Pancreatic Adenocarcinoma

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Pancreatic ductal adenocarcinoma is the second most common malignancy of the gastrointestinal tract, with an estimated 32,000 new cases diagnosed in the United States in 2005.[1] Often detected at an advanced stage of disease, which precludes effective and curative treatment, pancreatic adenocarcinoma has a well-recognized poor prognosis. A multimodality and multidisciplinary approach, with collaborative expertise from gastroenterologists, surgeons, interventional radiologists, oncologists, psychiatrists, and palliative care specialists, is often needed for optimal management of patients with pancreatic cancer given their complexity, debilitation, and varied needs. This article reviews the presentation and evaluation of patients with pancreatic adenocarcinoma and discusses the management of these patients.

TAKE HOME POINTS

- Despite extensive investigation, pancreatic cancer has a poor prognosis as most patients are diagnosed at an advanced stage of disease.
- Evaluation of patients with suspected pancreatic cancer is focused on complete tumor staging and identifying patients with potentially resectable disease.
- Patients with resectable disease should undergo definitive surgical therapy whenever possible.
- In patients with unresectable disease, treatment regimens include chemotherapy, radiation therapy, endoscopic approaches, or a combination thereof. Some of these treatments are purely palliative
- Pancreatic cancer is best treated in a multidisciplinary setting by oncologists, gastroenterologists, surgeons, psychiatrists, and palliative care specialists.

EPIDEMIOLOGY

The incidence of pancreatic adenocarcinoma is 12.5 and 9.5 cases per 100,000 persons in men and women, respectively.[1] It is the fourth leading cause of cancer death. Unfortunately, neither the incidence nor the survival rate of pancreatic adenocarcinoma has changed significantly over the past 25 years, and 5-year survival remains poor at approximately 4%.[2] Currently, there is no established screening regimen for pancreatic adenocarcinoma.

Pancreatic adenocarcinoma affects all ethnic groups, but African Americans appear to have a higher incidence and decreased survival as compared to Caucasians.[1] African Americans are more likely to be diagnosed at an advanced stage of disease, with fewer tumors located in the head of the pancreas; patients with tumors in the head of the pancreas often present earlier due to biliary obstruction and have greater potential for resectability.[1] African Americans also have higher rates of K-ras mutations, which have been associated with more aggressive and often poorly differentiated tumors.[3]

Risk Factors

Multiple factors have been shown to increase the risk for developing pancreatic adenocarcinoma, including age, underlying medical conditions, lifestyle, and genetic factors. The median age at diagnosis is 72 years, with 57% of cases occurring in patients aged 65 to 84 years and 12% occurring in those older 85 years.[1] In addition, any factor that causes inflammatory changes in the pancreas, with resultant scarring and fibrosis, increases the risk for pancreatic cancer. Causes of chronic pancreatitis include alcohol use, hypercalcemia, recurrent and severe acute pancreatitis, chronic obstruction (by benign cysts, cystic neoplasms, or pancreatic duct stones), and hereditary pancreatitis.[4] The increased risk for developing pancreatic adenocarcinoma associated with chronic pancreatitis is independent of gender, country of origin, or etiology of chronic pancreatitis.[5,6]

There is a well-recognized association between pancreatic adenocarcinoma and diabetes mellitus.[7] Glucose intolerance may occur as a consequence of pancreatic insufficiency in chronic pancreatitis, and diabetes often manifests shortly before or soon

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after malignancy is discovered. It has been proposed that 1% of diabetics over age 50 years will be diagnosed with pancreatic adenocarcinoma within 3 years after meeting the criteria for diabetes.[8] Obesity also has been investigated as a factor contributing to pancreatic adenocarcinoma. Reports have suggested that patients newly diagnosed with pancreatic adenocarcinoma were more likely to have had an elevated body mass index 20 years prior to being diagnosed with cancer.[9]

The use of tobacco products consistently has been reported as a significant risk factor for pancreatic adenocarcinoma, with the risk rising with increasing pack-years of tobacco use and decreasing after tobacco cessation.[10] In current smokers, the relative risk for developing pancreatic adenocarcinoma is 2.5.[11] It is estimated that 25% of pancreatic adenocarcinomas can be attributed, at least in part, to cigarette smoking.[11] Smokeless tobacco products also have been shown to increase risk.[12] Patients predisposed to pancreatic adenocarcinoma based on their genetic factors, underlying medical conditions, or body habitus should be encouraged to avoid all tobacco products.[13] Alcohol itself has not been proven to directly increase the risk of pancreatic adenocarcinoma, although alcohol use can lead to chronic pancreatitis.[14]

