequently, the liver mass is identified when imaging studies are obtained for evaluation of nonspecific abdominal complaints. Needle biopsy of the mass will usually reveal adenocarcinoma. Careful review by an experienced pathologist along with the use of specific histologic staining techniques will be required to determine that the mass is a cholangiocarcinoma and not a metastatic lesion. Data cited in this review disclose
that serum levels of CA 19-9 > 100 ng/mL suggest the diagnosis of cholangiocarcinoma. Other data cited in the report suggest that postoperative reductions of CA 19-9 levels are associated with improved survival. The authors emphasize the fact that hyperbilirubinemia interferes with interpretation of CA 19-9 levels. Repeat evaluation after biliary drainage relieves the hyperbilirubinemia may be helpful. Imaging with CT or MRI studies can identify characteristics that differentiate cholangiocarcinoma from metastatic lesions. The authors note that CT and MR images will frequently disclose bile duct dilation in patients with intrahepatic cholangiocarcinoma; dilated bile ducts are infrequently noted in metastatic lesions. Imaging findings are described in detail in the body of the article and readers may want to review this information.

Even with the use of these adjuncts, the nature of the tumor may remain obscure. Endoscopic evaluation of the upper and lower gastrointestinal tract as well as CT imaging of the abdomen, thorax, and pelvis may be required to exclude an extrahepatic primary. PET scanning may be useful to identify primary and metastatic disease. Poultsides and colleagues review several reports documenting the identification of metastatic disease by PET scanning, not disclosed with other imaging studies, changed management in nearly one-third of patients. The available data support the use of preoperative PET scanning in patients suspected of having cholangiocarcinoma. Staging laparoscopy has been reported as potentially useful for detection of unsuspected intraperitoneal metastatic disease. In two reports of small series cited by these authors, laparoscopy prevented a nontherapeutic laparotomy in up to one-third of patients. Because of small case numbers reported, there are insufficient data to recommend routine laparoscopy at this time.

Poultsides and associates report that complete removal of the tumor with negative resection margins is the objective of surgical therapy. Many patients with intrahepatic cholangiocarcinoma present with large, locally advanced tumors that invade surrounding structures. Resection of the liver, the extrahepatic biliary system, involved hepatic artery, portal vein, adjacent diaphragm, and vena cava may be necessary. The authors cite data that extended hepatectomy is needed in approximately 80% of patients who achieved R0 resection. Removal of the supraduodenal biliary ductal system was required in up to 30% of patients achieving a R0 resection. Despite the need for complex operations to excise tumors completely, reports from centers specializing in hepatobiliary surgery report mortality rates of 2% or less. Controversy persists regarding the use of routine lymphadenectomy for patients with intrahepatic cholangiocarcinoma. Lymph-node involvement with tumor has been reported in more than 30% of patients where lymph nodes were examined. Other data, by contrast, document no improvement in survival when lymphadenectomy is added to the resectional procedure.

The report next reviews outcomes of treatment stratified according to tumor stage. The main factors associated with poor overall outcomes were the presence of vascular invasion, multifocal tumors, and lymph-node positivity. Poultsides and colleagues note that the definition of multifocality may be difficult because tumors with satellite lesions tend to behave more like large, single tumors whereas tumors with intrahepatic metastases behave like multifocal tumors. In the data provided, positive resection margins were also associated with poor outcomes. The authors note that recurrence in the liver, adjacent lymph nodes, or peritoneum occurs in up to 40% of patients followed for more than two years. Overall five-year survival ranges from 14%–40%, depending on margin status and lymph node positivity. These data strongly suggest the need for more effective local and systemic therapies. Among the therapies available for unresectable patients, patients with recurrence, and patients with metastatic disease, chemotherapy, localized radiation therapy, and transarterial chemoembolization have been used. Outcomes vary with the best median survivals in the 22-month median survival range.41 Systemic therapy is also recommended for resected patients who are lymph node positive.

Development of a nomogram for prediction of survival rates after treatment for intrahepatic cholangiocarcinoma is described in by Hyder and coauthors42 in Surgery, 2014. The authors used outcomes data from specialized centers located in Europe, Asia, and the United States. Outcomes information for more than 514 patients was included. The authors found that factors influencing survival rates were patient age, tumor size, number of tumors, vascular invasion, and the presence of cirrhosis. The predictive nomogram they developed was relatively
accurate with a c-statistic of more than 70%. An illustration of the nomogram with instructions for its use is reproduced as Figure 3.

**Orthotopic liver transplantation for cholangiocarcinoma**

The use of chemoradiation therapy followed by orthotopic liver transplantation may be useful in carefully selected patients with small (less than 3 cm), but unresectable, hilar cholangiocarcinomas. Transplantation is not offered to patients with intrahepatic cholangiocarcinoma because of rapid recurrence of cholangiocarcinoma in the transplanted liver. Liver transplantation offers the advantage of complete excision of the tumor and one common site of recurrence/metastasis (the original hepatic site of the tumor). Data relevant to outcomes of this intervention are presented in a review by Grossman and Milliss in *Liver Transplantation*, 2010. The authors summarize outcomes results for patients with cholangiocarcinoma. Data indicate that five-year survivals of more than 80% have been reported with the use of chemoradiation followed by orthotopic liver transplantation. Of interest is that a significant proportion of the treated patients did not have cholangiocarcinoma in the explanted liver. Review of pretreatment pathology disclosed that clear-cut cholangiocarcinoma was not present in some of the preoperative specimens. Some of the tissue samples used for diagnoses were intraductal brush biopsies. These biopsies may have contributed to the surprising rate of negative findings in explanted livers. These findings raise the question whether all treated patients actually had cholangiocarcinoma and whether a subgroup of patients might have been discovered with particularly susceptible tumors.

The Mayo Clinic reports of liver transplantation for cholangiocarcinoma have been among the most thoroughly researched. An update of the Mayo Clinic experience is by Rosen and coauthors in *Transplant International*, 2010. The authors review the conception and development of the Mayo protocol. Currently, fine-needle aspirate examinations of lymph nodes have provided prechemotherapy evidence of unsuitability for the protocol. Only 15% of patients fail to complete the full protocol that includes chemotherapy and radiation therapy followed by a staging operation just before transplantation. For patients who complete the protocol and undergo transplantation, five-year survivals of 63% for de novo cholangiocarcinoma and 73% for cholangiocarcinoma in patients with primary sclerosing cholangitis have been observed.

Data from a single-center, retrospective analysis of experience with chemoradiotherapy followed by orthotopic liver transplantation as a treatment strategy for patients with advanced hilar cholangiocarcinoma are presented in a study by Duignan and coauthors in *HPB Oxford*, 2014. The authors selected 27 patients with advanced tumors for their chemoradiotherapy protocol (brachytherapy combined with 5-fluorouracil and external beam radiotherapy followed by orthotopic liver transplantation in patients who remained progression-free). They enrolled 27 patients and 20 patients were eligible for transplantation. Hospital
mortality was 20% and was mostly because of primary graft nonfunction or major vascular thrombosis. The overall four-year survival in successfully treated patients was 61%. The authors concluded that this approach was feasible and offered benefits for properly selected patients.

**Sclerosing cholangitis**

Primary sclerosing cholangitis is a chronic inflammatory disease of the biliary tract that results in multiple biliary strictures. Biliary obstruction leads to biliary cirrhosis and patients with primary sclerosing cholangitis are at increased risk for the development of cholangiocarcinoma. Primary sclerosing cholangitis is associated with inflammatory bowel disease in up to 80% of patients. Most patients have ulcerative colitis. There is evidence that primary sclerosing cholangitis may have a genetic component. A summary of findings in this area is reviewed by Karlsen and coauthors\(^46\) in *Gastroenterology*, 2010. Data reviewed in the article disclose that the incidence of primary sclerosing cholangitis in the United States and in Norway is about 1/100,000. Approximately 10% of patients diagnosed with primary sclerosing cholangitis will develop cholangiocarcinoma. The ulcerative colitis associated with primary sclerosing cholangitis is associated with a five-fold higher risk of colon cancer than in patients with ulcerative colitis and no cholangitis. The authors note that heredity studies suggest a genetic component to primary sclerosing cholangitis, but the relationships are complex. It is challenging to determine whether the changes in genetic factors discovered in patients with sclerosing cholangitis are primary factors in the disease or the result of the chronic inflammatory state.

**Chronic pancreatitis**

Chronic pancreatitis is a painful and debilitating condition that commonly develops in patients with a history of several bouts of acute pancreatitis from alcohol ingestion. Other processes leading to chronic pancreatitis are discussed in the next segment of this section. Although pain is the most consistent source of disability from chronic pancreatitis these patients may suffer from weight loss because of anorexia or, in some cases, malabsorption because of pancreatic exocrine insufficiency. Diabetes may develop from loss of pancreatic islets because of ongoing fibrosis and calcification of the gland. Patients with chronic pancreatitis are also at risk for the development of pancreatic cancer.

Research efforts to illuminate causative mechanisms leading to chronic pancreatitis have contributed to an improved understanding of this disease. One mechanism of progression to chronic pancreatitis is suppression of the degradation of trypsin by chymotrypsin. A study by Beer and coauthors\(^47\) in *Gut,* 2013, sought to carry out a functional analysis of chymotrypsin variants to determine which, if any, of these contributed to the development of chronic pancreatitis. The authors evaluated secretion, activity, and degradation in 32 chymotrypsin variants. The analysis showed that less than half the variants were pathogenic and contributed to progression of chronic pancreatitis. The pathogenic chymotrypsin variants contributed to the development of chronic pancreatitis by altering secretion, catalytic activity, and proteolytic stability. The pathogenic variants caused endoplasmic reticulum stress but it did not appear to contribute to the development of chronic pancreatitis. The authors concluded that their dataset could potentially contribute to the identification of pathogenic variants of chymotrypsin.

Pancreatic fibrosis is the major mechanism leading to loss of endocrine and exocrine function in patients with chronic pancreatitis. An article presenting data from a study designed to evaluate a treatment to reverse the development of fibrosis is by Ishiwatari and coauthors\(^48\) in *Gut,* 2013. The authors determined that pancreatic stellate cells contributed to the development of fibrosis and that this abnormality was similar to an abnormality in hepatic stellate cells that contributed to hepatic fibrosis. They had successfully treated hepatic fibrosis with siRNA directed against collagen-specific chaperone protein gp46. The siRNA was encapsulated in vitamin A-coupled liposomes. Administration of the siRNA suppressed collagen deposition and reversed the process of fibrosis in the pancreases of experimental animals. The authors concluded that this treatment showed promise for reversal of fibrosis in chronic pancreatitis.
Early diagnosis of chronic pancreatitis can assist in identifying patients for treatment. An article evaluating endoscopic ultrasound and endoscopic secretin-stimulated pancreatic secretory testing as means of achieving an early diagnosis of chronic pancreatitis is by Albashir and coauthors\(^5\) in the American Journal of Gastroenterology, 2010. The authors report data from 25 patients who underwent endoscopic ultrasound fibrosis scoring and/or endoscopic secretin-stimulated pancreatic secretion testing within 12 months of having a pancreatic resection. Fibrosis scores and results of secretin tests were evaluated in relation to histologic fibrosis assessments conducted by an expert pancreatic pathologist. The authors found that both ultrasound fibrosis scores and secretion testing had sensitivities in the 85% range for the diagnosis of early chronic pancreatitis. Specificity for each test was 100%. When the results of the tests were combined, sensitivity increased to 100%. The authors concluded that endoscopic ultrasound and secretion testing are valuable for the diagnosis of early chronic pancreatitis.

Patients with chronic pancreatitis are known to be at risk for secondary diabetes, nutrient malabsorption, and malignancy. A population-based study to identify precisely the risks for development of comorbid conditions and cancer is by Bang and coauthors\(^6\) in Gastroenterology, 2014. The authors examined data from a Danish national registry. Nearly 12,000 patients (cases) who were diagnosed with chronic pancreatitis were compared with more than 119,000 controls. Data were collected for the interval 1995–2010. During this interval, 46% of the patients died compared with 13% of the controls. Cases had a nearly seven-fold increased risk of pancreatic cancer compared with controls. Cancer was the cause of 11% of deaths occurring in cases compared with 3.3% of controls. Patients had significantly increased risks for pulmonary disease, cerebrovascular disease, and diabetes but not myocardial infarction. The authors concluded that chronic pancreatitis significantly increases risks for pancreatic cancer and comorbid conditions.

The epidemiology of pancreatitis and pancreatic cancer are reviewed in an article by Yadav and Lowenfels\(^7\) in Gastroenterology, 2013. The authors review data indicating that acute pancreatitis due to gallstones is effectively treated with cholecystectomy, which virtually eliminates the risk for development of chronic pancreatitis and pancreatic cancer. Acute pancreatitis from other causes (mainly alcohol ingestion) can lead to chronic pancreatitis and a long-term increased risk of pancreatic cancer. The authors review epidemiologic data that confirm chronic pancreatitis is more likely to affect men, and is more commonly observed in black patients and in patients with non-O blood type. Tobacco use is the most important factor associated with increased risk for pancreatic cancer in patients with chronic pancreatitis. The authors conclude that interventions that have potential value for reducing cancer risk in patients with chronic pancreatitis would be cessation of tobacco use and elimination of alcohol intake.

Additional data on the relationship of chronic pancreatitis and the risk of developing pancreatic cancer are presented in an article by Raimondi and coauthors\(^8\) in Best Practices and Research in Clinical Gastroenterology, 2010. The authors note that the link between chronic pancreatitis and pancreatic cancer is most clearly demonstrated in patients with early onset chronic pancreatitis (e.g., tropical or hereditary pancreatitis). For these patients the lag period between initial diagnosis of pancreatitis and the development of pancreatic cancer averages more than two decades. Pancreatitis with an onset of a year or less before the diagnosis of pancreatic cancer is most likely associated with ductal obstruction from the malignancy. Interestingly, only 5% of patients with chronic pancreatitis will develop pancreatic cancer. Development of pancreatic cancer in patients with chronic pancreatitis is thought to be related to ongoing genetic damage that produces small, pancreatic intraepithelial neoplasms that evolve, over time, into malignant disease.

Screening patients with pancreatic cancer is currently not feasible because of the relatively small incidence of the disease in patients with chronic pancreatitis. The authors conducted a systematic review of the literature to determine if there was any indicator that might identify patients with chronic pancreatitis who are at increased risk for pancreatic cancer. The literature analysis identified the presence of kRAS mutation in pancreatic juice as a possible indicator of increased risk, but study results to date have not consistently shown benefit. Additional research is necessary.

Chronic obstruction of the pancreatic ductal system due to fibrosis is thought to produce ongoing chronic inflammation in the pancreas, which can contribute to
the risk for development of pancreatic cancer. Whether pancreatic surgical procedures designed to relieve obstruction and reduce ongoing inflammation impact the risk of cancer is a question posed in a study by Ueda and coauthors in Surgery, 2013. The authors report results of a nationwide survey conducted in Japan. The study included data on 506 patients who had at least two years of followup after the diagnosis of chronic pancreatitis. The authors emphasize the importance of the two-year follow-up requirement because of the fact that diagnosing pancreatic cancer is challenging in patients with chronic pancreatitis. Thus, patients developing cancer within a short period (1 year or less) after diagnosis probably represent missed diagnoses. Including these patients inflates the risk for developing cancer over long-term followup after the diagnosis of chronic pancreatitis. The authors found that the risk of developing pancreatic cancer in patients with chronic pancreatitis was significantly increased compared with healthy controls. Of interest was the fact that patients treated surgically for chronic pancreatitis had a significantly reduced risk of developing pancreatic cancer. The authors hypothesize that relief of ductal obstruction and reduction of chronic inflammation may reduce tissue damage and the risk of pancreatic cancer.

Practice guidelines for the diagnosis and management of chronic pancreatitis are available from the Society for Surgery of the Alimentary Tract at www.ssat.com. The guidelines note that the incidence of chronic pancreatitis is 5–10/100,000 in the United States. The pain of pancreatitis can be continuous and persistent, intermittent, or postprandial. Upper abdominal pain in the central region of the abdomen with radiation to the back is one of the most typical pain patterns. Pain may be severe; a large proportion of patients with chronic pancreatitis require narcotics for pain relief. Ongoing fibrosis of the gland leads to calcification of the pancreas that is visible on imaging. Development of pseudoaneurysms of the splenic, pancreaticoduodenal, or mesenteric vessels can lead to atypical gastrointestinal bleeding. One cause of pancreatic pain is ductal obstruction from single or multiple strictures. The guidelines note that defined areas of obstruction of the pancreatic duct leading to ductal dilation identify patients who might respond to surgical procedures to relieve the obstruction and the associated pain. Identification of ductal abnormalities and the effective endoscopic and surgical approaches to relieve obstruction are discussed in a later segment of this section. In patients without ductal dilation, pancreatic resection might lead to pain relief. The guidelines emphasize the importance of assessment of quality of life, narcotic use, employment status, and continued alcohol use in order to determine the best approach to managing the symptoms in individual patients. The best results of nonoperative or operative management of chronic pancreatitis are observed in patients who are compliant with enzyme replacement (discussed below) and nutritional programs. Abstinence from alcohol and controlled narcotic use is also important in achieving therapeutic success. Regarding the risk of pancreatic cancer, the guidelines note that marked elevations of serum levels of CA 19-9 in patients who are not jaundiced is a finding that should raise suspicion for developing pancreatic cancer.

Specific subtypes of chronic pancreatitis

Two specific subtypes of chronic pancreatitis not from alcohol or biliary tract disease are discussed here. In each of these conditions, the definition of chronic pancreatitis is important because these patients commonly present with intermittent attacks of pain rather than constant pain. It is tempting, therefore, to classify the episodes of pain as recurrent acute pancreatitis rather than chronic pancreatitis. Classifying the patients as recurrent acute pancreatitis results from the fact that this subgroup does not develop pancreatic calcifications and exocrine and endocrine insufficiency of the pancreas may not be a prominent component of the clinical presentation.