GENETIC FACTORS

Investigators have identified genetic factors involved in the pathogenesis of chronic pancreatitis and, by extension, pancreatic adenocarcinoma. However, less than 5% of pancreatic adenocarcinoma cases are thought to be related to genetic predisposition.[15] Mutations in *PRSS1*, the cationic trypsinogen gene, increase the risk for acute and chronic pancreatitis.[15] *PRSS1* encodes the protein product trypsinogen, the inactive zymogen of trypsin, a proteolytic pancreatic enzyme. In patients with the *PRSS1* mutation, cationic trypsinogen in the pancreas can be prematurely activated, promoting pancreatic inflammation and scarring. Studies have also shown that patients with alcoholic chronic pancreatitis have a higher prevalence of mutations of the serine protease inhibitor Kazal type 1 (*SPINK1*) gene, which codes for a pancreatic secretory trypsin inhibitor.[16] It is thought that *SPINK1* inhibits activated trypsin within the pancreas, preventing autolysis when trypsinogen becomes prematurely activated. *SPINK1* mutations thus allow unchecked trypsin activity, leading to inflammatory changes in the pancreatic parenchyma.[17] A higher frequency of *SPINK1* mutations has also been demonstrated in patients with idiopathic chronic pancreatitis than in controls.[17]

Another well-studied gene is the cystic fibrosis transmembrane receptor (*CFTR*). *CFTR* is responsible for dilution and alkalinization of pancreatic secretions, and dysfunction results in inspissated juices. The changes in the pancreatic parenchyma seen in cystic fibrosis are quite similar to those of chronic pancreatitis. Although *CFTR* mutations have been identified in patients with acute and chronic pancreatitis and in some pancreatic adenocarcinomas, the exact role of *CFTR* mutations in the development of pancreatic adenocarcinoma remains unclear.[18]

The *BRCA1* gene codes for proteins that regulate DNA damage repair. It has been associated with inherited breast and ovarian cancer and has also been shown to be down-regulated in the pancreatic tissue of patients with chronic alcoholic pancreatitis and pancreatic adenocarcinoma. Pancreatic tumors in patients with normal *BRCA1* expression had an improved 1-year survival rate compared to those with reduced or absent *BRCA1* staining.[19]

Finally, the *p16*^{INK4} gene codes for a protein responsible for cell growth arrest. Studies have shown that patients with mutations in this gene had an increased risk of pancreatic adenocarcinoma.[20,21]

Pancreatic adenocarcinoma has also been associated with several genetic syndromes and disorders characterized by increased risk for malignancy. Errors in genes that are responsible for DNA mismatch repair, which include hMLH1, hMSH2, hMSH3, and hMSH6, can lead to faulty DNA repair of nucleotide mismatches that can occur during DNA replication. Areas prone to this type of mismatch error are termed microsatellites, and if not corrected, these errors can increase the risk of cancer development. Gastrointestinal cancers, especially those associated with the hereditary nonpolyposis colorectal cancer syndrome (including pancreatic adenocarcinoma), have been associated with high-frequency microsatellite instability. In a study of pancreatic adenocarcinoma patients, high-frequency microsatellite instability was associated with poor tumor differentiation.[22]

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by the development of numerous polyps in the colon and, if not treated with colectomy, the universal development of colorectal cancer. Compared with the general population, patients with FAP and their first-degree relatives have a four-fold increased risk for developing pancreatic adenocarcinoma.[23] Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder distinguished by hyperpigmentation of mucus membranes and the development of hamartomatous polyps of the gastrointestinal tract. PJS patients have a 130-fold increased risk of developing pancreatic adenocarcinoma as compared

with the general population.[24] Surveillance programs for pancreatic adenocarcinoma have been recommended in PJS patients and consist of endoscopic, radiographic, and biochemical marker follow-up.[25] A familial pancreatic adenocarcinoma syndrome has also been suggested, but most cases of familial aggregation do not consistently demonstrate known associated genetic mutations.[26]

DIAGNOSIS AND STAGING

Clinical Presentation

Establishing a diagnosis of pancreatic adenocarcinoma is often difficult as presenting symptoms may be subtle or even absent. Although lesions arising in the head of the pancreas may cause biliary obstruction (with accompanying jaundice) due to compression of the common bile duct, lesions in the remainder of the gland may be largely asymptomatic until the disease is advanced and/or metastatic. Symptoms may be vague and nonspecific, including anorexia, fatigue, malaise, and nausea. Significant unintentional weight loss is a hallmark of the disease and may be attributed to malabsorption due to pancreatic exocrine dysfunction combined with anorexia. A common presenting complaint is epigastric abdominal pain radiating to the back, often indicating retroperitoneal invasion. A recent diagnosis of diabetes mellitus in an older patient or new onset of unexplained acute pancreatitis may be warning signs as well.[8]

Patients with tumors in the head of the pancreas will frequently present with painless jaundice. Patients may complain of scleral icterus as well as cholestatic side effects, including pruritus, dark urine, and light-colored stools. Depression may be present prior to the diagnosis of pancreatic adenocarcinoma and may correlate with increasing pain symptoms.[27] Migratory thrombophlebitis (ie, Trousseau's syndrome) and venous thrombosis as well as a palpable gallbladder (Courvoisier's phenomenon) may also occur in patients with pancreatic adenocarcinoma.[28,29]

The diagnostic evaluation of patients with known or suspected pancreatic adenocarcinoma typically involves several objectives: identifying the primary tumor's pathology, size, and location within the pancreas and obtaining comprehensive staging of the disease, which determines subsequent management options. Staging is based on the American Joint Committee on Cancer (AJCC) TNM criteria,[30] which assess tumor size, vascular involvement, and the presence or absence of lymph node metastasis or distant metastases (**Table**). The sixth edition of the AJCC criteria has been modified to reflect that T3 lesions are considered potentially resectable and T4 lesions are unresectable; stage III disease indicates unresectable locally advanced disease and stage IV represents metastatic disease. Accurate staging allows for expeditious institution of therapy or palliative measures, both important in this disease with an extremely poor prognosis.[31]

Table. Staging of Pancreatic Cancer

Primary tumor (T)	
Tx	Tumor size cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ*
T1	Tumor limited to pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
Mx	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
Stage 0	Tis, N0, M0
Stage IA	T1, N0, M0
Stage 1B	T2, N0, M0
Stage IIA	T3, N0, M0
Stage IIB	T1, N1, M0
	T2, N1, M0
	T3, N1, M0
Stage III	T4, any N, M0
Stage IV	Any T, any N, M1

*This also includes "PanInIII" classification.

Adapted with permission from Greene FL, editor. AJCC cancer staging manual. American Joint Committee on Cancer. 6th ed. New York: Springer-Verlag; 2002:160.

Imaging Studies

The initial work-up of patients in whom pancreatic adenocarcinoma is suspected often includes a transabdominal ultrasound to assess for the presence of biliary tract disease. Its sensitivity and specificity in diagnosing pancreatic adenocarcinoma (estimated at 76% and

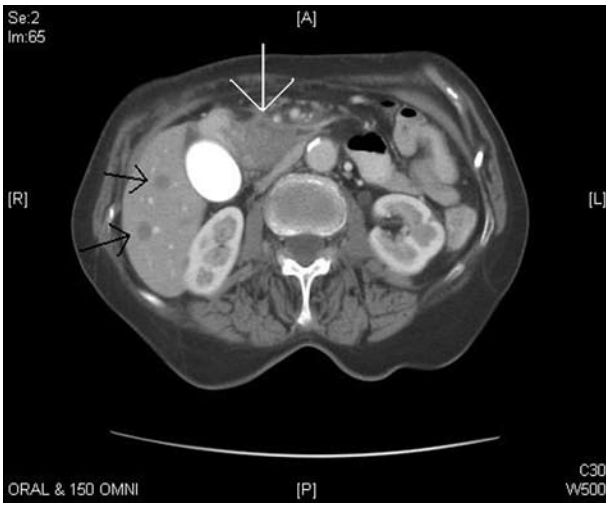

Figure 1. Computed tomography scan showing hypodense mass in the head of the pancreas (*white arrow*) with multiple hepatic lesions consistent with metastases (*black arrows*).

75%) and in determining resectability (83% and 63%) are inferior to other imaging modalities.[32] Therefore, transabdominal ultrasound is not the preferred method in detecting pancreatic adenocarcinoma or in staging.

Computed tomography (CT). CT scans have assumed a critical role in the evaluation of patients with known or suspected pancreatic adenocarcinoma. CT scanning should be the first test used if pancreatic malignancy is suspected because of its sensitivity and its ability to evaluate the pancreas, the peripancreatic blood vessels, liver, and biliary tree as well as any tumor present (**Figure 1**). Both intravenous and oral contrast should be administered for optimal results. Triple-phase scans first obtain images without contrast, then 20 to 25 seconds after contrast is administered (arterial phase), and finally 60 to 80 seconds after contrast (portal venous phase), depending on institutional protocol. The arterial phase demonstrates the pancreatic parenchyma and aids in diagnosing the primary tumor, which often appears hypodense. The portal venous phase enhances the liver and allows for evaluation for liver metastases.[33] Pancreatic protocol CT images should have a reconstruction slice thickness of 1 to 3 mm for the best visualization of the pancreatic parenchyma.