Autoimmune pancreatitis

Chronic pancreatitis associated with clinical, laboratory, imaging, and biopsy evidence of autoimmune disease fulfills criteria for the diagnosis of autoimmune chronic pancreatitis. Resolution of symptoms and pancreatic mass lesions with corticosteroid therapy confirms the diagnosis. A small proportion of patients develop severe fibrotic scarring of the pancreas and these patients may be candidates for surgical therapy. A review of autoimmune pancreatitis presenting with symptoms and signs of acute pancreatitis was included in the first issue in
Chronic pancreatitis | BILIARY TRACT & PANCREATE, PART II

The two-issue series focusing on surgical diseases of the biliary tract and pancreas. At this time, we will discuss information pertinent to the diagnosis and management of autoimmune pancreatitis presenting with signs and symptoms of chronic pancreatitis.

The first article discussed is by Finkelberg and coauthors in the New England Journal of Medicine, 2006. The authors open their review by stressing that autoimmune chronic pancreatitis is a heterogeneous disease associated with duct abnormalities, pancreatic masses, diffuse glandular sclerosis, and cholangitis. They note that the disease is uncommon. A report cited in the article estimates that 11% of patients with pancreatitis will have evidence of autoimmune disease. Clinical and biochemical confirmation of the diagnosis is present in 40% of patients considered to have the disease. The disease is diagnosed in men more often than in women and most patients are older than 50 years of age.

The exact pathogenesis of autoimmune pancreatitis is unclear. Abnormalities of HLA haplotype as well as autoantibodies against carbonic anhydrase and lactoferrin have been identified in patients diagnosed with autoimmune pancreatitis. Hypergammaglobulinemia is common and IgG4 antibodies have been identified. Whether these are primary causes or secondary responses to the disease is unclear. Experimental evidence cited by the authors documents the appearance of histologic changes of autoimmune pancreatitis in animals immunized against carbonic anhydrase and lactoferrin. Both of these substances are found in the cells of organs commonly involved in autoimmune disease, such as the kidney, lung, and biliary tract. The authors also cite data confirming that patients diagnosed with autoimmune pancreatitis have elevated numbers of CD4+ T-lymphocytes in peripheral blood samples. Experimental evidence cited in the article documents the development of autoimmune pancreatitis in animals injected with amylase-sensitized CD4+ T-lymphocytes. Pathologically, the most common characteristic of autoimmune pancreatitis is a periductal lymphocytic and plasma cell “collar.” Similar lesions are often found in the gallbladder, renal tubules, and lung.

Clinical manifestations of autoimmune pancreatitis most often include jaundice and abdominal pain. Episodic severe abdominal pain characteristic of acute pancreatitis is a rare clinical finding. Nearly 20% of patients will have associated ulcerative colitis or Crohn’s disease. Endoscopic retrograde cholangiopancreatography (ERCP) examination will frequently disclose a long, smooth stricture of the pancreatic duct. The authors point out that differentiation of autoimmune pancreatitis from other conditions causing ductal strictures is possible because of the appearance of ductal stricture. In other disorders the strictures are multiple and short compared with the long, smooth strictures of autoimmune pancreatitis.

CT imaging of patients with autoimmune pancreatitis will disclose a sausage-shaped, homogeneous enlargement of the pancreas with surrounding enlarged lymph nodes. Involution of the tail of the gland is commonly observed. ERCP will disclose ductal stricture with loss of right-angle duct branches. Histologic diagnosis can be confirmed with needle biopsy guided by endoscopic ultrasonography. Data cited by the authors indicate that typical imaging and histologic findings, combined with a response to corticosteroid treatment, has been suggested as a criterion for diagnosis of autoimmune pancreatitis.

A table listing the diagnostic criteria for autoimmune pancreatitis promulgated by the Japan Pancreas Society is included with the article and is reproduced as Figure 4. When a patient has the appropriate clinical, laboratory, and histologic criteria for the diagnosis of autoimmune pancreatitis, a course of corticosteroid therapy is indicated. Resolution of CT imaging findings, especially complete disappearance of any pancreatic mass on imaging two to four weeks after beginning corticosteroid therapy, provides confirmation of the diagnosis. Because malignant pancreatic masses can diminish in size during corticosteroid therapy, Finkelberg and colleagues stress that complete resolution of CT imaging findings is important. Finkelberg and associates provide a diagnostic and treatment algorithm for management of autoimmune pancreatitis. They note that surgical excision of suspicious masses is an acceptable approach for patients without typical histologic findings on needle biopsy. If histologic confirmation of autoimmune pancreatitis is found on pathologic examination of the excised tissue, corticosteroid therapy can be instituted. The diagnostic and treatment algorithm is reproduced as Figure 5.

Additional data relevant to the management of patients suspected of having autoimmune pancreatitis, presenting with a discrete mass suspicious for malignancy, are
presented by Asbun and coauthors in Surgery, 2014. The authors report consensus findings from a panel of experienced pancreatic surgeons. They note no malignancy is found in 5%–13% of patients who undergo pancreatoduodenectomy for a suspicious pancreatic mass. Histologic evidence of autoimmune pancreatitis is discovered in up to 43% of such patients. The authors report that their panel agreed that techniques to confirm the presence of malignancy, such as needle aspiration biopsy, endoscopic ultrasound guided biopsy, and ductal brushings obtained at the time of ERCP, are specific, but lack sensitivity, are operator dependent, and expensive. The panel reached agreement that histologic proof of pancreas cancer is not absolutely necessary before proceeding to pancreatectomy, but significant evidence of autoimmune pancreatitis should prompt a short course of corticosteroid therapy to attempt to confirm the diagnosis.

Surgical therapy for autoimmune pancreatitis may be useful for patients with refractory pain and sclerosing pancreatitis localized to resectable portions of the pancreas. An experience with the surgical management of this disease is the focus of an article by Schnelldorfer and coauthors in the Journal of Gastrointestinal Surgery, 2007. The authors reviewed a single-center registry consisting of 161 patients who had undergone operation for chronic pancreatitis. Review of pathologic specimens identified eight patients...
with findings consistent with autoimmune pancreatitis. These patients were asked to complete a survey instrument assessing overall outcomes with an emphasis on pain control, return to work, and satisfactory quality of life. Quality of life was assessed with a standard questionnaire.

All patients had undergone the original operation because of suspicion of pancreatic cancer or disruption of the pancreatic duct. Seven of eight patients were alive and responded to the survey with a mean follow-up interval of more than five years. Five patients noted complete relief of pain or significant improvement in pain status. All five of these patients had returned to work and considered their health status good. Two patients had persistent pain and had been treated with corticosteroids without response. Schnelldorfer and associates note that pain relief for this subgroup of patients with chronic pancreatitis was equivalent to that observed after operation for other forms of chronic pancreatitis. The most common long-term complication observed in these patients was biliary stenosis requiring endoscopic intervention. The one death in this series was in a patient with severe cholangitis and sepsis from biliary stenosis. The authors conclude that pancreatic resection is effective in controlling pain in the majority of patients with autoimmune pancreatitis when scarring and fibrosis are localized to a resectable portion of the gland.

The recognition of two distinct subtypes of autoimmune pancreatitis has improved the accuracy of histologic diagnosis of this disease, reduced the need for surgical intervention, and identified differing patterns of treatment response and recurrence rates for each subtype. Information on outcomes for each subtype is the focus of an article by Hart and coauthors in Gut, 2013. Treatment of relapsing Type 1 autoimmune pancreatitis with this drug achieved maintenance of remission in 10 of 12 (83%) patients. Side effects of treatment were few, and all were minor. The authors conclude that this approach is potentially useful for patients who have persistent relapses of Type 1 autoimmune pancreatitis despite therapy with steroids and immunomodulators.

**Idiopathic chronic pancreatitis**

Idiopathic chronic pancreatitis is discussed in the article by Clain and Pearson in Current Gastroenterology Reports, 2002. The authors stress that efforts to exclude biliary and alcohol etiologies of pancreatitis are central to the diagnostic strategy. A careful history and physical examination supplemented by endoscopic ultrasound and ERCP with bile sampling will assist in establishing the absence of these etiologies of chronic pancreatitis. Some patients with ductal dilation will need to be evaluated for intraductal pancreatic mucinous neoplasm (discussed in detail later). Clain and Pearson stress the recent interest in sphincter of Oddi dysfunction and pancreas divisum as causes of idiopathic acute and chronic pancreatitis. They note that convincing data supporting the use of sphincterotomy and stent placement for relief of pain in patients with idiopathic pancreatitis are not available. As noted previously, establishing the fact that the patient may have chronic rather than recurrent acute pancreatitis will help guide plans for long-term evaluation and management of this group of patients.
Clinical presentation and imaging diagnosis of chronic pancreatitis

As noted in the foregoing discussions, most patients with chronic pancreatitis will present with persistent upper abdominal pain and weight loss. A history of one or more episodes of acute pancreatitis are documented in most patients. Severity of pain is such that narcotic drugs are frequently required for initial management. The overall therapeutic approach is based on the suspected etiology of the pancreatitis, whether the process is diffuse or localized within a portion of the gland, the anatomy of the ductal system as seen on imaging studies, whether pseudocyst is present, and the overall health status of the patient.

Imaging of the pancreas, the pancreatic duct, and the biliary tract are essential to the diagnosis and therapeutic planning for these patients. For a discussion of the use of imaging we turn to an article by Kim and Pickhardt in Surgical Clinics of North America, 2007. The authors caution that conventional CT imaging of the pancreas requires typical changes of fibrosis, atrophy, and calcification of the gland in order to confirm the diagnosis. Patients may have significant pain, weight loss, pancreatic exocrine insufficiency, and endocrine insufficiency without these changes. CT imaging is limited, therefore, in confirming the diagnosis. With progression of the disease, changes occur in the branches of the pancreatic duct and, ultimately, in the main pancreatic duct. These changes then become visible on CT imaging and can be confirmed with ERCP and/or MRI. Overall, CT imaging is useful for evaluating the pancreatic parenchyma. ERCP is most useful for documenting the anatomy of the ductal system. MRI has the potential to demonstrate changes in both the ductal system and the parenchyma. If equipment and expertise in MRI are available, this modality offers an opportunity for a noninvasive evaluation of the pancreatic and biliary ductal system.

The authors note that recent data support the use of MRI with secretin injection to dilate and improve the visualization of the pancreatic duct. No gadolinium contrast material is required for completion of this examination. Secretin injection results in dilation of the pancreatic duct because of its action to cause contraction of the muscle of the sphincter of Oddi. MRI with secretin stimulation provides good visualization of the main pancreatic duct, but is limited in its ability to visualize branch ducts. ERCP is the most useful modality for anatomic definition of the main and branch ducts. Kim and Pickhardt note that MRI and ERCP are useful for assessing the severity of chronic pancreatitis.

Severity scoring is possible using a standard scoring system such as the Cambridge score, which the authors discuss. Imaging can also assist the clinician in determining the presence and severity of complications of chronic pancreatitis. Common complications include pseudocyst formation, pseudoaneurysm formation in adjacent arteries, and splenic vein thrombosis. CT imaging with contrast is the most accurate means of determining size and location of pseudocysts and pseudoaneurysms.

An article focusing on the relationship of pancreatic ductal anatomy to outcomes of complications of acute and chronic pancreatitis is by Nealon and coauthors in the Journal of the American College of Surgeons, 2009. This report is a detailed, retrospective, medical record review of a single-center experience with 563 patients with complications of acute or chronic pancreatitis. The most common complication was pseudocyst formation, which is the focus of the article. The hypothesis of the authors is that spontaneous resolution of pseudocysts can be predicted accurately by the associated anatomy of the pancreatic duct. A secondary hypothesis is that as the anatomic abnormalities of the duct progress, there is a decreasing chance that spontaneous resolution of the pseudocyst will occur. The authors relied on ERCP images for documentation of ductal anatomy. They note that MRI is less invasive and may be preferable in some patients, but the ductal anatomy is often obscured by the pseudocyst and this limits the usefulness of MRI in patients with complications of pancreatitis. In the authors’ classification system, a Type 1 duct is a normal duct and the classification is subcategorized by connection of the pseudocyst to the duct (1B) or not (1A). A Type 2 duct is a strictured duct and is likewise subcategorized. Type 3 ducts have ductal disconnection and Type 4 ducts have changes consistent with chronic pancreatitis. During followup, the authors noted that 87% of Type 1 duct pseudocysts resolved spontaneously compared with only 3% of pseudocysts associated with ductal changes of chronic pancreatitis.
The clinical implication of these data is that most pseudocysts associated with chronic pancreatitis will require decompression. The authors provide data on outcomes of treatment in their patients and note that 142 of 153 patients with findings of chronic pancreatitis required operative intervention. Transpapillary drainage was not attempted in patients with chronic pancreatitis and external drainage was associated with persistent pancreatic fistula in all patients where this was attempted.

The authors note that patients with chronic pancreatitis are at risk for the development of pancreatic cancer. The overall lifetime risk is 4%. Single imaging studies are limited in their ability to diagnose malignant change in the pancreas because of the overlap between the findings of chronic pancreatitis and pancreatic cancer. Both diseases can present with a pancreatic mass and with ductal dilation. Sequential imaging studies, if available, may assist in differentiating the changes of pancreatic cancer and chronic pancreatitis.

Nonoperative management of chronic pancreatitis

Effective nonoperative management of the symptoms of pancreatitis includes pain control, nutritional management, and a strategy for achieving and maintaining abstinence from alcohol. At some point in the management of patients with chronic pancreatitis, a trial of pancreatic enzyme replacement is implemented. An article discussing this approach to the management of pain and nutritional consequences of pancreatic exocrine insufficiency is by Winstead and Wilcox in Pancreatology, 2009. The authors note that strategies for management of pain in patients with chronic pancreatitis are complicated because the cause of the pain has not been clearly identified. Traditionally the pain of pancreatitis has been thought to result from increased intraductal pressure from ductal stricture and obstruction. Data exist, however, that suggest that the pain of chronic pancreatitis may be centrally mediated.

The rationale for use of pancreatic enzyme replacement as a means of controlling the pain of chronic pancreatitis is based on the understanding that extrinsic pancreatic enzyme replacement stimulates receptors in the proximal small intestine that trigger a negative feedback mechanism that depresses pancreatic enzyme secretion and reduces pancreatic ductal pressure. The existence of other mechanisms of pancreatic pain, including perineural fibrosis, colonic hypermotility, and uninhibited cholinergic stimulation of pancreatic secretion, make interpretation of the results of enzyme replacement studies difficult. Of the proposed mechanisms, only colonic hypermotility would potentially respond to enzyme replacement because the hypermotility is perpetuated by steatorrhea resulting from pancreatic exocrine insufficiency.

The authors note that there are nine English language reports of trials of pancreatic enzyme replacement and five of these showed no improvement in pain. The studies are severely limited because of lack of power analyses that would guard against Type 2 statistical errors, failure to assess pain using standard instruments, and the use of crossover experimental designs. Most of the available studies lack strict control for continued alcohol use in the subjects included in the studies. Based on the available data, the authors suggest that clinicians should follow guidelines promulgated by the American Gastroenterological Association that recommend the use of enzyme replacement strategies. Studies documenting control of alcoholism and use of standard pain assessments are needed.

Another report that investigated the use of pancreatic enzyme replacement is by Shafiq and coauthors in Cochrane Database Systematic Reviews, 2009. This report used standard systematic literature review strategies to identify 10 trials involving more than 350 patients. The data reviewed confirm the effectiveness of pancreatic enzyme replacement for reducing fecal fat. The improvement in pain in the studies reviewed favored the use of enzyme replacement, but the improvement in pain scores did not reach statistical significance. The authors recommend that enzyme replacement be used in accordance with available guidelines using the most economical of the available drugs.

Operative management of chronic pancreatitis

Operative intervention can relieve pain in patients with chronic pancreatitis by relieving main and branch-duct obstruction, resecting localized areas of the pancreas that are severely diseased and disconnected from the ductal system, relieving biliary obstruction, and when there is
suspicion of pancreas cancer development, resection using standard techniques. The conceptual foundation of the surgical management of chronic pancreatitis rests on the understanding that debilitating symptoms of chronic pancreatitis (pain, for the most part) are largely because of obstruction of the pancreatic ductal system with resulting increased ductal pressure causing pain.

Total pancreatectomy with islet cell transplantation has emerged as an option for the management of patients with chronic pain and exocrine insufficiency from diffuse fibrosis of the pancreas. Three articles reporting outcomes for total pancreatectomy with islet cell transplantation are discussed at this time. The first article is by Walsh and coauthors in the Journal of Gastrointestinal Surgery, 2012. The authors assessed pain levels, narcotic usage, quality of life, and insulin requirement in a prospective, cohort study that included 20 patients who had total pancreatectomy and islet cell transplantation for chronic pancreatitis. The patients were enrolled over a three-year interval and median followup was 12 months. Most patients reported moderate to severe pain preoperatively. Postoperatively, pain improved with 80% of patients reporting no or mild pain. Of interest is that despite pain improvement, only 30% of patients stopped taking narcotic pain medication. The follow-up data showed that there was significant improvement in all domains of quality of life. Insulin was necessary in 80% of patients.

The second article reviewed is by Morgan and coauthors in the Journal of Gastrointestinal Surgery, 2012. The authors report a retrospective review of data in a prospectively maintained patient database. The study included outcomes data on 33 patients who underwent total or near-total pancreatectomy with islet cell autotransplantation. The authors assessed quality of life and narcotic usage at 6 and 12 months following operation. The data analysis showed that there was improvement (more than 65% improvement) in quality of life in all domains at 6 months. There was no significant additional improvement at 1 year. There was significant reduction in narcotic usage at 6 and 12 months, but only 23% of patients were able to completely discontinue narcotic usage. The authors concluded that extended pancreatic resection with islet cell transplantation was beneficial for patients with debilitating chronic pancreatitis pain.

Hereditary or genetic pancreatitis affects younger patients. Because of this, the risk of debilitating pain and pancreatic cancer is higher compared with chronic pancreatitis from other causes because of the longer duration of disease. The final article reviewed in this section is by Chinnakotla and coauthors in the Journal of the American College of Surgeons, 2014. The authors present long-term outcomes data on patients who underwent total pancreatectomy with islet cell transplantation for hereditary or genetic chronic pancreatitis. The authors report data from 80 patients. The hereditary patients were younger, had longer durations of pancreatitis, higher fibrosis scores, and lower islet yield than patients with pancreatitis from other causes. Despite these adverse circumstances, quality of life improved in all domains assessed. Over nearly 3,000 patient-years of followup, no instances of pancreatic cancer were observed. The authors concluded that patients with hereditary or genetic pancreatitis are good candidates for total pancreatectomy and islet cell transplantation. Operation should be considered early for such patients because of the potential for prevention of pancreatic cancer.

Adequate control of diabetes following total pancreatectomy and islet cell transplantation is related to islet yield in the resected pancreas. Most patients who are candidates for this approach to treatment of chronic pancreatitis have undergone earlier surgery for chronic pancreatitis. The effect of previous operations on the islet yield at the time of total pancreatectomy is the focus of an article by Wang and coauthors in Transplantation, 2013. The authors report islet yield and insulin requirement data from 76 patients who had undergone prior procedures for treatment of chronic pancreatitis prior to total pancreatectomy and islet cell transplantation. Patients who had undergone no procedure or prior endoscopic treatment had the lowest levels of pancreatic fibrosis, the highest islet yields, and the lowest risk for long-term insulin requirements. Patients who had undergone pancreatectoduodenectomy or pancreatic head resection (Beger procedure) had intermittent levels of fibrosis and islet yield. The lowest islet yields were in patients who had undergone distal pancreatectomy. The authors note that this is not surprising because the highest concentration of islet cells is in the mid and distal pancreas. The authors concluded that these data will be helpful in guiding...
choices for patients who have undergone prior pancreatic procedures and are considering total pancreatectomy and islet cell transplantation.

An article reviewing various procedures designed to relieve ductal obstruction is by Andersen and Frey\(^{6,8}\) in *Annals of Surgery*, 2010. The authors open their review with a discussion of the origins of pancreatic pain. They emphasize the role of ductal obstruction, but they stress that the variant of chronic pancreatitis associated with the most severe pain is “small duct disease.” In this variant, there are an increased number of pancreatic sensory nerves and there is damage to these nerves from chronic inflammation. Operations designed for management of chronic pancreatitis and the associated pain are intended to decompress or resect areas of small duct disease. Andersen and Frey cite data indicating that pancreatic C nerve fibers contain substances that can activate the inflammatory process and, as such, the nerves may contribute to ongoing inflammation which perpetuates severe pain in patients with chronic pancreatitis. Resected tissue from chronically inflamed pancreata show areas of microcyst formation and scattered areas of acute ongoing inflammation. These changes contribute to the chronic pain, but there is excellent pain relief after these changes are resected. The damaged tissue contributing to pain in patients with the small duct disease variant of chronic pancreatitis is frequently located in the head of the gland. Pain from dysfunction of the pancreatic sensory nerves is thought to be the main source of pain in patients without evidence of ductal obstruction and ductal hypertension. They report stresses that long-term medical therapy of pain in patients with chronic pancreatitis fails in the majority of patients. Although data cited in the review indicate that long-term medical management of pain is associated with symptom improvement, there is nearly universal pancreatic endocrine insufficiency and the patients are often disabled with a poor quality of life.

The two main categories of operations for chronic pancreatitis are designed to decompress the obstructed ductal system or resect diseased tissue. Resections of portions or the entire pancreas have been used. Andersen and Frey note that procedures directed toward ablating pancreatic sensory nerves have been associated with unsatisfactory results and these are no longer used. The authors emphasize the recent emergence of “hybrid” procedures that include both decompressive and resectional components.

The authors continue their review by recounting the historical development of surgical approaches for chronic pancreatitis. They note that the association of biliary disease with acute and chronic pancreatitis led to the understanding that removal of stones from the biliary tract would benefit patients when these stones were obstructing the pancreatic ductal system. The recognition that not all patients with chronic pancreatitis had biliary tract disease led to efforts to detect and remove stones from the pancreatic ductal system. Several attempts to decompress the pancreatic duct by anastomosing the duct to the intestinal tract failed because the entire duct system was not decompressed. Developed by several surgeons, opening the entire pancreatic duct, from the neck to the tail of the pancreas, with anastomosis to a defunctionalized limb of jejunum, became known as the Puestow procedure. Although relief of pain occurred in more than 80% of patients undergoing the Puestow procedure, failure in the remaining 20% was found to be the result of residual inflammation and ductal obstruction of the pancreatic tissue adjacent to the main duct in the neck, body, and tail of the gland as well as in the head of the pancreas.

The Izbicki modification of the Puestow procedure addresses the obstructed small ducts of the neck, body, and tail of the pancreas by resecting a groove of pancreas that includes the ventral wall of the main duct as well as tissue surrounding the duct. The enteric anastomosis is to pancreatic tissue adjacent to the duct and not to the duct wall itself. The addition of this maneuver to the Puestow procedure improved results, but did not address residual disease and ductal obstruction in the head of the pancreas. Modifications of the Puestow procedure (hybrid procedures referred to previously) developed to address the decompression of small ducts in the head (Frey procedure, Beger procedure).

The next section of the review article discusses the development of nerve interruption procedures for the management of pancreatic pain. The authors note that bilateral thoracic sympathectomy provides short-term relief of pain in patients with chronic pancreatitis, but recurrence of pain and narcotic usage is observed in most
of the patients followed long term. Celiac neurolysis with 50% alcohol has been shown to be effective for the management of patients with pain from pancreatic cancer although this evidence is not strong. Because most of these patients do not survive more than one year, the short-term relief is acceptable. Most clinicians have avoided the use of alcohol neurolysis in patients with pancreatitis and the use of other drugs has been associated with long-term recurrence of pain.

A novel approach to pancreatic denervation was division of the pancreas over the portal vein with division of the splenic artery and splenic vein, followed by complete dissection of the body and tail of the pancreas until the only remaining attachments were to the splenic vessels. A localized resection of the pancreatic head was included in this procedure leaving a small cuff of pancreas attached to the duodenum. Short-term pain relief was reported with this procedure but long-term follow-up data were not reported. Andersen and Frey speculate that the resection of the head of the pancreas was most likely the reason for the reported pain relief in these patients.

The authors next discuss resectional procedures for the management of chronic pancreatitis. They note that pancreaticoduodenectomy has been used for the treatment of chronic pancreatitis for more than 70 years. Progressive improvements in outcomes of pancreaticoduodenectomy have occurred with long-term pain relief now reported to occur in 71%–87% of patients. Operative mortality is generally less than 5%, but troublesome morbidity is observed in more than 40% of patients. Modifications of pancreaticoduodenectomy to reduce morbidity have included the use of the pylorus-preserving approach and several technical maneuvers to reduce pancreatic fistula rates. Distinct benefit of pylorus preservation has not been demonstrated in patients with chronic pancreatitis.

Andersen and Frey discuss two of the most popular “hybrid” procedures for chronic pancreatitis. These procedures seek to relieve pancreatic duct obstruction and combine this approach with resection of localized areas of chronic pancreatic inflammation in the head of the gland. The first procedure discussed is the Beger procedure that includes resection of the pancreatic head up to the duodenal wall and establishes drainage of the distal pancreatic duct with an end-to-end anastomosis of the pancreatic duct to a loop of defunctionalized jejunum. If there is evidence of pancreatic duct obstruction in the remaining pancreatic remnant, a side-to-side pancreatic-jejunal anastomosis can be constructed. The principle technical challenge of the operation is to preserve the blood supply to the duodenum. Careful protection of the gastroduodenal artery trunk is necessary. Clear illustrations of the technique of the Beger procedure are included in the article by Andersen and Frey and readers are encouraged to review these illustrations. New diabetes occurs in up to 20% of patients after the Beger procedure and pain relief is observed in 85% of patients followed for more than five years. Andersen and Frey cite data from several prospective and retrospective reports documenting equivalent short-term outcomes and morbidity for the Beger procedure and conventional pancreaticoduodenectomy.

A report by Diener and coauthors in Annals of Surgery, 2008, presents a systematic review of the available literature and compares effectiveness of the Beger procedure to traditional pancreaticoduodenectomy. Data from four randomized clinical trials and several other reports were analyzed and more than 1,200 patients were included in the analysis. The authors concluded that mortality, perioperative morbidity, and long-term development of endocrine insufficiency were equivalent in the two groups. The data disclosed that hospital length of stay, transfusion volumes, and weight gains were all better in the patients who underwent the Beger procedure. There was a statistically significant superiority of the Beger procedure in the production of long-term pain relief.

The final hybrid procedure discussed by Andersen and Frey is the Frey procedure. This operation combines a lateral pancreatic-jejunosotomy with an excavation of the pancreatic head. The pancreatic head tissue is resected to include all tissue up to the intrapancreatic portion of the common bile duct. The posterior capsule of the neck of the pancreas is preserved. This approach contrasts with conventional pancreaticoduodenectomy and the Beger procedure because the neck of the pancreas is transected in both of these latter operations. The duct of Wirsung to the uncinate process is used as a landmark to improve preservation of the posterior capsule of the neck of the pancreas. The body and tail of the pancreas as well as the excavated portion of the head of the pancreas are...
covered by a side-to-side pancreaticojejunostomy. Modifications of the operation have been reported and these primarily involve variations in the amount of pancreatic head excavated or in the preservation or resection of the ducts of Wirsung to the uncinate process. Comparisons of this procedure and its variants to the Beger procedure have shown less perioperative morbidity and resource consumption with the Frey procedure. Long-term outcomes, in terms of pain control, have been equivalent for the two procedures. The Frey procedure consistently achieves higher quality-of-life scores compared with the Beger procedure.

Long-term pain relief after the Frey procedure is the focus of a retrospective medical record review by Negi and coauthors in *British Journal of Surgery*, 2010. This report presents data on 60 patients who underwent the Frey procedure and were followed for a mean of 6.4 years. Significant partial or complete pain relief was observed in 75% of patients. Pain scores were reduced from a mean of 76 preoperatively to 10 at long-term followup. Failures of pain control were associated with preoperative opiate use, a pattern of continuous pain, and perioperative complications. The authors conclude that the Frey procedure is effective in producing long-term pain relief in patients with chronic pancreatitis.

**Editorial comment:** As understanding of the roles of pancreatic ductal obstruction and localized chronic pancreatic inflammation has progressed, safe and effective operations that combine efforts to relieve pancreatic ductal obstruction with resection of localized foci of chronic inflammation (mostly in the head of the pancreas) have developed. Long-term pain relief is possible in nearly 80% of patients and the safety of the operations, in terms of mortality and morbidity, has been established. Over long-term followup, a significant proportion of patients will develop pancreatic endocrine insufficiency, but likely from continued progression of chronic pancreatitis rather than as a consequence of the operation.

**Endoscopic management of complications of chronic pancreatitis**

Recognition of the role of pancreatic ductal obstruction in the production of complications of chronic pancreatitis and documentation that complications such as pseudocyst formation (discussed in the next section) and biliary obstruction might respond to endoscopic therapy has led to use of ERCP and stenting of biliary and pancreatic duct strictures especially when the strictures are single and located near the ampulla.

The first article reviewed is by Attasaranya and co-authors in *Surgical Clinics of North America*, 2007. The authors provide a detailed review of the available literature. They stress that reports of long-term pain relief in patients treated with endoscopic stenting for chronic pancreatitis associated with ductal stricture are few in number. Most of the available reports are retrospective analyses of small groups of patients followed usually for less than two years. Pain relief was observed in more than 80% of patients in two reports involving fewer than 80 patients. Recurrent pain was observed in more than 30% of patients following stent removal. Patients treated with endoscopy routinely underwent multiple procedures for stent replacement. Endoscopic management of biliary obstruction from chronic pancreatitis was challenging; results were generally inferior to results of surgical bypass for relief of jaundice.

A randomized, prospective trial comparing endoscopic management of chronic pancreatitis to surgical decompression of ductal obstruction is by Cahen and coauthors in the *New England Journal of Medicine*, 2007. These authors randomized 39 patients to receive endoscopic therapy including lithotripsy of pancreatic stones or lateral pancreaticojejunostomy. The authors noted significantly improved pain relief in the patients treated surgically. They hypothesize that pancreatic ductal stenting may provide inferior pain relief because the pancreatic stents might obstruct side branches of the main pancreatic duct and this might lead to persistent pain. They cite data that long-term results of pancreatic duct stenting were effective in one report (cited in the article) because patients were restented “on demand” whenever pain recurred. They note that stenting may be effective only with multiple procedures performed over an extended interval.
Editorial comment: From the information reviewed, it is apparent that endoscopic transpapillary stenting for relief of pain caused by pancreatic ductal stricture is associated with an increased number of procedures and a lower frequency of complete or near complete pain relief. This intervention is appropriate for patients with isolated stricture of the duct near the ampulla and for patients with pain from chronic pancreatitis where operation would be associated with prohibitive risk of death or complications. By contrast, transpapillary drainage may be preferable in patients with chronic pancreatitis complicated by pseudocyst formation with ductal communication and little or no pain. This topic is discussed next.

Management of pseudocysts in patients with chronic pancreatitis

Pseudocysts associated with chronic pancreatitis differ from those observed following an episode of acute pancreatitis in a number of ways. In patients with chronic pancreatitis, pseudocyst formation is often a complication of ductal obstruction. Symptoms accompanying the finding of pancreatic pseudocyst may be caused by the pseudocyst (biliary obstruction, enteric obstruction, gastrointestinal bleeding). Pain accompanying the diagnosis of pseudocyst in patients with chronic pancreatitis can be caused by the pseudocyst or by associated ductal obstruction and/or chronic inflammatory mass.

A systematic review of the literature on the management of pseudocyst is by Cannon and coauthors73 in the Journal of the American College of Surgeons, 2009. Evidence that supports various approaches to the management of pseudocyst in patients with chronic pancreatitis is reviewed. They note the evidence supporting the available recommendations is midrange in quality and further randomized, prospective trials are needed. They stress the importance of assessments of ductal anatomy to determine whether there is a connection from the cyst to the duct.

The patterns of ductal involvement with pseudocyst are described in a review article on the management of pseudocysts by Bergman and Melvin74 in Surgical Clinics of North America, 2007. The review cites a three-level classification system where Type 1 pseudocysts are pseudocysts associated with a normal duct system. Type 2 cysts are associated with ductal stricture and Type 3 cysts are associated with changes in the ductal system consistent with chronic pancreatitis. Bergman and Melvin agree with the assertions in the evidence-based review by Cannon and coauthors73 that careful documentation of ductal anatomy using ERCP and MRI will disclose the connection of the pseudocyst with the ductal system and assist the clinician in selection of an approach to pseudocyst drainage.

Depending on the presence of pain, the approaches available include transpapillary endoscopic stenting for drainage, endoscopic transluminal drainage, open cyst enterostomy, or laparoscopic cyst enterostomy. Bergman and Melvin note that transpapillary drainage with stenting is the usual first-line approach to patients with chronic pancreatitis and a pseudocyst that has a ductal connection. Endoscopic, laparoscopic, or open cyst enterostomy can be used when transpapillary approaches fail or the presence of ductal obstruction prevents the use of this approach. The review of pancreatic ductal disease and the association of various ductal anatomic patterns with complications of pancreatitis was the focus of the article by Nealon and coauthors61 that was discussed earlier in the overview. Nealon’s article proposed a fourth pattern of ductal anatomy in which a section of the main pancreatic duct was disconnected from the remaining duct. For patients with this pattern of ductal anatomy and an associated pseudocyst, endoscopic, laparoscopic, or open cyst-enteric drainage procedures would be appropriate.

External drainage can be used for patients who are poor operative risks because of cysts that have no connection to the ductal system and are, therefore, not amenable to transpapillary drainage with stenting. In patients with pain, management of the pseudocyst can be incorporated into a duct decompression operation (Frey procedure, discussed above) or a pancreatic resection. For resection of pseudocysts localized in the head of the pancreas, Bergman and Melvin prefer the duodenum preserving resection of Beger. They note that pseudocysts that complicate chronic pancreatitis, which do not have a connection to the ductal system, are managed according to symptoms, size of the cyst, and cyst location in high-risk areas such
as the tail of the pancreas near the splenic hilum. They emphasize that cysts adjacent to major vessels and/or the splenic hilum should be excised, if possible, to prevent bleeding.

Cannon and coauthors stress that acute bleeding episodes can be managed with angiographic embolization followed by delayed operation on the pseudocyst. They also note that left-sided portal hypertension caused by splenic vein thrombosis in conjunction with pseudocyst formation in patients with chronic pancreatitis can be effectively managed with distal pancreatectomy and splenectomy with inclusion of the pseudocyst in the resected specimen.

A helpful algorithm summarizing approaches to pancreatic pseudocyst appears in a review by Behrns and Ben David in the Journal of Gastrointestinal Surgery, 2008. The algorithm is reproduced as Figure 6. This article also describes an approach to a pancreatic pseudocyst located in the head of the pancreas and associated with chronic pancreatitis. In patients with chronic pain from chronic pancreatitis, this approach is a modification of the Frey procedure. The operation effectively excises or drains the localized pseudocyst and opens the main pancreatic duct to ensure that areas of obstruction are decompressed. Behrns also provides a valuable description of a method of draining the bile duct into the Roux-en-Y pancreaticojejunostomy in patients with associated obstruction of the distal biliary tract. Readers are encouraged to review this article for details and illustrations of the procedures described.

**Pancreatic fistula**

Pancreatic fistulas may be internal (pancreatic ascites and pleural effusion) or external. External fistulas occur as a result of percutaneous drainage of pseudocysts or peripancreatic fluid collections. External pancreatic fistula is one of the most important complications of operations on the pancreas.

The review of the diagnosis and management of pancreatic fistula begins with a discussion of an article by Morgan and Adams in Surgical Clinics of North America, 2007. The article opens with emphasis on the common features of all types of pancreatic fistula, disruption of the pancreatic duct. Fistulas occurring in the setting of biliary pancreatitis are usually associated with disruption of the duct in the neck of the gland. Postoperative pancreatic fistulas occur where the “hand of man” has been; for example, in the tail of the gland after splenectomy or at the site of pancreaticojejunostomy after procedures for the treatment of pancreatitis or pancreatic neoplasia. Morgan and Adams describe a stepwise approach to pancreatic fistula. They note that peripancreatic fluid collections, pancreatic ascites, and pancreatic pleural effusion can be tolerated for a short period to allow for hemodynamic stabilization, replacement of fluid and electrolytes, and implementation of enteral (preferably) or parenteral nutrition. Clinical evidence of hypoxemia from lung compression from pleural effusion or pressure on the diaphragm or vena cava from ascites may dictate early chest tube drainage or percutaneous external drainage of the area of pancreatic ductal leak in patients with ascites. Percutaneous image-guided techniques are useful for draining peripancreatic fluid collections. The authors note that imaging evidence of a pseudocyst might identify the area of ductal leak. They

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**Figure 6**

Algorithm for management of pancreatic pseudocysts. Reproduced from Behrns and Ben David with permission.
stress that activation of pancreatic secretions may occur in patients with pancreatitis or pancreatic anastomotic leak. Postoperative pancreatic fistula drainage may contain enteric secretions as well. Skin irritation is a result of contact of these secretions, and precautions to protect the skin are needed.