The sensitivity and specificity of conventional CT scan for diagnosing pancreatic tumor have been estimated at 86% and 79%.[31] Estimates of conventional CT's ability to determine resectability vary, with an approximate sensitivity and specificity of 82% and 76%.[32] Helical or spiral CT scans allow for rapid image collection and minimize patient artifact. The sensitivity and specificity of helical CT for diagnosing pancreatic tumors are 91% and 85%, and for determining resectability they are 81% and 82%.[32] In a study by Midwinter et al[34] that compared imaging findings with operative findings, the sensitivity and specificity of helical CT for determining superior mesenteric and portal venous involvement were 56% and 100%.

CT scans are also important in evaluating peripancreatic lymphadenopathy, which may be due to metastatic spread or may be inflammatory/reactive in nature. Conversely, normal sized lymph nodes may appear benign but may harbor micrometastases.[35] In the Midwinter et al study,[34] the sensitivity and specificity of helical CT in evaluating nodal status (in the celiac axis, portal vein, hepatic artery, and superior mesenteric artery fields) was 33% and 86%, respectively. Although lymph nodes are part of the staging evaluation for pancreatic adenocarcinoma, the presence or absence of adenopathy does not solely influence management decisions.

Endoscopic ultrasound (EUS). EUS represents an important advance in the diagnostic evaluation of patients with pancreatic adenocarcinoma. EUS uses videoendoscopes with built-in ultrasound probes that provide precise and detailed endoluminal sonographic images of gastrointestinal organs and can sample pathologic lesions through fine needle aspiration (FNA). An advantage of EUS for pancreatic disease is that EUS probes can be placed in close proximity to a target organ without the impedence of skin and subcutaneous tissues.

EUS is a highly accurate tool for evaluating pancreatic masses. Pancreatic tumors will typically appear as nonhomogeneous, hypoechoic solid masses with irregular borders. EUS is superior to transabdominal ultrasound and conventional CT in detecting pancreatic tumors less than 2 cm in diameter and may be better than helical CT as well.[36,37] The sensitivity of EUS for detecting pancreatic adenocarcinoma has been reported as 93%.[38] EUS has also been effective in predicting the absence of pancreatic adenocarcinoma, with a negative predictive value of 100% in one study.[39]

With the ability to sample tissue, EUS can accurately differentiate benign from malignant lesions.[40] EUS-guided FNA can safely and accurately diagnose pancreatic adenocarcinoma when prior tissue acquisition attempts by CT or endoscopic retrograde cholangiopancreatography (ERCP) have failed or been indeterminate, and EUS-guided FNA is now a first-line modality for tissue acquisition (**Figure 2**).[41] The advantages of EUS-guided FNA include real-time imaging and a low complication rate (< 0.5%).[41]

EUS can also readily identify peripancreatic lymph

nodes and their morphology, which often suggests whether the nodes are malignant or represent benign peritumoral reactive adenopathy. Malignant lymph nodes frequently can be differentiated from benign nodes by their round shape, smooth regular border, size (> 1 cm), and hypoechoic nature.[40] Worrisome lymph nodes can be sampled with FNA for more accurate staging. EUS is able to detect the proximity of the tumor to key blood vessels (eg, celiac artery, superior mesenteric artery, portal vein), any irregularity of the vessel wall, and the loss of an intervening tissue plane between the tumor and surrounding vasculature. In one study, the sensitivity of EUS for diagnosing vascular involvement was 100% versus 50% for helical CT,[38] although other studies of EUS have reported sensitivities and specificities in the range of 50% to 60%.[42] The accuracy of EUS in detecting vascular involvement of pancreatic tumors will improve with technological advances.[42] Given the benefits of EUS, physicians should consider this modality prior to committing patients to surgery or palliation.[34,43–45]

Positron-emission tomography (PET). PET scanning can be useful in differentiating benign from malignant conditions as malignant tumors have increased glucose metabolism.[46] Intravenously injected ^{18}fluorodeoxyglucose (FDG) is taken up by metabolically active normal and tumor cells. As it decays, ^{18}fluorine emits positrons, which collide with electrons to emit photons that are registered with the PET detector. Tumors are seen as areas of intense activity, representing increased FDG uptake and photon emission. In a recent advance, helical non-enhanced CT is performed concomitantly with FDG-PET, allowing precise localization of detected "hot spots." This modality may be helpful in detecting additional distant metastases in patients with pancreatic adenocarcinoma.[47]

Magnetic resonance imaging (MRI). MRI can be used in patients with iodine allergy or renal insufficiency, and it can obtain images in a variety of planes. MRI can provide excellent images of the peri-pancreatic vessels with the addition of MR angiograms and venograms and is often helpful as an adjunctive test after inconclusive CT or EUS evaluation. MRI has lower sensitivity (84%) and specificity (82%) compared with helical CT (91% and 85%) in detecting pancreatic tumors, but the difference between these modalities in determining resectability is not statistically significant.[32]