CT imaging and magnetic resonance cholangiopancreatography are useful for documenting the anatomy of the pancreatic fluid collection, confirming the location and anatomic features of a pseudocyst, and defining the pancreatic ductal anatomy. ERCP is valuable because the images can define the anatomy of the pancreatic duct. ERCP has a therapeutic potential as well. Sphincterotomy and ductal stenting can relieve ductal obstruction and reestablish normal enteric drainage for pancreatic secretions. Once pancreatic ductal anatomy has been defined and drainage of secretions has been achieved, spontaneous closure of pancreatic fistula can be expected in more than two-thirds of patients, according to data cited by Morgan and Adams. Adjunctive measures such as octreotide administration may reduce the volume of pancreatic secretions and assist in maintenance of electrolyte balance. Studies of octreotide therapy have documented that the drug does not prevent pancreatic fistula or increase the chance of spontaneous fistula closure.

Operative management of the pancreatic fistula is selected based on the location of the fistula and the cause of the fistula. Fistulas in the body and tail of the pancreas can be managed with distal pancreatectomy. Direct anastomosis of the fistula tract to a defunctionalized loop of intestine is a reasonably safe alternative but is associated with recurrence or with pseudocyst formation from fibrosis of the fistulous tract between the duct and the enteric anastomosis. Internal fistulas can be treated with tube thoracostomy or percutaneous drainage, as appropriate, along with nutritional support and pancreatic “rest” (nothing by mouth).

Endoscopic approaches may be helpful in the management of pancreatic fistula. Placement of stents can normalize the pressure in the duct and reduce the drainage volume. Spontaneous closure can then be facilitated. An article describing results of endoscopic ductal drainage in patients with internal pancreatic fistula is by Pai and coauthors in Gastroenterology, 2009. The report provides data on 15 patients with pancreatic ascites and/or pleural effusion. Nearly two-thirds of the patients had chronic pancreatitis. Endoscopic therapy was placement of a 7F stent via a 5-mm papillotomy. Twenty-eight patients were included in the reported data. Fistulas had been refractory to drainage therapy for a minimum of three weeks prior to endoscopic therapy. Stent placement was successful in all and complete resolution of the pancreatic leak occurred in 26 patients. Stents were removed after five weeks and none of the fistulas recurred over a follow-up interval that averaged 17 months. Complications included severe pain, fever, and infected drainage fluid but there were no deaths after treatment. The authors conclude that the endoscopic approach is safe and effective as the first therapeutic approach for patients with refractory internal pancreatic fistulas.

Morgan and Adams continue their review with a discussion of postoperative pancreatic fistula. Fistula formation occurs in 10%–20% of patients after distal pancreatectomy or pancreaticoduodenectomy. They note a three-level classification system of postoperative pancreatic fistula has been proposed by the International Study Group on Pancreatic Fistula. According to data provided by Morgan and Adams, grade A and B fistulas are usually successfully managed by drainage and supportive care. Grade C fistulas are associated with sepsis and these require aggressive drainage with stabilization using the principles of “damage control” (open incision with vacuum-assisted closure, external and internal pancreatic and biliary drainage). Revision of the pancreatic-enteric anastomosis will usually be required when sepsis is controlled.

Neuroendocrine tumors of the pancreas

Neuroendocrine tumors of the pancreas include functioning and nonfunctioning subtypes. Neuroendocrine tumors are rare neoplasms that involve the pancreas, gastrointestinal tract, and pituitary gland. The tumors frequently metastasize and outcomes have traditionally
been poor, but recent research into the basic metabolic and genetic characteristics of neuroendocrine tumors has identified characteristics of the tumors that may facilitate early diagnosis through tumor markers. Genetic changes in neuroendocrine tumors are associated with favorable responses to drug treatment. Two examples of these lines of research are discussed in this section.

The first article reviewed is by Thorns and coauthors27 in Anticancer Research, 2014. The authors assessed microRNA levels in pancreas tissue, pancreatic islets, neuroendocrine tumor tissue, and in serum. The data analysis showed that microRNA signatures were distinctly different in the three tissue types with virtually no overlap between the groups. When microRNA was assayed in serum of normal volunteers and patients with neuroendocrine tumors, the analysis showed that 13 types of microRNA were more abundant in the serum of patients with neuroendocrine tumors compared with normal volunteers. The authors concluded that microRNA assays may be helpful tumor markers that could facilitate early diagnosis of neuroendocrine tumors.

The second article reviewed is by Ohki and coauthors29 in Proceedings of the National Academy of Sciences, 2014. The authors report studies of the PHLDA3 gene locus. The data from their study shows that this gene undergoes loss of heterozygosity, and also undergoes methylation in patients with neuroendocrine tumors. This “two-hit” phenomenon is associated with rapid growth and progression to metastatic disease. Loss of the protective effect of the PHLDA3 gene suppresses the MEN1 gene, which also contributes to tumor progression. These genetic changes result in loss of repression of the Akt pathway. This event is important because the drug Everolimus works to restore the repression of the Akt pathway and has shown promise in treatment of patients with pancreatic neuroendocrine tumors.

An article that presents data on the effectiveness of Everolimus is by Yao and coauthors28 in the New England Journal of Medicine, 2011. The authors report a randomized, prospective trial comparing Everolimus to placebo in more than 400 patients. The data analysis showed that treatment with Everolimus significantly prolonged median survival in patients with advanced pancreatic neuroendocrine tumors. Functioning neuroendocrine tumors of the pancreas include insulinomas, gastrinomas, VIPomas, somatostatinomas, and glucagonomas. Each of the tumor subtypes presents interesting diagnostic and therapeutic challenges. As with nonfunctioning neuroendocrine tumors, the main objective in the management process is to localize the tumor and then resect it with maximum preservation of functioning pancreatic tissue. Although most of the neuroendocrine tumors are benign, malignant forms do exist. Resection is the most desirable approach for malignant neuroendocrine tumors. If the tumor cannot be resected because of involvement of vital structures or because of metastatic disease, excellent long-term survival can be obtained in most instances by debulking the primary tumor and the metastatic foci. In this section, we review several helpful articles that discuss the biologic behavior, diagnosis, and treatment of pancreatic neuroendocrine tumors.

The first article discussed is a review of the topic of pancreatic neuroendocrine tumors by Abood and coauthors81 in Surgical Clinics of North America, 2009. The authors open the discussion by noting that there are approximately 2,500 cases of pancreatic neuroendocrine tumors occurring in the United States each year. These tumors account for about 2% of pancreatic neoplasms. The peak age at diagnosis is from 30–60 years and the tumors occur in women and men with equal frequency. The authors emphasize that diagnosis of neuroendocrine tumors is often delayed because of the nonspecific nature of the symptoms the tumors cause. Because of the delay in diagnosis, which results because malignant neuroendocrine tumors frequently do not secrete hormones in sufficient quantities to cause typical neuroendocrine syndrome symptoms, many patients with malignant neuroendocrine tumors already have metastatic disease at the initial clinical presentation. Sites of metastasis are most commonly in the liver and occasionally in bone.

Additional information regarding neuroendocrine tumors of the pancreas is found in a review by Davies and Conlon82 in Current Gastroenterology Reports, 2009. The authors note that pancreatic neuroendocrine tumors may be functional or nonfunctional. Functioning tumors present with symptoms consistent with the hormone secreted by the tumor. Nonfunctioning tumors produce
symptoms consistent with the size of the primary (mainly abdominal pain) and the presence of metastatic disease. The cell of origin of pancreatic neuroendocrine tumors is a topic of continuing debate. The tumors may originate from pancreatic islet cells or from pluripotent cells of the pancreatic ductal epithelium. Nonfunctioning pancreatic neuroendocrine tumors do not produce endocrine symptoms, either because they secrete hormones in insufficient quantities to cause symptoms or they secrete an inactive hormone precursor. Davies and Conlon point out that neuroendocrine tumor cells have common histologic characteristics, including cells staining positive for chromogranin A, synaptophysin, and neuron-specific enolase. The authors provide a simplified algorithm for diagnosis and management of pancreatic neuroendocrine tumors. This algorithm is reproduced as Figure 7.

Because the diagnosis of neuroendocrine tumors can be challenging, PET imaging has been suggested as a means for improving diagnostic accuracy. Data relevant to this topic is presented in an article by Haug and co-authors in the Journal of Nuclear Medicine, 2012. The authors reviewed PET images in 104 patients suspected of having neuroendocrine tumors. The data analysis showed that PET imaging had an accuracy that approached 90% for the diagnosis of neuroendocrine tumors. The positive predictive value was 90%. The authors concluded that PET imaging should be an integral part of the diagnostic evaluation of patients with suspected neuroendocrine tumors.

Because of the significant risk of early recurrence of nonfunctioning neuroendocrine tumors that are resected, interest in methods of recurrence prediction has increased. An article reporting a method that makes use of tumor macrophage infiltration as a means of predicting recurrence is by Wei and coauthors in Annals of Surgery, 2014. The authors report a retrospective medical record review of 97 patients seen in a single institution over a 17-year interval. Recurrence occurred after resection in 14% of patients. In 10 patients, recurrence was diagnosed on the first imaging study done 6 months after resection. The authors evaluated the use of the CD68 score that assesses infiltration of tumor tissue by tumor macrophages. The data analysis showed that a high CD68 score was a strong predictor of early tumor recurrence. The authors concluded that these findings could be used to adjust surveillance protocols so that recurrence could be diagnosed at an earlier time after initial resection.

Prediction of prognosis for patients with neuroendocrine tumors is important because reported overall median survivals after diagnosis and initial therapy range from 6 months to 20 years. A second article comparing the two most commonly used prognostic indicators, mitotic count and Ki-67 index, is by Khan and coauthors in the British Journal of Cancer, 2013. The authors determined accuracy of these two prognostic indicators in 285 patients with metastatic neuroendocrine tumors. The data analysis showed that the Ki-67 index was the most accurate prognostic index. The authors also evaluated the cut-off value for Ki-67 index of 2% as a marker for a patient group with a good prognosis. Their analysis suggested that a cut-off of 5% was more appropriate for identification of patients with a good prognosis. Using the cut-off value of 5% accurately identified patients with Grades 1 and 2 tumors.
that were associated with 10-year survivals of near 50% compared to Grades 3 and 4 patients who had near zero 10-year survivals.

An article focusing on the clinical and pathologic characteristics of cystic and solid neuroendocrine tumors is by Koh and coauthors in *Surgery*, 2014. The authors performed a systematic review of the literature and identified seven studies of acceptable quality that compared outcomes of 152 cystic neuroendocrine tumors with 915 solid tumors. The data analysis showed that cystic tumors were less likely to be located in the head and uncinate process of the pancreas and were more likely to be benign than the solid tumors. Cystic tumors were less aggressive than solid tumors. Overall survival was nearly 90% at five years for both tumor types. The authors suggest that cystic tumors, especially small tumors (2 cm or less in diameter) could be treated with pancreas-preserving operations. They concluded that there was insufficient data to determine whether cystic neuroendocrine tumors represented a distinct pathological entity.

As noted above, pancreas preserving excision techniques have been suggested for the management of small neuroendocrine tumors of the pancreas. The management of these tumors is the focus of the next two articles reviewed in this section of the overview. The first article reviewed is by Gaujoux and coauthors in the *Journal of Clinical Endocrinology and Metabolism*, 2013. The authors report outcomes data on 46 patients with asymptomatic, small, nonfunctioning suspected pancreatic neuroendocrine tumors. Patients enrolled in a surveillance program and sequential imaging studies were performed. Most of the tumors were in the pancreatic head. Over the course of the surveillance protocol, six patients had an increase in tumor size of 20% or more. Eight patients underwent surgical procedures to remove the tumor. Five patients chose surgery after enrollment and three patients were operated on because of tumor growth. Procedures included distal pancreatectomy, central pancreatectomy, and tumor enucleation. All tumors were low grade and there was no evidence of nodal metastasis or neurovascular invasion.

The second article reviewed is by Toste and coauthors in the *Journal of Gastrointestinal Surgery*, 2013. These authors retrospectively reviewed a single-center experience with 116 patients who underwent excision of pancreatic neuroendocrine tumors. They found that tumor size of 2 cm or less, negative lymph-node status, younger age, and lower tumor grade were all predictive of improved long-term survival. Overall five-year survival was 84% and 10-year survival was 73%. For lymph-node-negative patients the 10-year survival was 86%. For tumors 2 cm or less in diameter, the rate of lymph-node metastasis was 7.4%. Pancreas-preserving procedures were possible in most patients, but only four patients were treated with enucleation. Pancreatoduodenectomy was performed in 41 patients. The authors concluded that conservative pancreatic resection with lymph-node dissection was an appropriate approach for acceptable-risk patients with small neuroendocrine tumors. The data presented suggest that observation would be an acceptable approach in patients at increased operative risk.

Available data indicate that although lymph-node metastasis is less frequent in patients with small tumors, the identification of lymph-node metastasis has significant implications for long-term prognosis. An article presenting data on the value of regional lymphadenectomy in the management of patients with pancreatic neuroendocrine tumors is by Hashim and coauthors in *Annals of Surgery*, 2014. The authors present outcomes data on 136 patients reviewed retrospectively in a single center seen over an 18-year interval. The authors found that overall incidence of lymph-node metastasis was 38% and lymph-node metastasis was more likely in patients with tumors greater than 1.5 cm in diameter. Overall survival was significantly better in patients who did not have lymph-node metastasis. Of interest was that two patients with tumor size less than 1 mm had lymph-node metastases. Data on length of survival for these patients was not reported separately. The authors conclude that evaluation of regional lymph nodes is an important component of operative therapy for pancreatic neuroendocrine tumors.

With the increasing interest in enucleation and limited resections for small pancreatic neuroendocrine tumors, reports of methods for improving localization of small tumors and reducing the risk of postoperative pancreatic fistula have appeared. Two such articles are reviewed at this time. The first is by Law and coauthors in *Surgical Endoscopy*, 2013. The authors note that placement of a fiducial using endoscopic ultrasound guidance has been shown to be a useful means of localizing mediastinal and pancreatic tumors for stereotactic radiation therapy. These
devices are easily visible using endoscopic ultrasound and the authors hypothesized that these could assist in the localization of small pancreatic neuroendocrine tumors that were amenable to pancreas-preserving procedures. They report experience with two patients who had tumors less than 1 cm in diameter. Fiducial placement was done with endoscopic ultrasound guidance. The devices were successfully located using intraoperative ultrasound and removed completely when the tumor was enucleated. There was no evidence of pancreatitis in the area of fiducial placement. The authors conclude that this is a potentially useful means of improving localization of small neuroendocrine tumors of the pancreas.

The second paper reviewed evaluates the use of nasopancreatic stenting as a means of documenting the relationship of the tumor to the main pancreatic duct and reducing the risk of pancreatic fistula after removal of a small tumor of the pancreas. The article is by Misawa and coauthors91 in the Asian Journal of Endoscopic Surgery, 2013. In a single patient case report, the authors confirm that the stent permitted accurate determination of the relationship of the tumor to the main pancreatic duct. Such documentation has potential value as a means of reducing the risk of ductal injury and pancreatic fistula.

The management of the primary neuroendocrine tumor when there are concomitant unresectable liver metastases is a challenging problem. An article that presents data on this problem is by Bertani and coauthors92 in Surgery, 2014. The authors report experience with 12 patients. The patients were evaluated by a multidisciplinary team. Operation was chosen because of ongoing clinical problems related to the primary tumor (gastric outlet obstruction, bleeding, pancreatitis) that could not be managed nonoperatively, because of symptoms related to functioning tumors, to allow therapies to be focused on the liver metastases, or to potentially improve the effectiveness of pharmacologic therapy. Over the course of followup, the authors found that survival was significantly better in patients who had the primary tumor removed. Whether the patients who had operations might have been better operative risks and better candidates for long-term survival is not reported. The authors hypothesize that tumor debulking might have contributed to the improved survival they observed.

Insulinoma

Davies and Conlon82 note that the first operation for insulinoma was performed in 1927. The tumor was bulky and metastatic disease was present. The first benign insulinoma was successfully resected in 1929 and the patient survived for 20 years with good symptom control. Davies and Conlon mention that most insulinomas are sporadic, but about 5% of patients will develop insulinoma as a component of the MEN-1 syndrome.

Additional detail about the diagnosis and management of insulinoma is found in a review by Mathur and coauthors93 in Surgical Clinics of North America, 2009. Mathur and associates review the clinical diagnosis of insulinoma, noting that symptoms of hypoglycemia include altered consciousness, confusion, seizures, and other symptoms. Hypoglycemia occurs with concurrent hyperinsulinemia. The symptoms are usually ameliorated by food intake. Although most hypoglycemic episodes occur in the fasting state, postprandial hypoglycemia may be present in up to 23% of patients, according to a report by Placzkowski and coauthors94 in the Journal of Clinical Endocrinology and Metabolism, 2009. These authors report a single institution review of medical records. Nearly 150 patients documented to have insulinoma were reviewed.

Postprandial hypoglycemia was the only pattern noted in 6% of patients. Mathur and coauthors93 stress that exogenous insulin administration and several drugs may cause hyperinsulinemia. The origin of hyperinsulinemia from an insulinoma can be confirmed by inability to suppress serum levels of proinsulin with sulfonylurea and by confirmation of elevated levels of peptide C. Because peptide C is a product that remains after conversion of proinsulin to insulin, elevated levels of peptide C indicate an endogenous source of insulin.

Historically, localization of insulinoma was achieved by palpation of the pancreas at operative exploration. Interest in improving preoperative localization has increased as the use of laparoscopic enucleation has become an accepted and effective means of treating insulinoma. Mathur and coauthors93 note that helical CT imaging, ultrasonographic imaging, and somatostatin receptor scintigraphy have permitted successful localization in about 80% of patients. Intraoperative palpation with adjunctive intraoperative ultrasonography has been used when preoperative localization fails.
Methods of localization have included the use of PET scanning, glucagon-like peptide-1 receptor scanning, portal venous sampling for insulin after sequential, selective, injection of calcium into the pancreatic arterial supply, and the use of endoscopic ultrasonography.

Use of PET scanning for insulinoma localization is the topic of an article by Tessier and coauthors in the Journal of Clinical Endocrinology and Metabolism, 2010. These authors reviewed 43 diagnostic imaging procedures performed in 37 patients. Successful localization was achieved in only one patient because uptake of the indicator in the whole pancreas prevented successful imaging. The authors conclude that PET scanning was of limited value for localizing insulinomas. A small series evaluating glucagon-like peptide-1 scintigraphy is reported by Christ and coauthors in the Journal of Clinical Endocrinology and Metabolism, 2009. These authors report data from six patients. Successful preoperative localization was achieved in all six patients. The authors recommended additional study of this method of preoperative localization of insulinomas.

The experience at the National Institutes of Health with localization of insulinomas by selective intraarterial calcium injection, with portal venous sampling for insulin, is reported in an article by Guettier and coauthors in the Journal of Clinical Endocrinology and Metabolism, 2009. The report is a medical record review of 45 patients with clinical and biochemical evidence of insulinoma. Calcium stimulation correctly localized the insulinoma preoperatively in 84% of patients. The false-negative rate was 11% and the false positive rate was 4%. The authors conclude that calcium stimulation is a useful, albeit invasive, measure for localization of insulinoma. The test is more accurate than CT imaging, MRI, and ultrasonography.

The single-center review by Placzkowski and coauthors noted a progressive decline in the number of patients who did not have successful preoperative localization as experience with endoscopic ultrasonography and calcium stimulation increased at their institution. In the most recent interval reviewed, the frequency of “blind” explorations of the pancreas was reduced to zero. The most effective means of localizing the tumors were the invasive procedures, particularly endoscopic ultrasonography and calcium stimulation. Davies and Conlon cite data indicating successful preoperative localization of insulinomas in 98% of instances.

Mathur and coauthors review options for nonoperative management of patients with insulinoma. They note that dietary therapy with consumption of several small meals over the course of each 24-hour period is a useful first step in controlling the symptoms of hypoglycemia. Pharmacologic therapy with diazoxide achieves symptom control, at least temporarily, in about 50% of patients. Use of octreotide is helpful in some patients, but is limited by the development of tachyphylaxis. Other medications used include phenytoin, calcium-channel blockers, beta-blocking drugs, and glucocorticoids. Surgical therapy of insulinoma is also reviewed by Mathur and colleagues. They note that laparoscopic enucleation of the tumor is usually possible if the tumor is benign and can be accurately localized. Pancreatic fistula is the most important perioperative complication and occurs in up to 35% of patients, depending on the report reviewed. Most of the fistulas are successfully managed without reoperation using drainage, nutritional support, and octreotide therapy.

Summaries of clinical series of laparoscopic enucleation for insulinoma are found in reports by Karoliotis and Sgourokis and by Isla and coauthors. In the first report, 12 patients followed prospectively are reviewed. Five patients had laparoscopic procedures and one patient required conversion to an open procedure. All tumors were localized preoperatively or intraoperatively and were successfully removed. No instances of multiple tumors were reported. Pancreatic fistula developed in 20% of the laparoscopic procedures and in 29% of the open procedures. At median followup of over four years, one patient had recurrence of hypoglycemia that was successfully managed medically. Isla and associates also report a single institution experience with 21 patients. All procedures began laparoscopically, and one conversion to an open procedure was necessary. Pancreatic fistula developed in three patients. No follow-up interval data is given but the authors state that there have been no documented recurrences of hypoglycemia.

Because of the occurrence of multiple tumors, laparoscopic resection is not recommended for patients with insulinoma associated with the MEN-1 syndrome. A dis-
Discussion of the management of insulinoma in this patient group is found in a review by Akerstrom in Surgical Clinics of North America, 2009. Data cited in this review support the use of enucleation of insulinomas in the head of the pancreas with distal pancreatectomy performed at the initial procedure to achieve optimum protection against tumor recurrence. For the occasional patient with recurrent, multiple insulinomas from MEN-1, resection of the residual pancreas and duodenum may be indicated. Acceptable mortality, morbidity, and long-term outcomes have been achieved, according to a report by Gauger and coauthors. Outcomes of surgical therapy for insulinoma are excellent with control of hypoglycemic episodes in more than 95% of patients. During follow-up intervals of more than 10 years, recurrence of symptoms is observed in some patients but medical therapy is usually effective in managing recurrences.

Mathur and coauthors move on to the management of malignant insulinomas. They review data indicating that overall survival for surgically resected malignant insulinomas exceeds 60% with 10-year survivals of more than 30%. Recurrence of symptoms is observed in approximately 85% of patients followed long term. Recurrent tumors are frequently multiple, suggesting associated MEN-1 syndrome. For patients with unresectable metastatic disease, chemotherapy, and biotherapy using somatostatin and interferon offer opportunity for reasonable palliation. For patients with multiple hepatic tumors, chemoembolization and ablative therapy with radiofrequency ablation or cryoablation may be helpful.

Gastrinomas

A useful review of the history of diagnosis and management of gastrinoma is by Yeung and Pasieka in the Journal of Surgical Oncology, 2009. The authors note that the first report of a pancreatic tumor associated with gastroduodenal ulcer disease was in 1946. In 1955, Zollinger and Ellison reported two patients with fulminant gastroduodenal ulcer disease and pancreatic and duodenal tumors. One of these patients likely had MEN-1 syndrome. In 1956 the syndrome of severe gastroduodenal ulcer disease, with associated pancreatic and duodenal tumors, was named the Zollinger-Ellison syndrome. For more than 20 years after these original observations, the focus of therapy was reduction of gastric acid secretion with total gastrectomy. After the discovery that the hormone secreted by the tumors was gastrin, and that the tumors could be localized to the pancreas and duodenum, the focus of management changed to surgical resection of the hormonally active tumors. Surgical resection is effective, even in malignant tumors with metastases. Localizing tumors in the duodenal wall remains a challenge.

Aboud and coauthors note that the majority of gastrinomas are sporadic. About 20% of these tumors will be associated with MEN-1 syndrome. As with other MEN-1 tumors, multicentricity is common. Data cited in the review indicate that a significant proportion of gastrinomas are malignant and have metastases documented at the time of the original operation. Long-term survival is good, however, with many series reporting 10-year survivals of more than 90%.

A useful review of the topic of gastrinoma is by Morrow and Norton in Surgical Clinics of North America, 2009. The authors note that the traditional clinical presentation of the Zollinger-Ellison syndrome (gastrointestinal ulceration in the jejunum and a non-beta cell pancreatic islet tumor) has evolved over time. Most patients in current series present with abdominal pain, diarrhea, heartburn, nausea, and weight loss. Because these symptoms are associated with a variety of gastrointestinal disorders, delays in diagnosis averaging more than five years are common in current reports reviewed by these authors. Data cited by Morrow and Norton indicate that gastrinoma associated with MEN-1 syndrome is more likely to present with esophageal symptoms. The authors also cite data that the widespread use of proton-pump inhibitors may be contributing to the delay in diagnosis. They stress that suspicion of gastrinoma should be increased when patients present with recurrent abdominal pain, diarrhea, and weight loss, especially if these symptoms are associated with refractory ulcer disease. The diagnosis is confirmed by documenting a marked increase (more than 10 times normal) of serum gastrin levels in patients with a gastric pH less than 2.1. Imaging using CT scanning and somatostatin receptor scintigraphy is useful to document the presence of the tumor. Endoscopic ultrasonography added to these two imaging modalities is useful for preoperative localization.
Although laparoscopic approaches are useful for patients with insulinoma, this approach has limited utility in patients with gastrinoma because many gastrinomas are located in the medial wall of the duodenum and are located only by careful palpation via a lateral duodenotomy and the use of intraoperative ultrasonography. Although 90% of gastrinomas are located in the “gastrinoma triangle” (neck of the pancreas, medial wall of the duodenum at the junction of the second and third portions, and the cystic duct) tumors will occur outside of this area, frequently in the duodenal wall. Careful exploration is necessary to assure optimum symptomatic outcomes. Morrow and Norton recommend enucleation of pancreatic and duodenal gastrinomas when possible. Whipple resection has been suggested as a means of controlling duodenal disease. Morrow and Norton note that pancreaticoduodenectomy may offer the hope of complete removal of occult duodenal disease, but the operation has a significant associated morbidity and the altered postoperative anatomy of the upper abdomen makes management of recurrent tumor or metastatic disease difficult. They prefer to use pancreaticoduodenectomy in young, good-risk patients with large pancreatic head tumors.

Morrow and Norton review the components of operative intervention for gastrinoma. The procedure includes open laparotomy, complete mobilization of the pancreas and duodenum, careful palpation of the pancreas, and the adjunctive use of intraoperative ultrasonography. Duodenotomy is indicated in all explorations with palpation of the duodenal wall and examination with ultrasound. Enucleation of all discovered pancreatic and duodenal tumors is indicated. In the few patients where the tumor is not found, excision of the lymph nodes in the region of the pancreas and duodenum may disclose lymph-node primary tumor. If no tumor is discovered after a thorough search, the literature available supports performance of a highly selective vagotomy. The authors note that the cure rate for resection of gastrinomas in patients with MEN-1 approaches zero because of multiplicity of tumors. They cite data in support of tumor resection as a means of reducing the risk of delayed metastasis in malignant tumors. They also note gastrinoma is more easily managed in patients with MEN-1 who undergo parathyroidectomy prior to resection of gastrinoma. The authors note that the reported cure rate for resected sporadic gastrinoma is 60% within a few months after operation. At five years, the cure rate is 40%.

Some patients are candidates for repeat operation for management of recurrent or metastatic gastrinoma. This topic is addressed by Grobmyer and coauthors104 in the Journal of the American College of Surgeons, 2009. In this report, the authors discuss the management of nine patients drawn from a group of 37 patients who underwent primary operation for gastrinoma at their center. These nine patients underwent 15 reoperations for management of recurrent or metastatic gastrinoma. Operations included liver resection and ablation of liver lesions for patients with metastatic disease. Isolated small bowel gastrinomas were excised in two patients. “Biochemical” cure of gastrinoma was achieved in four patients and these patients had extended survivals ranging from four to 12 years. During followup, no patient died of metastatic gastrinoma. The authors recommend that an aggressive approach to reoperation for treatable recurrent or metastatic gastrinoma is an effective tool resulting in long-term patient survival and control of gastrinoma symptoms.

**VIPoma, glucagonoma, and somatostatinoma**

Abood and coauthors81 supply a useful summary of the diagnosis and management of three, rare, pancreatic neuroendocrine tumors: VIPoma, glucagonoma, and somatostatinoma. VIPoma is associated with often debilitating, watery diarrhea. The WHDA syndrome (watery diarrhea, hypochloremia, dehydration, and achlorhydria) is a common presenting clinical pattern in these patients. Elevation of fasting serum levels of vasoactive intestinal peptide above 500 pg/mL, in association with secretory diarrhea, confirms the diagnosis. The mean age of patients with VIPoma is 50 years and there is a slight female predominance. Most VIPomas are located in the pancreas. Commonly, tumors are localized in the distal left pancreas, and distal pancreatectomy can be used to manage these patients. Treatment of the diarrhea preoperatively with octreotide will result in patient stabilization and a safer operation. Metastatic disease is present in up to 50% of patients at the time of the initial operation.
Glucagonoma is a very rare pancreatic tumor presenting clinically with “4D syndrome” (type 2 diabetes, deep venous thrombosis, depression, and dermatitis). Most patients present with large tumors located in the tail of the pancreas with frequent lymph node and distant metastasis. The clinical symptoms typically result in weight loss that may require preoperative nutritional support. Distal pancreatectomy and postoperative octreotide therapy are effective treatment measures.

Patients with somatostatinoma present clinically with the “somatostatinoma syndrome” (type 2 diabetes mellitus, hypochlorhydria, steatorrhea, and cholelithiasis). Somatostatinoma syndrome is most often encountered in patients with pancreatic tumors. Patients with duodenal tumors frequently have associated Von Recklinghausen syndrome. Large pancreatic and duodenal tumors require pancreaticoduodenectomy. Although nearly half of patients with this tumor will have metastatic disease at the time of initial operation, the five-year survival, even with metastases, is 60%. In completely resected patients without metastatic foci, the five-year survival is 100%.

An article presenting data on the effectiveness of an anti-somatostatin drug on outcomes of metastatic somatostatinoma is by Caplin and coauthors in the New England Journal of Medicine, 2014. The authors report a randomized, prospective, double blind trial evaluating the anti-somatostatin drug lanreotide. They enrolled 204 patients. Nearly all the enrolled patients had no tumor progression in the three months prior to enrollment. All tumors were low grade (Ki-67 index < 10%). The analysis showed that progression-free survival was significantly better in the patients treated with lanreotide. The only adverse side effect observed was diarrhea in 26% of the treated patients. The authors concluded that lanreotide was beneficial in the management of patients with metastatic somatostatinoma.

Pancreatic cystic and mucinous neoplasms

In this section of the overview, we review articles on cystic and mucinous neoplasms of the pancreas. Interestingly, mucinous neoplasms can have cystic and solid components. In addition, there are cystic neoplasms that are separate entities with varying risk of malignancy. Both benign or malignant neoplasms are discussed. The risk of progression of a benign lesions to malignancy, as well as the risk of developing a pancreatic cancer associated with a preexisting cystic or mucinous neoplasm, are topics debated in the literature. This subject is important because small lesions could potentially be observed with imaging or treated with pancreas-preserving resections if dependable evidence that the lesion is benign and the risk of progression is low can be confirmed. We open the discussion with a review of cystic neoplasia of the pancreas.

Cystic neoplasms of the pancreas

The first article discussed is by Kimura and coauthors in Pancreas, 2012. The authors note that serous cystic neoplasms of the pancreas consist of clusters of cysts filled with clear fluid. The lesions are termed microcystic or macrocystic depending on the size of the cyst components of the tumor; a solid variant is included in the lesion classification. A drawing illustrating the various lesion types is reproduced as Figure 8. There has been debate
about the risk of progression of serous cystic neoplasia to malignancy; in this article, the authors report a multi-institutional trial organized by the Japan Pancreas Society to attempt to answer this question. Data on 172 patients with serous cystic neoplasia were analyzed. Nearly 60% of patients had the microcystic tumor type. Solid tumors were observed in 3.5% of patients. Symptomatic tumors (pain, palpable mass) were more likely to be macrocystic or mixed-type lesions. Diagnosis of serous cystic neoplasm was best achieved using endoscopic ultrasonography to demonstrate the “honeycomb” appearance of the lesion. Surgical resection was carried out on all tumors that were 4 cm or more in diameter. Liver metastases were discovered in two of these patients. Despite the presence of liver metastases, there was no tumor related death observed over long-term followup extending to nearly 20 years. The authors conclude that malignancy is rare in patients with serous cystic neoplasia (approximately 1% of patients) and that outcomes are good even when metastasis is diagnosed. The authors recommend excision of tumors 4 cm in diameter or larger or when tumors are symptomatic.

Data from a study of growth rates of pancreatic serous cystic neoplasia provides a contrasting viewpoint on the use of tumor size to determine the need for operative treatment. Results are presented in an article by Malleo and coauthors in Gut, 2012. The authors report results of tumor size monitoring using sequential MRI in 145 patients with asymptomatic pancreatic serous cystic neoplasms. The data analysis showed that significant growth was not observed (growth rate less than 0.1 cm/year) for the first seven years of observation. After seven years, growth rate increased to 0.6 cm/year. A macrocystic or mixed-type appearance on imaging and the presence of other malignant neoplasms were predictors of increased growth. Tumor size at the time of diagnosis was not related to subsequent tumor growth.

The authors conclude that tumor size should not be used to determine the need for operation in asymptomatic patients. They recommend sequential MRI at two-year intervals with surgical excision recommended if tumor growth occurs or if the patient becomes symptomatic. Additional data on the use of tumor growth to determine therapeutic strategy for pancreatic serous cystic neoplasia are presented in an article by El-Hayek and coauthors in Surgery, 2013. The authors report long-term follow-up data on 145 patients whose records were extracted from a prospectively maintained database. Diagnosis was made with imaging, endoscopic ultrasound, and/or fine-needle aspiration of cyst fluid. The findings are in agreement with the previously reviewed report. Most of the patients were women in the fifth or sixth decade of life at the time of diagnosis. The authors conclude that tumor doubling required a minimum of 12 years and that development of symptoms is the most common indication for operation. They agree that tumor size at diagnosis should not be used to determine the need for operation.

A review of pancreatic mucinous and cystic neoplasia of the pancreas is by Verbesey and Munson in Surgical Clinics of North America, 2010. The authors open the review by noting that most cystic neoplasms of the pancreas are asymptomatic and are discovered when abdominal imaging is used for evaluation of an unrelated complaint or diagnosis. Most of the involved patients are women, who are, on average, more than 60 years of age. Pancreatic cystic neoplasms are commonly found on autopsy studies. One study cited by these authors noted that small cystic lesions of the pancreas were discovered in nearly half of autopsied patients when the entire pancreas was examined.

A valuable review by Turner and Brugge in Current Gastroenterology Reports, 2010, provides an algorithm for the diagnosis and management of pancreatic cystic neoplasms. This algorithm is reproduced as Figure 9. Turner and Brugge note that the three varieties of pancreatic cystic lesions include inflammatory (pseudocysts, discussed previously), serous cysts (almost always benign), and mucinous cysts (premalignant or malignant). The authors note that a history of pancreatitis is helpful in determining whether a cystic lesion is a pseudocyst or not. They stress, however, that intraductal pancreatic mucinous neoplasms are frequently associated with mild forms of pancreatitis making differentiation a challenge. Clinical predictors of malignant cysts include jaundice, elevated transaminase levels, and older age. Other data cited by these authors document malignant histology after surgical resection of cystic lesions in 10% of patients clinically asymptomatic.

Imaging of patients with cystic lesions relies primarily on CT and MRI. Pancreatic protocol CT imaging may be very helpful. A microcystic appearance on imaging suggests benign serous cystic neoplasms. ERCP may be
helpful if mucin is visualized at the papilla. Cyst fluid analysis is useful for determining the nature of the lesion. Endoscopic ultrasonography is a valuable adjunct to locate the cyst for needle aspiration. The presence of cells that can be evaluated microscopically, elevated CA 19-9 levels, and DNA analysis of fluid will assist in differentiating serous from mucinous lesions.