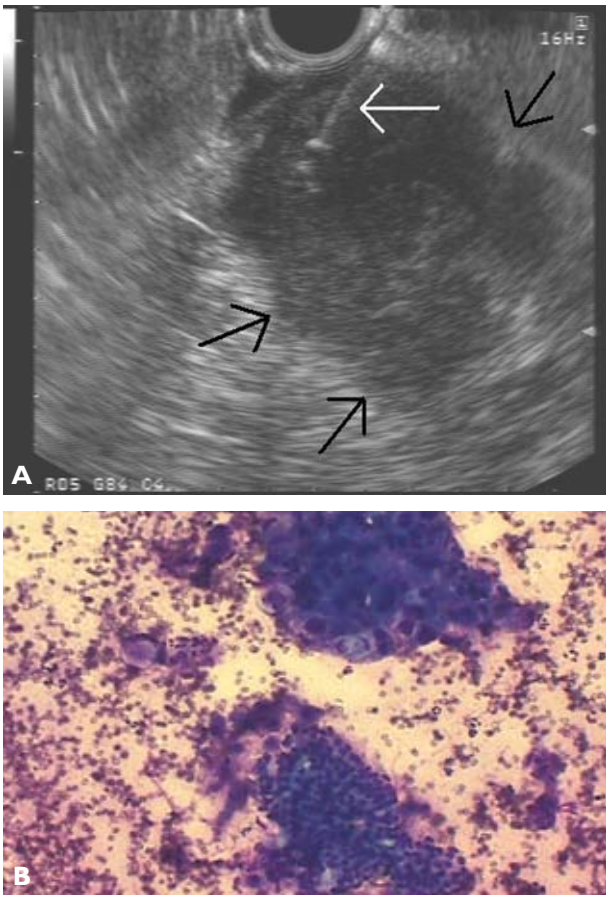

Figure 2. (**A**) 7.5-Endoscopic ultrasound (EUS)–guided fine needle aspiration (FNA) of a solid pancreatic mass. Needle is marked by the *white arrow*, and the borders of hypoechoic mass lesion are marked by *black arrows*. (**B**) Cytologic specimen from EUS–guided FNA showing both normal pancreatic tissue (*bottom*) and malignant cells (*top*). (DifQuik stain, magnification 10x).

Laparoscopy

Staging of pancreatic tumors was previously accomplished with exploratory laparotomy. It is estimated that 20% to 35% of tumors initially determined to be resectable will be found to be unresectable at surgery.[31] Minimally invasive surgery with laparoscopy is able to directly visualize small metastases involving the peritoneum or liver and undetected vascular invasion that may not be seen on CT, avoiding formal laparotomy.[31] Given current advances in imaging technology, staging laparoscopy is probably best reserved for patients with locally advanced pancreatic adenocarcinoma with unclear vascular involvement despite a thorough evaluation with noninvasive testing. Laparoscopy will expedite the initiation of proper treatment in these patients.

Serum Tumor Markers

Serum tumor markers are often ordered in the diagnostic work-up of patients with suspected malignancy. Carbohydrate antigen (CA) 19-9, originally named

gastrointestinal cancer antigen, is a monoclonal antibody produced in response to a colon cancer–derived cell line and is elevated in the majority of patients diagnosed with pancreatic adenocarcinoma.[48,49] A serum level between 500 and 1000 U/mL is almost exclusively associated with malignancy. However, CA 19-9 also can be elevated in gastric, biliary, and colon cancers as well as in pancreatitis, hepatitis, cholangitis, and cirrhosis.[50] The sensitivity and specificity of CA 19-9 in diagnosing pancreatic adenocarcinoma are 80% and 90% when a cutoff of 37 U/mL is used.[49] CA 19-9 has a positive predictive value of 59%. It should be remembered that even an accurate tumor marker will add little diagnostic benefit in a patient with other findings strongly suggestive of cancer.[50] CA 19-9 has some predictive value for survival, response to therapy, and recurrence of disease in patients with unresectable disease after chemoradiation therapy.[51] The level of CA 19-9 elevation may correlate with the grade and size of the tumor as well as the presence of metastatic disease.[48]

Although carcinoembryonic antigen (CEA) has limited value, levels can be high in pancreatic adenocarcinoma. CEA and CA 19-9 are best used in patients who have a high pretest probability for pancreatic malignancy and are not effective in general population screening.