Data on the results of management of all types of cystic neoplasia of the pancreas are presented in an article by Talukdar and Reddy in *Clinical Gastroenterology and Hepatology*, 2014. The authors note that the important types of cystic neoplasms of the pancreas include serous cystic tumors, solid pseudopapillary tumors, and mucinous cystic lesions. They include cystic neuroendocrine tumors and intraductal pancreatic mucinous neoplasms in their discussion. (These lesions are discussed in other sections of the overview dealing with neuroendocrine lesions and intraductal mucinous pancreatic neoplasia.)

The authors first review the management of serous cystic neoplasia. They note several studies have recommended that size of the tumor at the time of diagnosis not be used to determine the need for operation. They cite data from other studies that suggest a relationship between tumor diameter more than 6 cm and subsequent rapid growth, and an increased risk of symptomatology. They recommend that these tumors be considered for resection. For small, asymptomatic lesions they recommend imaging at six-month intervals. In their review of solid pseudopapillary lesions, they note that these lesions are noteworthy because they occur most commonly in young patients and have an aggressive pattern of growth and symptom development. A five-year survival of 95% was reported in this group of patients.

These findings are confirmed in a single-center, retrospective analysis of 64 patients by Estrella and coauthors in the *American Journal of Surgical Pathology*, 2014. These authors confirmed the increased incidence of this lesion in young patients with mean age of 33 years. Long-term outcomes of surgical resection are good, with survival rates in the 95% range. Because of the young age of patients with mucinous cystic neoplasia, and the excellent long-term outcomes, surgical excision should be considered at the time of diagnosis. In their discussion of mucinous cystic neoplasia, the authors note that for small lesions with no imaging signs of malignancy (calcification in the wall of the tumor, mass-forming lesions, a nodularity of the tumor capsule), observation can be considered. Surgical resection with lymphadenectomy is recommended for all lesions with imaging findings suggestive of malignancy.

A review of a large clinical experience with resections for pancreatic cystic neoplasia is presented in an article by Valsangkar and coauthors in *Surgery*, 2012. The authors...
present a retrospective analysis of more than 800 patients who underwent surgical excision of pancreatic cystic neoplastic lesions treated over a 33-year interval in a single institution. They note the frequency of operation increased over time as more lesions were discovered incidentally by cross-sectional imaging. The rate of malignancy decreased in parallel with this phenomenon and dropped from more than 40% to 12%. Mucinous cystic neoplasms and serous cystic neoplasms were the most common cystic lesions resected. The authors include intraductal mucinous tumors in this retrospective study (these lesions are discussed in the next section of the overview). The authors report an overall survival rate at five years of 87%, but perioperative complications were observed in 38% of patients. The significant perioperative morbidity prompted the authors to suggest that careful selection criteria (symptoms and lesion size) be included in the decision for surgical therapy.

The final article discussed in this section of the overview is by Kim and coauthors\textsuperscript{14} in Abdominal Imaging, 2013. The authors present data relevant to imaging findings for a rare benign pancreatic cystic neoplasm, lymphoepithelial cyst. The authors note that these lesions consist of pancreatic cysts lined by squamous epithelium and surrounded by lymphoid tissue. The authors report imaging and epidemiologic data on eight patients. They note lymphoepithelial cysts were more likely to be located in peripancreatic locations than other cystic lesions. The lesions were nearly always microlobulated and medium-sized. The lesions showed no involvement with the pancreatic ductal system. They were most often diagnosed in men in the 50–70 year age group. There were no instances of diagnosis of malignancy with these lesions. The authors confirmed that these lesions are benign and do not require resection unless symptomatic.

**Intraductal pancreatic mucinous neoplasm**

Intraductal pancreatic mucinous neoplasms (IPMN) include a variety of neoplastic lesions that can be benign or malignant and may be cystic or solid. Their biologic behavior varies, in part, based on the relationship of the lesion(s) to the pancreatic ductal system.

Consensus guidelines for the diagnosis and management of IPMN have been promulgated by the International Association of Pancreatologists and are presented in an article by Tanaka and coauthors\textsuperscript{15} published in Pancreatology, 2012. The guidelines recommend that main-duct lesions be classified based on the diameter of the main pancreatic duct. Dilation of the duct more than 5 mm but less than 10 mm is termed a “worrisome feature.” Dilation more than 10 mm is defined as “high-risk” finding. The guidelines note that worrisome features on imaging (CT or MRCP) include thickening and nodularity of the duct walls. If a cystic lesion is present, diameter more than 3 cm and wall nodularity are termed “high-risk stigmata.”

Recent data suggest that endoscopic ultrasound may be useful for diagnosis of IPMN and detection of malignant change in the primary lesion and/or associated pancreatic carcinoma. An article presenting data in support of this approach is by Kamata and coauthors\textsuperscript{16} in Endoscopy, 2014. The authors report data on 167 patients followed prospectively. Endoscopic ultrasound was superior to cross-sectional imaging for initial diagnosis. In lesions selected for imaging surveillance, the incidence of cancer diagnosis was 4% at 5 years and 9% at 10 years. At all time intervals, endoscopic ultrasound was superior to other imaging modalities for diagnosis of pancreatic cancer. The guidelines note resection is recommended for all lesions in the “high-risk” category. The guidelines recommend resection of all main-duct lesions and for any branch-duct lesion that is associated with dilation more than 3 cm and any worrisome feature or high-risk stigmata. Conservative pancreas resections using central pancreatectomy or enucleation (see later discussion) can be considered for small lesions. The guidelines note that noninvasive lesions require no formal followup. Surveillance of malignant lesions for recurrence can be done with imaging based on margin status. Negative margins can be followed with imaging at two and five years. Patients with positive margins undergo imaging at six-month intervals.

A study designed to test the validity of the consensus guidelines is by Jang and coauthors\textsuperscript{17} in the British Journal of Surgery, 2014. The authors examined data from a prospectively maintained database, including 350 patients with histologic diagnosis of IPMN. The authors found that the sensitivity and balanced accuracy for the new guidelines were slightly improved compared with the old guidelines were slightly improved compared with the old.
guidelines. These improvements came with a slight reduction in specificity for the new guidelines. The analysis showed that duct diameter, the presence of mural nodules visible on imaging, and CA 19-9 levels > 37 units/mL were all strong predictors of malignancy. In the discussion section of their article, the authors emphasize that CA 19-9 levels did not have sufficient sensitivity to be used as diagnostic tools without complementary imaging. They suggest that diagnosis and assessment of the risk of malignancy be achieved using a personalized, single-patient-specific approach to imaging and assessment of tumor markers.

Because the goal of therapy for main-duct and branch-duct IPMN is to tailor therapy based on the risk of malignancy, assessment of risk requires knowledge of the natural history of these lesions. An article reviewing the natural history of main-duct IPMN is by Roch and coauthors in *Annals of Surgery*, 2014. This article is provided as a full-text reprint accompanying some formats of *SRGS*. The authors report long-term follow-up data on 503 patients assigned to nonoperative therapy based on the presence of severe comorbidities or because of patient choice. Nonoperative therapy was chosen because of minimal ductal dilation in 7% of patients. The data analysis showed that the risk of progression to cancer over the first seven years of followup was 13%. Main-duct dilation at diagnosis, the development of significant dilation, elevated CA19-9, and elevated alkaline phosphatase predicted the development of cancer. The authors recommend careful selection of patients for nonoperative therapy and use of predictive factors to determine indications for resection during followup. The data showed the development of one predictive factor indicated increased risk of cancer development, and the emergence of a second factor increased risk markedly during followup.

The development of pancreatic ductal carcinoma from IPMN occurs in a small proportion of patients and can be predicted by main-duct involvement, main-duct dilation, and tumor markers such S100A4, p53, and CD24. Comparison of tumor characteristics and natural history for pancreatic adenocarcinoma and pancreatic cancer diagnosed in association with IPMN is the focus of an article by Kang and coauthors in *Pancreas*, 2013. The authors report tumor marker and survival data from 59 patients. There were 35 patients with minimally invasive IPMN or invasive IPMN and 24 patients with IMPN and an associated pancreatic ductal carcinoma. The data analysis showed that the pancreatic ductal carcinoma, in association with IPMN, had biologic behavior and tumor marker characteristics similar to spontaneous pancreatic cancers. The data analysis suggests that while pancreatic cancer can develop through progression of IPMN, pancreatic cancer associated with IPMN is a distinct entity with biologic characteristics similar to spontaneous pancreatic malignancy.

Additional data on the risk of progression to malignancy in patients with IPMN are presented in an article by Correa-Gallego and coauthors in *Annals of Surgical Oncology*, 2013. The authors present data from a group of 219 patients who underwent resection for main-duct or branch-duct IPMN. Preoperative imaging studies were reviewed by a hepatobiliary radiologist blinded to the ultimate outcomes data. The data analysis showed that the risk for high-grade dysplasia was 15% for branch-duct lesions and 33% for main duct-lesions. Invasive carcinoma was found in 15% of branch-duct lesions and 41% of main-duct lesions. Data analysis further indicated patients with a history of weight loss and a solid tumor appearance of the lesion on imaging had an increased risk of high-grade dysplasia and invasive carcinoma in branch-duct lesions. For main-duct lesions, male gender and a prior history of malignancy were additional risk factors. It should be noted that there is a risk of selection bias in this study. Because all patients were resected, they were probably at increased risk of malignancy based on clinical and imaging features.

For branch-duct IPMN, observation is recommended for small lesions (less than 3 cm diameter). Recent guidelines recommend observation for branch-duct lesions with larger diameter (4 cm or larger). An article examining the safety of this recommendation is by Sahora and coauthors in *Annals of Surgery*, 2013. The authors report long-term follow-up data on 562 patients. The data analysis showed that the risk of development of cancer in lesions 3 cm or less over the course of five years of followup was 6%, while the risk increased to 9% in patients with lesions more than 4 cm in diameter. The authors concluded that branch-duct lesions could be safely managed according to the older guidelines, but risk for malignancy increased if the new guideline recommendations were followed.
A sharply contrasting viewpoint is presented in the final article discussed. The article by Fritz and coauthors in *Annals of Surgery*, 2014, focuses on the risk of developing cancer in patients with branch duct IPMN. This article is provided as a full-text reprint accompanying some formats of SRGS. The authors report data from more than 500 patients. Their most important finding was that there was an increased risk of malignancy in patients with branch-duct IPMN regardless of duct size. Twenty-nine percent of patients with preoperative imaging diagnosis of branch-duct IPMN had main-duct involvement on histologic analysis. The authors concluded that malignancy risk is significant in all forms of IPMN and, thus, resection at the time of diagnosis or very careful followup is necessary.

Clinicians must realize that the diagnosis of branch-duct IPMN by imaging is associated with a significant error rate in terms of missing main-duct involvement. Assessment of risk of malignancy should be done with great care. In their discussion, the authors cite data from other clinical series confirming the risk of error in diagnosis on imaging. They note that data from their series and other reports show that malignancy developed in the absence of high-risk stigmata, such as mural nodules. Given these reports of significant imaging error rates, reconsideration of recommendations in existing practice guidelines may be necessary.

Operative management of benign tumors of the pancreas, including low-risk IPMN, is the focus of a review by Morgan and Adams in *Surgical Clinics of North America*, 2010. These authors note CT imaging is used to document lesion size in tumors of the body and tail of the pancreas. In small tumors, lesion size may be further delineated with the assistance of endoscopic ultrasound. Distal pancreatectomy can be accomplished using open or laparoscopic approaches and, for benign lesions, preservation of the spleen is encouraged. Successful splenic preservation is achieved by using a technique that preserves the short gastric vessels. Laparoscopic approaches can be used to enucleate lesions in the distal pancreas. Caution is warranted, however, to make sure that enucleated lesions are not in proximity to the main pancreatic duct. Although pancreatic fistula is a risk, laparoscopic enucleation and resection of benign tumors are reported in several series cited by Morgan and Adams. Overall morbidity (40%) and pancreatic fistula rates (11%) were equivalent for open and laparoscopic procedures. Hospital length of stay, blood loss, and time to complete recovery were all shorter with the laparoscopic approach.

Data supporting the safety of pancreas-preserving procedures, such as central pancreatectomy and enucleation for small pancreatic tumors with a low risk of malignancy, are reported with increasing frequency. An article discussing the potential benefits of central pancreatectomy is by Xu and coauthors in the *European Journal of Surgical Oncology*, 2013. The authors conducted a systematic review of the literature and found nine acceptable studies including more than 700 patients. The included studies compared outcomes of central pancreatectomy compared with distal pancreatectomy. The data analysis showed that central pancreatectomy was associated with a higher overall complication rate, and pancreatic fistula rate, than distal pancreatectomy. Perioperative mortality, hospital length of stay, and overall long-term mortality were equivalent for the two procedures. Over long-term followup, distal pancreatectomy had a significantly higher risk for pancreatic exocrine insufficiency compared with central pancreatectomy.

An article presenting outcomes data for enucleation of small pancreatic lesions is by Cauley and coauthors in *The Journal of Gastrointestinal Surgery*, 2012. This article is provided as a full-text reprint accompanying some formats of SRGS. The authors compared outcomes in 45 patients undergoing enucleation of small pancreatic lesions (mean diameter 2.8 cm) compared with outcomes in patients undergoing pancreatoduodenectomy (n=38) or distal pancreatectomy (n=52). The data analysis showed that operative time was shorter and there was less blood loss in patients undergoing enucleation. Enucleation patients had a significantly reduced rate of ICU admission. Complication rates, including pancreatic fistula, did not increase in patients undergoing enucleation. Over long-term followup, risks for pancreatic endocrine and exocrine insufficiency were significantly reduced in patients undergoing enucleation. The authors concluded that enucleation was safe and associated with good outcomes in properly selected patients with small lesions.
Pancreatic adenocarcinoma

A clearly written and useful review of pancreatic cancer is by Hidalgo in the *New England Journal of Medicine*, 2010. The review serves as the departure point for the discussion of pancreatic adenocarcinoma. Hidalgo opens the discussion by noting that statistics regarding pancreatic cancer in the United States continue to be pessimistic. The malignancy is the fourth most common cause of cancer death. It is a disease of elderly patients and less than 20% of patients present with potentially curable disease. The overall five-year survival is less than 5% when all patients with the disease are considered. The most compelling risk factor for pancreatic cancer is cigarette smoking. Among smokers, the risk of pancreatic cancer is four-to-five-fold higher compared with nonsmokers. Pancreas cancer tends to cluster in families and evidence supports both genetic and environmental factors that contribute to this risk. Other risk factors include cirrhosis and chronic pancreatitis.

Because clinical data confirm that patients with negative lymph nodes, small tumors, and low-grade tumors have better outcomes than other patient groups, methods for detecting tumors at these early stages would be of significant benefit. Is there an interval where screening for pancreatic cancer might offer an opportunity for early diagnosis? Data relevant to this question are presented by Yachida and coauthors in *Nature*, 2010. The authors performed genome sequencing on pancreatic cancer tissue from seven patients with metastatic disease. They found that the genetic makeup of the metastatic lesions was derived from genetic signatures in the primary tumor tissue. Quantitative analysis of the timing of development of metastatic capability indicated that more than a decade was required for development of malignant genomic characteristics and an additional five years was required for acquisition of metastatic capability. Once metastatic capability was acquired, patient death occurred within two years. The authors concluded that a window for effective screening for pancreatic adenocarcinoma exists if a screening methodology can be developed.

Additional perspective on long-term survival from pancreatic cancer is presented in an article by Sinn and coauthors in the *Journal of Surgical Oncology*, 2013. The authors report long-term survival data gleaned from a randomized, prospective trial of gemcitabine administered following resectional surgery performed with curative intent. The overall five-year survival of patients enrolled in the study was 15%. Of 54 patients who survived five years or longer, tumor tissue specimens were obtained in 39 patients and the diagnosis of pancreatic adenocarcinoma was confirmed in 38 patients on re-review of the histology. Using multivariate logistic regression analysis, the authors identified small tumors, low-grade tumors, negative lymph-node status and active treatment with gemcitabine as strong predictors of long-term survival. The authors concluded that long-term survival is possible in a select group of patients with pancreatic adenocarcinoma.

Hidalgo moves on to a discussion of the biology of pancreatic cancer. He notes that the prevailing theory of pancreatic cancer development is that progressive dysplasia of duct epithelium occurs. Dysplasia is associated with accumulation of kRAS mutations; these genetic abnormalities cause the accumulation of proteins that are “locked” into a formulation that favors the progression of dysplastic epithelium. Hidalgo notes that other genetic abnormalities involving the TP53 gene and the CDKN2A gene are documented. Progressive genetic damage leads to the development of premalignant intraepithelial pancreatic neoplasms (as noted earlier). Hidalgo stresses the importance of the dense surrounding stromal tissue in pancreatic cancer. This layer is more than a mechanical barrier. There is evidence of high quantities of factors that favor proliferation and invasion of cancer cells within the stroma.

An article by Tanaka and coauthors in *Langenbeck’s Archives of Surgery*, 2012, presents perspectives on the role of the dense connective tissue in the process of local recurrence of pancreatic cancer. The authors report data from autopsies of 14 patients gathered from a group of 41 patients who underwent curative surgical resection for pancreatic adenocarcinoma at a single center. The authors found evidence of local recurrence in 36% of patients that was not visible on imaging studies obtained while the patients were alive. A similar proportion of patients with R1 resection had recurrence. Recurrences consisted
of scattered, viable malignant cells encased in fibrotic stromal tissue. The authors hypothesize that the connective tissue stroma is protective of viable cancer cells.

Hidalgo\textsuperscript{26} notes that cancer cells recovered from connective tissue stroma may represent targets for future therapeutic experiments. Finally, the author notes that 1%–5% of pancreatic cancer cells are pancreatic stem cells that have the capacity to self-replicate. These cells are very resistant to radiation and chemotherapeutic agents, which might explain the resistance of pancreatic cancer to many of these therapies. The author goes on to discuss the clinical, laboratory, and imaging measures used to diagnose and stage pancreatic carcinomas. Patients with tumors in the head of the pancreas will frequently present with biliary obstruction and jaundice. He notes that systemic symptoms such as weight loss, deep venous thrombosis, and increasing abdominal girth are seen in significant numbers of patients. The pain of pancreas cancer is dull, continuous, and involves the upper abdomen. Pancreatitis can occur if there is pancreatic ductal obstruction. Tumors that invade the gastric or duodenal wall may present with gastrointestinal hemorrhage. CT imaging will usually confirm the presence of a pancreatic mass, and imaging will provide most of the information needed to determine if the patient is resectable or not.

Resectability is usually defined as a tumor less than 3 cm in diameter without nodal involvement outside of the peripancreatic nodes. Tumors adjacent to the portal vein, splenic vein, or superior mesenteric vein can sometimes be resected along with a portion of the portal vein. Conventional staging systems are used to determine resectability and these are discussed in the next segment. The use of vascular resection in the management of patients with pancreatic cancer is also discussed later in the overview.

Staging of pancreatic cancer uses the American Joint Cancer Staging Committee system. This is a typical TNM staging system. The system is reproduced as Figure 10. Resection is possible in patients with T1, T2, and T3 tumors. Obvious involvement of mesenteric arteries, distant metastases, and involvement of lymphodes other than peripancreatic nodes are contraindications to resection. When the tumor is adjacent to the superior mesenteric or portal vein, resection may be possible. A discussion on portal vein resection with pancreaticoduodenectomy is presented later. The staging system presents overall median survivals for the various T levels of pancreatic adenocarcinomas. The median survival for T1 and T2 tumors approaches two years, while median survival for T3 tumors is just over one year. Outcomes of surgical treatment of pancreatic adenocarcinomas are presented in a subsequent section of this overview.

Operative approaches to pancreatic cancer

In his review, Hidalgo notes that the operation for pancreatic adenocarcinoma will vary depending on the location of the tumor. For lesions in the head of the pancreas, pancreaticoduodenectomy is the operation of choice. Distal pancreatic resections to the left of the head and neck regions of the pancreas are required for tumors in the body and tail of the pancreas.

Because most patients with tumors in the head of the pancreas present with biliary obstruction, the question of the value of preoperative biliary drainage will arise. The presence of cholangitis is a clear indication for biliary drainage. If operation needs to be delayed, biliary drainage may be desirable. The first article is by van der Gaag...
and coauthors\textsuperscript{30} in the *New England Journal of Medicine*, 2010. This article describes a randomized prospective trial conducted in multiple European centers. One hundred six patients were randomized to receive preoperative biliary drainage for four to six weeks before operation and 96 patients were randomized to undergo operation within one week of diagnosis. Biliary drainage was achieved by placing a stent via ERCP. The primary endpoints were the risk for complications of biliary drainage and of operation. Complications were observed in 37% of the patients undergoing immediate operation and in 74% of patients with preoperative biliary drainage. Mortality was not different in the two groups. Complications experienced by patients undergoing immediate operation were mainly pancreatic fistula, wound infection, and repeat laparotomy. Complications related to the biliary drainage procedure included bleeding, pancreatitis, and the need for repeat procedures because of stent malfunction. The authors conclude that preoperative biliary drainage exposes the patient to a significant risk of complications.

An editorial by Baron and Kazorek\textsuperscript{31} accompanied the van der Gaag article. The editorialists point out that the stents used in this study were plastic stents, known to be prone to occlusion. They speculate that the use of self-expanding metal stents or covered stents would have prevented most, if not all, stent occlusions observed in these patients. They further stress that placement of a dependable stent eliminates the necessity to perform formal biliary bypass operations in patients whose cancers are found to be unresectable. Baron and Kazorek recommend that stents be used selectively for patients with cholangitis, intense pruritus, and when operation cannot be scheduled within one week of diagnosis. Biliary drainage would also be indicated for patients who are candidates for neoadjuvant therapy protocols.

Patients who elect enrollment in a neoadjuvant therapy protocol would also be candidates for biliary decompression. At the time of the biliary decompression procedure, a tissue diagnosis could be obtained by examining brushings of the pancreatic duct and bile duct. Alternatively, needle biopsy of the primary tumor mass could be achieved. Eshuis and coauthors\textsuperscript{32} examine the effect of delay of operation on mortality in patients with pancreatic cancer. The patient group examined was the same as in the study by van der Gaag and associates. The authors observed no difference in mortality when patients whose operations were delayed by five weeks or more were compared with patients who underwent operation within a week of diagnosis.

Laparoscopic staging of suspected pancreatic cancer could reduce operative morbidity and assist in selecting patients for curative or palliative radiation therapy or chemotherapy. An article on this topic is by Schnellдорfer and coauthors\textsuperscript{33} in the *Journal of the American College of Surgeons*, 2014. This article is provided as a full-text reprint accompanying some formats of SRGS. The authors report a retrospective medical record review of results of staging laparoscopy using a standard technique for visualizing the peritoneal cavity in 136 patients. The data analysis showed that radiographically occult distant metastasis was discovered at laparotomy in 11% of patients. Staging laparoscopy was associated with an 88% false-negative rate largely because of the presence of metastatic disease on the posterior liver surface, paraduodenal retroperitoneum, the proximal jejunal mesentery, and in the lesser peritoneal sac. The authors conclude that preoperative laparoscopic staging has the potential to be beneficial if an extended examination of the high-risk areas noted above using advanced techniques is used to lower the false-negative rate.

**Pancreaticoduodenectomy for pancreatic head carcinomas**

During the 1990s, reduction of operative mortality for pancreaticoduodenectomy was achieved in several institutions. The achievement of these excellent operative outcomes was the result of a concentration of surgeon and institutional resources on the management of a specific disease. Models such as the one developed at Johns Hopkins Medical institutions provided much needed leadership that permitted institutional focus on other diseases, such as hepatobiliary surgery and esophageal surgery. Three landmark articles from the Johns Hopkins’ group are discussed at this time.

The first article is by Yeo and coauthors\textsuperscript{34} in *Annals of Surgery*, 1997. This article is a retrospective medical record review of 650 patients undergoing pancreaticoduodenectomy for a variety of benign and malignant tumors of the pancreatic head, duodenum, and distal bile duct. The most common tumor was adenocarcinoma of
the head of the pancreas. The authors note that typical pancreaticoduodenectomy was the main operation. Resection of nearby venous structures was done in 4% of patients. Pancreateicojejunostomy was the principle means of restoring pancreatic ductal drainage, although pancreaticogastrostomy was also used. Overall mortality was 1.4% and 190 procedures were completed in sequence without an operative mortality. The main complications were pancreatic fistula, delayed gastric emptying, and wound infection. Reoperation was needed for hemorrhage, abscess, or wound dehiscence in about 3% of patients. Long-term overall median survival approached two years. Factors associated with good long-term survival were no reoperation, duodenal carcinoma, tumor diameter of less than 3 cm, negative lymph nodes, and negative resection margins.

The extent of lymphadenectomy at the time of pancreaticoduodenectomy is the topic of an article by Yeo and coauthors in *Annals of Surgery*, 1999. The authors describe a randomized prospective trial comparing standard pancreaticoduodenectomy with extended pancreaticoduodenectomy (distal gastrectomy and extended retroperitoneal lymphadenectomy). The data disclose that the extended operation can be performed with perioperative mortality and morbidity similar to standard pancreaticoduodenectomy. The extended lymphadenectomy was not associated with a clear survival benefit.

Because a negative resection margin has been associated with improved long-term survival, debate has been ongoing about the need to extend pancreatic resection to achieve a negative margin. An article discussing this issue is by Hernandez and coauthors in *Annals of Surgery*, 2009. This article describes a group of 17 patients who underwent extended pancreas resection to achieve negative margins at the site of division of the pancreas after a positive microscopic margin was discovered at initial frozen section analysis. The data disclose that the patients who underwent extended resection had median survivals of 11 months, which was similar to patients who had known positive margins (R1 resections) on formal histologic analysis. Patients with R0 resections (negative margin on frozen section and permanent section) had median survival of 20 months. The authors suggest that a positive margin is an indicator of a more lethal tumor and that extending operation does not result in improved survival.

This topic is further discussed in an editorial by Buchler in *Annals of Surgery*, 2010. The authors note that data has become available that positive pancreatic margins may be associated with different survivals depending on the location of the positive margin. The authors confirm, however, that data on efforts to achieve positive margins has not confirmed survival benefit. The authors agree that a positive resection margin is most likely an indication of a highly lethal tumor type. They note that more research to define the biology of pancreatic cancer is needed.

### Vascular resection with pancreaticoduodenectomy for pancreatic head cancer

In a small proportion of patients undergoing pancreaticoduodenectomy for pancreatic head carcinoma (4% in the Johns Hopkins’ experience, discussed earlier), the only barrier to achieving a margin negative operation is adherence of the tumor to the superior mesenteric or portal vein. Often, this adherence is because of fibrotic adhesion and not tumor invasion. There has been ongoing interest in the effect of adding en bloc resection of the adjacent venous structures to standard pancreaticoduodenectomy in this patient group.

The effect of vascular resection on operative mortality and long-term survival is the focus of an article by Yekebas and coauthors in *Annals of Surgery*, 2008. The article describes experience with 136 patients who underwent resection of adjacent venous structures or mesenteric arterial structures with reconstruction during the course of pancreaticoduodenectomy. The authors note that operative mortality was 4% for both groups. Twenty-three of 77 patients undergoing vascular resection had inflammatory adhesion to the vessels and the remainder had true tumor invasion. Median survival for patients undergoing vascular resection was 15 months. This was superior to patients undergoing palliative therapy. The authors recommend vascular resection in selected patients for improved median survival.

Data confirming the safety of vascular resection and a beneficial effect on long-term survival are found in an article by Muller and coauthors in *Gastroenterology*, 2009. This article supplies data on more than 130 patients who underwent vascular resection in addition to pancre-
aticoduodenectomy for pancreatic ductal adenocarcinoma. Operative mortality for the patients who underwent vascular resection was 3.6%, which was equivalent to mortality in patients who did not have vascular resection. The authors found that three-year survival of patients undergoing vascular resection was 14%. They emphasize that vascular resection can be done safely and provides opportunity for improved long-term survival compared to palliative therapy.

With the advent of safe venous resection as a useful technique for improving outcomes of pancreatoduodenectomy, interest in reconstruction of the portal vein using the splenic vein has increased. In some patients, ligation of the splenic vein produces left-sided portal hypertension if the inferior mesenteric vein does not supply adequate portal drainage. Portal hypertension can also occur if there is cavernous transformation of the portal vein that prevents effective drainage after venous resection. Potentially useful approaches for effective management of these situations are reviewed by Christians and coauthors in Surgery, 2013. The authors report results in 11 patients who underwent extended venous resection with distal splenorenal shunt or mesocaval shunt. The data analysis showed that there was no mortality, but significant complications were encountered in four patients. The authors concluded that distal splenorenal shunt or mesocaval shunt are safe approaches to these complex patients and could provide useful strategies for patients who show a significant response to preoperative neoadjuvant therapy for advanced tumors.

Interest has also increased in the use of arterial resection as a means of obtaining potentially curative resections for patients with locally extensive pancreas adenocarcinoma. This topic is the focus of an article by this same group in Surgery, 2014. The authors report results in 10 patients who required arterial reconstruction following extended pancreatic resection. The most common procedure used was a saphenous vein graft between the celiac axis and the common hepatic artery. There was no perioperative mortality and significant complications were observed in 20% of patients. At a median followup of 21 months, 62% of patients were alive and free of disease. The authors concluded that this approach was safe and potentially useful, particularly in patients who have a positive response to neoadjuvant chemotherapy and/or radiotherapy.

Laparoscopic surgery for pancreas cancer

The first article discussed in this section is by Behrens and coauthors in Current Gastroenterology Reports, 2009. The authors provide a summary of the status of laparoscopic operations for pancreatic tumors. They note that preoperative staging laparoscopy has decreased in frequency with improvements in imaging. In experienced hands, laparoscopic pancreaticoduodenectomy is feasible, but it is associated with operative times of more than 10 hours in most cases. An article providing an analysis of clinical experience with laparoscopic pancreatic resection for cancer is by Kooby and Choo in Surgical Clinics of North America, 2010. These authors note that laparoscopic techniques have primarily been used for tumors of the left side of the pancreas. For these lesions, operative time and recovery time are shorter than for open procedures. Early data on oncologic outcomes have shown that the laparoscopic approach is associated with similar results as the open procedures. The authors note that laparoscopic pancreaticoduodenectomy has been reported in only a small number of patients.

An article describing a clinical series of more than 60 patients undergoing total laparoscopic pancreaticoduodenectomy for various pancreatic conditions is by Kendrick and Cusati in Archives of Surgery, 2010. These authors noted operative times averaging six hours, similar to time required for standard pancreaticoduodenectomy. Margin status and lymph nodes resected were similar to open procedures. No survival analysis is provided with this article. The authors recommend randomized controlled trials to compare open with laparoscopic pancreaticoduodenectomy.

Adjuvant and neoadjuvant therapy for pancreas cancer

Yeo and coauthors provide a review of the experience of the Johns Hopkins’ group with postoperative adjuvant chemoradiation therapy following pancreaticoduodenectomy for pancreas cancer. The article compares
three groups of patients. One group chose conventional postoperative chemoradiation therapy with conformal radiation to the area of the pancreas along with 5-fluorouracil. Extensive radiation and chemotherapy (radiation to the liver) was chosen by a second group, and a third group chose no postoperative therapy. Median survival approached 20 months in patients treated with chemoradiation therapy compared with 11 months in patients who did not receive treatment. The authors suggest that postoperative chemoradiation therapy was apparently beneficial in patients undergoing curative resection for pancreatic cancer.

A systematic review of the available literature on postoperative adjuvant chemoradiation therapy for pancreas cancer is by Iott and coauthors in World Journal of Gastroenterology, 2010. The article conducts a systematic review of available literature and concludes that adjuvant chemoradiation therapy provides a significant survival benefit following pancreaticoduodenectomy for pancreas cancer. This benefit was confirmed even though patients receiving adjuvant therapy were more likely to have unfavorable tumors and positive resection margins.

Because of the discouraging outcomes in terms of long-term survival for patients with pancreas cancer, there has been interest in neoadjuvant therapy protocols. An article describing experience with one such protocol is by Ohigashi and coauthors in Annals of Surgery, 2009. This article describes a clinical series of patients treated with preoperative chemoradiation therapy followed by resection of the tumor and postoperative liver perfusion with chemotherapy drugs. Thirty-one patients completed the therapy protocol and had potentially curative resections. Five-year survival in this group was 53%, with the development of local recurrence or liver metastasis in under 10% of patients for each type of recurrence. This encouraging data should stimulate prospective evaluations of neoadjuvant chemoradiation for patients with pancreas cancer.

Overall outcomes for carcinoma of the head of the pancreas

An article examining long-term outcomes of surgical therapy for pancreas cancer is by Schnelldorfer and coauthors in Annals of Surgery, 2008. These authors reviewed a prospectively maintained database containing data on more than 350 patients who underwent surgical treatment for pancreatic head cancer in a single institution. The data disclose five- and 10-year survival rates of 18% and 13%, respectively. These data show roughly equivalent results compared to other large series cited by these authors in the discussion section of the article. The highest five-year survival reported has been near 20%. Data are not given on the use of postoperative adjuvant therapy. The origin of this study was a center with the most experience in postoperative adjuvant therapy, so it is reasonable to conclude that many, if not most, of these patients were treated with postoperative chemoradiation. The authors conclude that five- and 10-year survival does not mean cure was obtained because most of their patients followed for more than 10 years died of recurrent pancreas cancer.

Cancer of the body and tail of the pancreas and metastasis

Surgical approaches for the management of malignancy of the body and tail of the pancreas are discussed in two articles reviewed at this time. The first is by Okada and coauthors in Surgery, 2013. This article describes a clinical series of patients treated with preoperative chemoradiation therapy followed by resection of the tumor and postoperative liver perfusion with chemotherapy drugs. Thirty-one patients completed the therapy protocol and had potentially curative resections. Five-year survival in this group was 53%, with the development of local recurrence or liver metastasis in under 10% of patients for each type of recurrence. This encouraging data should stimulate prospective evaluations of neoadjuvant chemoradiation for patients with pancreas cancer.
to have R0 resections and the one- and two-year survivals for these patients were 81% and 53%, respectively. The authors concluded that extended arterial resection was feasible and safe using their protocol in patients at high risk for histologic involvement of the celiac axis at the root of the splenic artery.

Interest in splenic preservation has increased as a means of avoiding local and delayed systemic infections in patients undergoing distal pancreatectomy. Whether preservation of the splenic artery is necessary in these patients is the question examined by Beane and coauthors150 in the Journal of the American College of Surgeons, 2011. The authors report a retrospective analysis of data from 86 patients who underwent distal pancreatectomy. Splenic preservation with splenic vessel preservation was accomplished in 45 patients and splenic vessel ligation was performed in 41 patients. These two groups of patients had outcomes compared to 86 carefully matched patients who underwent distal pancreatectomy with splenectomy. The data analysis showed that splenic vessel preservation was associated with a lower risk of splenic infarction and pancreatic fistula compared with splenic vessel ligation. There was no significant difference in operative complications in patients with splenic vessel ligation compared with patients who underwent splenectomy. The authors conclude that splenic preservation with splenic vessel preservation was the preferred technique.

Surgical management of cancers of the body and tail of the pancreas is reviewed in a classic article by Brennan and coauthors151 in Annals of Surgery, 1996. This article reviews experience from a single, large cancer center with carcinomas of the body and tail of the pancreas. The authors reviewed nearly 2,000 patients with carcinoma of the pancreas. Overall, nearly one-fourth of the patients with pancreatic head cancer were resectable; only 10% of the patients with carcinoma of the body and tail of the pancreas were resected. Overall median survival (12 months) was similar for both types of tumors. In the discussion included, the authors were asked whether they would be aggressive in removing adjacent organs and vascular structures to achieve complete tumor excision in patients with cancers of the body and tail of the pancreas. The authors indicated that resection of adjacent structures was done if it could be accomplished safely. Estimates were given that results of extensive resection were equivalent to less extensive resection and better when compared with no resectional therapy.