TREATMENT

Surgical Resection

The mainstay of potentially curative treatment is surgical resection in appropriate candidates. Patients with pancreatic head adenocarcinoma determined to be resectable traditionally have undergone the Whipple procedure (ie, pancreaticoduodenectomy). Tumors in the body and tail of the pancreas often present at an advanced stage of disease but could potentially be resected with a distal pancreatectomy and accompanying splenectomy. The Whipple procedure, first described in 1935 by Dr. Allen Oldfather Whipple, involves tumor resection followed by extensive intra-abdominal reconstruction to allow for proper gastric, pancreatobiliary, and small intestine drainage.[52] Specifically, the operation entails the tumor-resecting pancreaticoduodenectomy as well as the creation of several internal anastomoses, including pancreaticojejunostomy (as the pancreatic body and tail remain in situ), gastrojejunostomy, and hepaticojejunostomy (allowing internal biliary drainage as the distal common bile duct has an intrapancreatic course and is resected with the head of the pancreas).

At centers where this procedure is routinely performed, the mortality rate can be less than 5%.[53] Between 3% and 9% of patients experience biliary complications such as bile leak, cholangitis, and biliary obstruction.[54] T-tube drains are placed intraoperatively in the biliary tree to reduce these complications. Leakage of pancreatic fluid can also occur at the site of the pancreaticojejunostomy anastomosis in 5% to 10% of patients. Intra-abdominal abscesses may develop in 5% to 14% of patients, and the incidence of this complication has remained stable over time. Percutaneous drains may be attempted, but patients with ongoing infection will usually require reoperation. Serious hemorrhage occurs in 3% to 11% of patients. Early bleeding occurs within the first few hours after surgery and often indicates an operative misadventure. Late bleeding manifests days to weeks postoperatively and may be due to the formation of a pseudoaneurysm.[54]

A surgical variation is the pylorus-preserving Whipple procedure, which was introduced in 1943 for the treatment of periampullary tumors.[53] This procedure eliminates resection of the distal stomach (antrectomy) and instead forms an end-to-side gastrojejunal anastomosis. It was initially believed that this more physiologic anatomy would improve postoperative recovery and digestion, but studies have indicated that there was no difference in weight loss, gastric emptying, or postoperative recovery or mortality.[53,55] Other variations have been described in the literature, including extended lymph node dissection, but have shown no additional benefit.[56] Thus, the Whipple procedure remains the standard of care for curative-intent resection of pancreatic head adenocarcinoma.

Chemotherapy and Radiation Therapy

Large tumors are often located near the portal vein, and direct invasion occurs as a function of the proximity rather than the aggressiveness of the tumor. With advances in surgical technique, tumors previously deemed unresectable due to involvement of the superior mesenteric vein or portal vein can now undergo resection with vascular reconstruction at selected, high-volume centers.[56,57] Unfortunately, only 15% to 20% of patients have potentially resectable disease without vascular involvement at the time of diagnosis.[58] The majority of postoperative patients experience disease recurrence even after a presumably curative resection is performed due to the presence of undetected metastases.[59] Indicators of a poor prognosis include positive resection margins, tumor larger than 3 cm, a poorly differentiated tumor, and lymph nodes positive for malignancy.[56] Given the poor outcome of patients with presumably resectable disease, other treatment modalities have been investigated, including postoperative (adjuvant) and preoperative

(neoadjuvant) chemotherapy with or without external beam radiation therapy (EBRT).

The European Study Group for Pancreatic Cancer (ESPAC)[60] randomly assigned patients to receive adjuvant chemoradiotherapy (fluorouracil [5-FU] with EBRT), chemotherapy (5-FU), both, or observation alone. The investigators found no benefit to adjuvant chemoradiotherapy and reported reduced survival when this regimen was given before chemotherapy. These results should be viewed with caution as patient randomization was based in part on physician preference, and patients were allowed to receive additional treatments outside of study protocol; in addition, issues of quality control have been raised.[58] Ongoing studies include the ESPAC-3 trial with over 900 patients treated with 5-FU and leucovorin or gemcitabine, and the Radiation Therapy Oncology Group trial with patients randomly assigned to gemcitabine or 5-FU along with 5-FU-based chemoradiation.[58]

In locally advanced disease, the tumor involves vascular structures, making the disease unresectable. The Gastrointestinal Tumor Study Group[61] explored the effect of 5-FU combined with EBRT in patients with locally unresectable pancreatic cancer. Survival rates were higher in the 5-FU/EBRT group as compared with patients treated with radiation alone. Crane et al[62] selected patients with locally advanced disease for chemoradiation therapy with 5-FU or gemcitabine; although the gemcitabine group was younger, they experienced more systemic toxicity without significant benefit in disease progression. The current standard of care for unresectable pancreatic adenocarcinoma is 5-FU–based chemoradiation therapy.[58]

Patients with metastatic pancreatic adenocarcinoma benefit most from a multimodality approach that attempts to address their pain, obstruction, and psychological issues (*see* Palliation section). Chemotherapy in patients with advanced disease should be handled cautiously as these patients are the most susceptible to toxic side effects and are least likely to benefit. In a study that assigned previously untreated patients with advanced symptomatic pancreatic adenocarcinoma to weekly infusions of gemcitabine or 5-FU, the gemcitabine group had modest improvements in symptoms (pain, performance status, weight) and survival (1.2 months) over the 5-FU group.[63] Gemcitabine is currently the standard of care for patients with metastatic pancreatic adenocarcinoma.[58]

EBRT alone has application in some clinical scenarios, including postoperatively in patients with positive margins or malignant lymphadenopathy at the time of surgery. EBRT may also be used as a palliative modality for pain in patients with unresectable lesions, and EBRT has been shown to improve survival compared with no treatment.[64]

The role of neoadjuvant chemoradiotherapy has yet to be established.[59] The goals of this therapy would be to help downstage the tumor preoperatively to improve outcomes and to increase the number of patients who could receive therapy.

PALLIATION

Because most patients have unresectable disease and chemoradiation therapy frequently has suboptimal results, palliative treatment plays an important role in patient management. Some patients will develop gastric outlet obstruction as the tumor grows due to extrinsic compression of the distal stomach or duodenum. Symptoms include postprandial nausea, vomiting, abdominal bloating, and early satiety. These symptoms have a significant impact on patient quality of life. Patients may undergo palliative gastrojejunostomy via laparotomy or laparoscopy. Although highly effective, this procedure requires hospitalization, and some patients may be too weak to undergo surgery. Surgery in this setting should be reserved for patients with a good performance status and an expected survival of at least 6 months.[65] Another option is placement of a percutaneous endoscopic gastrostomy tube for gastric decompression with a jejunostomy tube for enteral feeding and hydration; however, this approach does not allow peroral feeding.

A third option is endoscopic placement of enteral self-expanding metal stents (SEMS). SEMS can be deployed across an obstructed duodenum to recanalize bowel and relieve obstructive symptoms. These stents have been used to palliate nonsurgical patients with obstruction due to gastric or pancreatic adenocarcinoma with excellent outcomes. Studies have shown a marked improvement in patients' ability to eat after SEMS placement.[65–69] Compared to surgical gastric bypass, SEMS placement is more beneficial in improving patients' quality of life. In a recent study, patients who underwent stenting were able to resume oral intake sooner and more frequently had improved performance scores.[69] In addition, SEMS placement results in shorter hospitalizations and better clinical outcomes compared to surgical alternatives.[68]

In an analysis of 606 patients, the technical success rate of SEMS placement was 97%.[65] Clinical success, defined by the resumption of or an improvement in previous oral intake, was 89%. Complications of SEMS placement include bleeding or perforation of surrounding structures (1%), obstruction with tumor or food particles (17%), stent migration (5%), unsuccessful