This same group provided additional data on extensive resection in an article by Shoup and coauthors152 in the Journal of Gastrointestinal Surgery, 2003. The authors provide data on 22 patients who underwent extended resection of adjacent organs (other than the spleen) as well as mesenteric veins for cancers of the body and tail of the pancreas. The authors noted that operative times and transfusion volumes were increased compared with patients who did not undergo extended resection. Mortality was equivalent to patients not undergoing extended resection. The authors noted that median survival exceeded 15 months, which was equivalent to patients resected for cure but did not undergo extended resection, and it was significantly better than patients not resected.

A brief review of data on metastatic lesions of the pancreas is provided by Morgan and Adams123 (referred to earlier). They note that metastatic tumors of the pancreas are rare. Most are highly vascular and easily localized with conventional imaging. If metastases are resectable, five-year survivals average more than 35%, with metastases from renal cell carcinoma having the best overall outcomes.

Pancreas transplantation

Whereas kidney, heart, liver, lung, and intestinal transplants are performed with the intent to save the life of the patient, pancreas and islet cell transplantation are performed to provide the patient with an improved quality of life. Freedom from the need for insulin therapy has been shown to significantly improve quality of life. In patients receiving pancreas and kidney pancreas grafts, long-term survival is better compared with survival of patients treated with insulin and patients receiving dialysis as therapy for renal failure.
An article describing the evolution of pancreas transplantation in a single European center is by Ollinger and coauthors in *Annals of Surgery*, 2012. This article is provided as a full-text reprint accompanying some formats of SRGS. The authors review their experience from 1979-2011 and identify factors that contributed to an increase in graft survival from 29% to 81.5%, and achievement of long-term patient survival more than 94%. The authors note that the best outcomes were observed in patients who underwent simultaneous kidney and pancreas transplantation. The authors attribute the improved outcomes to several factors, including a meticulous evaluation for cardiac disease preoperatively that reduced the frequency of cardiac events in transplant patients, improved immunosuppression using anti-thymocyte globulin and tacrolimus, which has greatly reduced acute rejection as well as chronic rejection and thrombotic events involving the grafted organ. The final factor leading to improved results involved improvements in graft selection and graft management, which-reduced the incidence of post-implantation pancreatitis and grafted organ swelling.

This review of pancreas and islet cell transplantation continues with a discussion of a classic article by Sutherland and coauthors in *Annals of Surgery*, 2001. This article is a retrospective review of experience with pancreas transplantation in a single institution over an interval of more than three decades. Case records of 1,194 patients who received a donor pancreas were reviewed. The authors of this article document improvement in clinical results over time and these occurred even though the ages of patients transplanted and the presence of comorbidities, such as cardiovascular disease, increased during the interval studied. They stress that at the time of publication, the results of islet cell transplants were not equivalent to the results of kidney-pancreas or isolated pancreas transplantation. The data reviewed in the article document the prolongation of survival in diabetic patients who receive a pancreas transplant. These benefits were noted in patients with diabetes complicated by nephropathy and neuropathy.

Sutherland and coauthors review factors they believe have led to improved clinical outcomes as well as increased availability of donor organs. These include splitting the donor pancreas to provide transplants to two recipients from one donor, and combining living donor kidney transplantation simultaneous with a cadaver pancreas transplant. Sutherland and colleagues review technical changes that have impacted clinical results of pancreas transplantation. They emphasize the use of bladder drainage of the pancreatic duct so that monitoring of urine amylase levels can be used for early detection of rejection episodes. They acknowledge that complications of bladder drainage do occur and data are cited that conversion to enteric drainage occurs in about 10% of patients. They stress that the most severe immediate surgical complication of pancreas transplantation, graft thrombosis, has decreased as experience has grown. They continue to use posttransplant anticoagulation as a means of decreasing the risk of graft thrombosis. Another technical improvement in pancreas transplantation is the use of portal venous drainage of the transplanted pancreas. Although this creates a more physiologic venous drainage and eliminates pseudo-hyperinsulinemia observed after transplantation with systemic venous drainage, significant improvements in outcomes traceable to the use of this form of venous drainage have not been documented.

Additional information on techniques of pancreas transplantation is found in an article by Boggi and coauthors in *Current Opinion in Organ Transplantation*, 2010. The authors open their review of this topic reporting notable improvements in outcomes of pancreas transplantation, although success is still limited by medical and surgical complications. They stress that assigning a complication, such as duodenal leak, to technical failure is challenging since viral infection and rejection both contribute this complication. They next review the currently used techniques of pancreas transplantation. They emphasize the use of “back table” procedures to evaluate and optimize arterial perfusion of the graft. The pancreas is generally excised from the donor along with the adjoining duodenum. The first, second, and part of the third portion of the duodenum are included. The arterial supply of the graft is generally through the superior mesenteric artery and splenic artery. Both of these trunks are revascularized using a Y-shaped graft from the donor iliac artery. A recent modification of the technique has employed back-table angiography of the graft to determine the need for reconstruction of the gastroduodenal artery.
In whole-organ grafts, the portal vein is available for venous drainage while the splenic vein is used in segmental pancreas grafts.

Placement of the engrafted pancreas is in the right iliac fossa because of more favorable anatomy of the right iliac vessels. The duodenum can be anastomosed to the bladder for drainage of the pancreatic duct. Recently, placement of the pancreas graft behind the right colon mesentery has permitted the use of duodenal-duodenostomy for enteric drainage of the pancreas, an arterial anastomosis to the right iliac artery, and venous drainage into the portal venous system. Boggi and associates review data on the various forms of venous drainage of pancreas grafts. They note that insulin and lipid metabolism are more likely to be normal after portal venous drainage, but an effect on outcomes has not been documented.

Complications of the various means of draining the pancreatic duct are discussed. Bladder drainage produces metabolic complications (hyperchloremic acidosis) and direct urological complications (bladder leak, hematuria, urinary infection, and urethritis). These complications are encountered in 10%–15% of patients. Complications of enteric drainage include intestinal bleeding and anastomotic leak. Data cited indicate that there is no significant difference in frequency of complications of pancreas drainage procedures although enteric drainage is associated with the best quality of life.

Sutherland and coauthors\textsuperscript{154} discuss the evolution of immunosuppression and note that improved outcomes of pancreas transplantation have occurred, in large measure, because of improved immunosuppression. Infection, especially Epstein-Barr viral infection, remains the most important complication of immunosuppression. Sequential biopsy of the pancreas graft is useful in maintaining optimum immunosuppression. The discussion section of the article concludes that pancreas transplantation is a proven, effective therapy for diabetes mellitus. Although the early costs are high, the long-term improvements in diabetic management, quality of life, and survival make this approach cost-effective as well.

A review of published data on pancreas transplantation is by White and Sutherland\textsuperscript{156} in \textit{Lancet}, 2009, indicate that more than 23,000 total pancreas transplants have been performed. Available data indicate that pancreas transplantation has some distinct advantages compared with nonoperative therapy of severe Type 1 diabetes. Control of glycosylated hemoglobin can be achieved with intensive insulin therapy but this comes at the expense of a significant frequency of hypoglycemia. Most transplants are done for Type 1 diabetes but nearly 8% of recipients have Type 2 diabetes. White and Sutherland note that pancreas-alone transplants are useful for diabetic patients with hypoglycemic unawareness, glomerular filtration rate (GFR) > 80mL/1.73 M\textsuperscript{2}, and minimal proteinuria. Nearly one-third of patients receiving a pancreas-alone transplant will require a future kidney transplant because of the effects of immunosuppressive agents (especially calcineurin inhibitors) on renal function. The need for later renal transplantation is even greater in patients with pretransplant GFR less than 80. The article cites data indicating that the rejection rate for pancreas transplants ranges from 5%–25%, depending on the immunosuppression strategy used. The combination of cyclosporine and tacrolimus is the most effective immunosuppression approach. Pancreas transplants are unlike other organ transplants in that T-cell suppression induction therapies are used before transplantation. The authors conclude their update by noting that more than 50% of candidates for pancreas transplantation die while on the transplant waiting list. Currently, waits of more than four years are common.

A final article that reviews the status of pancreas transplantation in the United States is by Greussner and coauthors\textsuperscript{157} in \textit{Current Opinion in Transplantation}, 2010. The authors note that there has been a decline in the number of pancreas transplants performed in the United States since 2002. Between 2004–2008, there was a 15% decline in the number of pancreas transplants performed. The most common type of transplant performed remains the simultaneous renal-pancreas transplant. Currently, 31% of transplant centers perform pancreas-alone transplants. Outcomes for pancreas transplantation continue to improve. Currently, more than 95% of patients with pancreas transplants will be alive at the end of one year posttransplant and three-year survival exceeds 90%. Graft survival at three years exceeds 80%. Cardiovascular disease and infections are the most common causes of posttransplant death. Infections are the most common cause of death within the first year after transplantation. Immunosuppression-associated malignancy accounted for
7% of late deaths. The authors cite data indicating that loss of the graft due to technical failure or rejection is a major factor associated with patient death. Enteric anastomotic leak and graft thrombosis are the most serious technical complications. Graft thrombosis is observed in 2.6%–5% of patients, depending on the type of transplant done. Enteric leak is observed in 0.5% of patients.

**Islet cell transplantation for management of diabetes**

The objectives of pancreas transplantation and islet cell transplantation are identical. Both treatments seek to relieve the diabetic patient of the need for exogenous insulin while achieving improved quality of life, reduced diabetes-related morbidity, and improved overall survival. Islet cell transplantation can potentially offer improved diabetes management without the need for a major operation. To date, the main disadvantage of islet cell transplantation has been the relentless emergence of recurrent need for insulin therapy during the first three years after islet cell transplantation. In this section of the overview, we review two articles focusing on the current status and future prospects for islet cell transplantation.

The first article discussed is by Fiorina and co-authors in the *American Journal of Transplantation, 2008*. The authors note that insulin dependence and recurrent hypoglycemic episodes represent the most common indications for islet cell transplantation. Islet cell function (assessed by C-peptide levels > 5 ng/mL) after transplantation averages 80% at 1,000 days for islet cell transplantation following kidney transplantation and 60% at 1,000 days posttransplant for islet cells transplanted alone. But most reports indicate that only 13% of patients will remain insulin-independent at three years posttransplant. Although functioning islet grafts effectively prevent hypoglycemia from insulin secretion, it is not clear, according to data cited by Fiorina and associates, whether this is because of reduced needs for exogenous insulin or restoration of normal glucose counterregulation. Transplanted islet cells do not restore normal glucagon counterregulation. Fiorina and colleagues review data on the effect of islet cell transplantation on the systemic complications of diabetes. They cite data indicating that normalization of myocardial metabolism has been observed in experimental animals but data in humans are lacking. Islet cell transplantation leads to improvements in vascular disease as evidenced by intimal thickness measurements in humans. Additional data indicate reductions in micro-albuminuria in patients following islet transplantation, indicating favorable effects on renal disease. Small studies have shown favorable effects on retinal blood flow and progression of neuropathy in patients after islet cell transplantation. In reviewing the data on maintenance of cell function following transplantation, the authors stress the importance of the development of tolerance-inducing drugs that will reduce the negative impact on cell function that results from the development of anti-HLA antibodies. They conclude that islet cell transplantation holds great promise; research to improve the longevity of functioning grafts should continue.

The second article discussed on islet cell transplantation is by Robertson in *Endocrinology and Metabolism Clinics of North America, 2010*. The author reviews data concerning pancreas and islet cell transplantation. He emphasizes that the success rate of islet cell transplantation is improving, but long-term freedom from insulin therapy and restoration of normal glucagon counterregulation are both better in pancreas transplant patients. For patients with fully functioning islet cell transplants, the freedom from insulin rate and beneficial effects on secondary complications of diabetes are equivalent to pancreas transplant patients. Unfortunately, long-term normal function of islet cell transplants is a goal that has not yet been achieved.


References


References | BILIARY TRACT & PANCREAS, PART II


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1. Choledochal cyst disease is characterized by an abnormal location of the junction of the pancreatic duct and the bile duct in the duodenal wall. The definition requires that the junction be at which distance from the ampulla of Vater?
   a) 15 mm  
   b) 2 mm  
   c) 3 cm  
   d) 8 mm  
   e) 20 mm

2. What is the preferred therapeutic approach for a patient with a Type III choledochal cyst presenting with chronic pain and evidence of sphincter of Oddi dysfunction?
   a) Pancreatoduodenectomy  
   b) Celiac ganglion neurolysis  
   c) Frey procedure  
   d) Endoscopic sphincterotomy  
   e) Distal pancreatectomy and splenectomy

3. According to data presented by Diao and coauthors, which of the following increases with increasing time between prenatal diagnosis of choledochal cyst and cyst excision with biliary reconstruction?
   a) Risk of cholangiocarcinoma  
   b) Risk of pancreatitis  
   c) Severity of liver fibrosis  
   d) Severity of renal damage  
   e) Risk of cerebral palsy

4. What proportion of choledochal cyst disease is diagnosed in adults?
   a) 33%  
   b) 20%  
   c) 50%  
   d) 75%  
   e) 5%

5. Data from the clinical series presented by Saluja and coauthors showed the most common complication of choledochal cyst in adults was which of the following?
   a) Chronic renal insufficiency  
   b) Cholangitis  
   c) Pancreatitis  
   d) Gallbladder cancer  
   e) Intracystic stone formation

6. According to Jang and coauthors, the most common malignancy associated with choledochal cyst disease is which of the following?
   a) Hepatocellular carcinoma  
   b) Cholangiocarcinoma  
   c) Gallbladder carcinoma  
   d) Pancreatic carcinoma  
   e) Duodenal carcinoma
7. Caroli syndrome is defined as which of the following?
   a) Intrahepatic biliary cysts with concomitant gallbladder cancer
   b) Intrahepatic biliary cysts with concomitant pancreatitis
   c) Intrahepatic biliary cysts with intracystic stone formation
   d) Intrahepatic biliary cysts with concomitant renal cysts
   e) Intrahepatic biliary cysts with concomitant duodenal ulcer disease

8. Data presented by Fuks and coauthors suggest that a tumor marker detectable in cyst fluid that would accurately diagnose mucinous cystic disease of the liver is which of the following?
   a) CEA
   b) TNF-alpha
   c) C-reactive protein
   d) CA 19-9
   e) Tumor-associated glycoprotein

9. Which of the following is the most common type of gallbladder polyp?
   a) Inflammatory polyp
   b) Adenomatous polyp
   c) Adenomyomatosis
   d) Cholesterol polyps
   e) Adenocarcinoma of the gallbladder

10. Data presented in the article by Pilgrim and coauthors indicate that the most dependable imaging finding that suggests the diagnosis of gallbladder cancer is which of the following?
   a) Presence of mural nodules
   b) Presence of gallbladder polyps
   c) Thickening and enhancement of the inner layers of the gallbladder wall
   d) Thickening of the outer layer of the gallbladder wall
   e) Presence of gallstones

11. After laparoscopic cholecystectomy for symptomatic cholelithiasis, adenocarcinoma is discovered in the mucosa of the excised gallbladder. Tumor cells are not observed beyond the lamina propria of the mucosal layer. What is the appropriate next step?
   a) Right hepatic lobectomy
   b) Resection of the gallbladder bed with regional lymphadenectomy
   c) Resection of the gallbladder bed with regional lymphadenectomy and bile duct resection
   d) Adjuvant radiation therapy to the gallbladder bed
   e) No further surgical therapy

12. Data presented by Hyder and coauthors suggest that all of the following reduce the chance for long-term survival in patients with cholangiocarcinoma except which one?
   a) Older patient age
   b) Presence of cirrhosis
   c) Decreasing serum level of CA 19-9
   d) Larger tumor size
   e) Presence of vascular invasion

13. Data reported by Duignan and coauthors indicate that the four-year survival following neoadjuvant chemoradiation and liver transplantation for patients with cholangiocarcinoma is which of the following?
   a) 5%
   b) 61%
   c) 33%
   d) 88%
   e) 18%
14. Which cells contribute to the process of pancreatic fibrosis in patients with chronic pancreatitis?
   a) Stellate cells
   b) Macrophages
   c) Beta cells
   d) Ductal epithelial cells
   e) T-lymphocytes

15. Risk factors for development of pancreatic cancer in patients with chronic pancreatitis include all of the following except which one?
   a) Tobacco use
   b) African-American ethnicity
   c) History of childhood irradiation
   d) Non-O blood type
   e) Male gender

16. A 43-year-old woman is found to have a 2.8-cm mass in the head of the pancreas. Ductal brushings obtained at ERCP and endoscopic ultrasound-guided needle biopsy of the mass do not confirm the diagnosis of pancreatic cancer, but suggest the diagnosis of autoimmune pancreatitis. The next step in treatment should be which of the following?
   a) Neoadjuvant chemoradiation therapy followed by pancreatoduodenectomy
   b) Prolonged biliary drainage
   c) Pancreatoduodenectomy
   d) A short course of corticosteroid therapy
   e) Sequential imaging followup to document lesion growth

17. Type 1 autoimmune pancreatitis can be differentiated from Type 2 disease on finding which of the following on tissue biopsy?
   a) Periductal neutrophil infiltration
   b) Infiltration of Ig-4 cells
   c) Serum amylase levels that are at least three times normal
   d) Patient age less than 15 years
   e) Presence of hyperbilirubinemia

18. Overall accuracy of PET scanning for the diagnosis of pancreatic neuroendocrine tumors is which of the following?
   a) 21%
   b) 38%
   c) 90%
   d) 64%
   e) 8%

19. International consensus guidelines suggest that resection of main-duct intraductal pancreatic mucinous neoplasms (IPMN) be considered for ductal dilation greater than which of the following?
   a) 15 mm
   b) 1.0 cm
   c) 2.0 cm
   d) 5 mm
   e) 2 mm

20. Data from the article by Ollinger and coauthors indicate that long-term patient survival in patients undergoing simultaneous kidney-pancreas transplantation is which of the following?
   a) 26%
   b) 50%
   c) 63%
   d) 78%
   e) 94%
Posttest | BILIARY TRACT & PANCREAS, PART II

The following four questions are required by the American College of Surgeons for accreditation purposes. You must complete these four questions before submitting your answers.

21. This issue met the stated learning objectives.
   a) Strongly agree
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   c) Neutral
   d) Disagree
   e) Strongly disagree

22. The content was relevant to my educational needs and practice environment.
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   b) Agree
   c) Neutral
   d) Disagree
   e) Strongly disagree

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   b) Agree
   c) Neutral
   d) Disagree
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   b) Agree
   c) Neutral
   d) Disagree
   e) Strongly disagree

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E-mail: srgs@facs.org

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