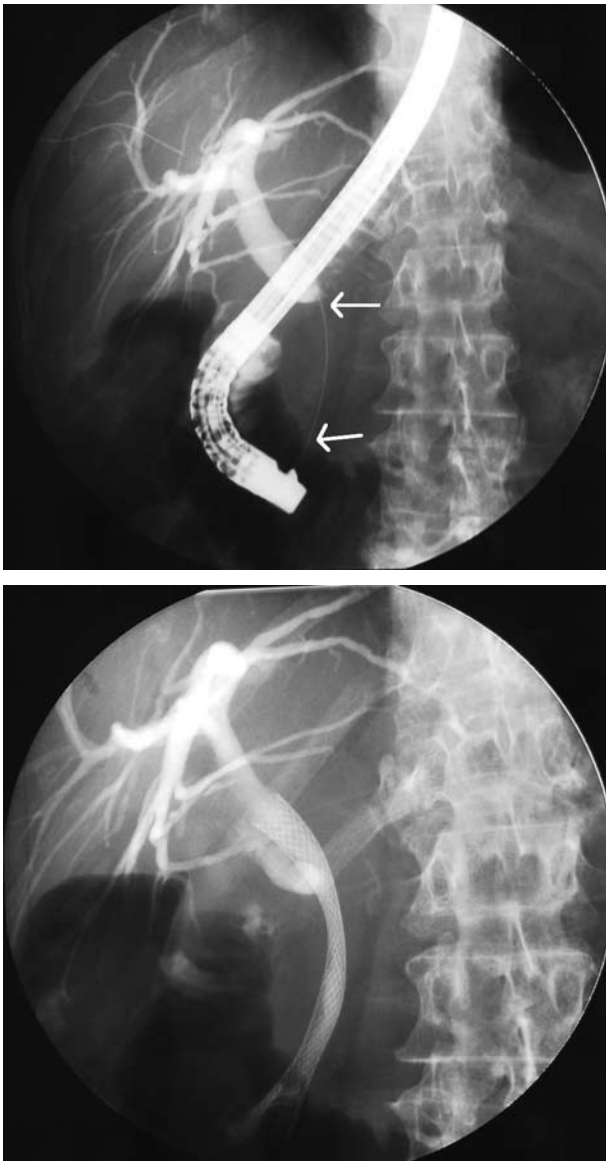

Figure 3. (**A**) Endoscopic retrograde cholangiopancreatography image of a distal common bile duct stricture (*arrows*) due to pancreatic cancer. (**B**) Same patient following placement of a biliary self-expanding metal stent across the stricture.

placement due to inability to cross the tumor (3%), and pain after placement (2%).[65] Enteral SEMS are relatively contraindicated in patients with peritoneal carcinomatosis who may have multiple areas of obstruction; symptoms in these patients may be unlikely to resolve until all obstructed areas are addressed.[65,67]

Due to the intrapancreatic course of the distal common bile duct, patients with tumors in the head of the pancreas will often develop biliary obstruction. Patients may experience anorexia, indigestion, pruritus, jaundice, and increased risk of cholangitis. Treatment involves the endoscopic placement of stents in the biliary tree, which provides symptomatic relief and improved quality of life (**Figure 3**).[66] Originally, only small-diameter plastic stents that often required periodic exchange (approximately every 3 months) due to clogging were used; large diameter biliary SEMS were developed in the 1980s.[70] Metal stents have a lower occlusion rate and remain patent up to 6 months or longer. The time to the first episode of obstruction is longer with metal stents, while plastic stents are associated with increased hospital length of stay, number of antibiotic days, and number of ERCP procedures.[71] A metal stent should be considered in patients with a median expected survival of 6 months.[72] Coated metal endobiliary stents that retard tumor ingrowth are now available but have some risk of migration.[70] If endoscopic stent placement is technically impossible, patients may undergo percutaneous biliary stent placement via interventional radiology. Endobiliary stenting is warranted whenever imminent curative or palliative surgery is not planned.

The physiologic effects of pancreatic obstruction are treated by the administration of oral pancreatic enzyme supplements to compensate for exocrine failure. Pancreatic ductal obstruction is not treated with stents in pancreatic cancer.

Most patients will experience pain during their disease course. Tumors in the pancreas often cause deep, constant epigastric abdominal pain that radiates to the back, and pain may also radiate to the upper back and shoulders.[73] Opioid analgesics are often required but are associated with multiple side effects, including somnolence, nausea, vomiting, and constipation. An alternative to pain medication is celiac plexus neurolysis (CPN), which consists of injecting ethanol and lidocaine to ablate nerve fibers. The celiac plexus receives afferent nerve fibers conveying pain sensation from the abdominal viscera and can be compressed by pancreatic tumors or become involved with metastatic disease. CPN can be achieved by surgical, percutaneous (with CT guidance), or endoscopic approaches and is highly effective.[73,74] Potential complications of a percutaneous CPN include lower extremity weakness, pneumothorax, and paresthesias.[75] Although chemoradiation therapy reduces pain in some patients, this approach, if considered, should be implemented early in the disease course.[75] Patients who have been excluded from standard chemoradiation due to unresectability may benefit from hypofractionated accelerated radiation therapy or short radiation treatment.[76]

There are many factors that contribute to patients' quality of life; along with pain control, weight stabili-

zation, and the ability to eat and maintain adequate independence, patients with pancreatic adenocarcinoma often suffer from depression, the severity of which can parallel pain intensity.[27] Adequate pain relief, counseling, and caregiver support can improve a patient's outlook.

PROGNOSIS

Factors that have been proposed to predict patient outcomes in pancreatic adenocarcinoma include symptoms at diagnosis, findings at surgery, and follow-up after treatment. Metastatic disease, pain, and decreased performance status at diagnosis have been shown to correlate with poor prognosis.[72,77] Most patients continue to lose weight and at the time of death have lost a median of 25% of their baseline weight.[78] Those able to stabilize their weight loss survived longer and had a better quality of life.[77] Patients who were symptom-free at the time of diagnosis may have the best prognosis, as their disease may be discovered incidentally and thus have lower tumor burden. Those who presented with jaundice had a better prognosis than those who complained of pain, fatigue, or nausea; patients who had back pain had a significantly worse prognosis.[79] Patients undergoing successful surgical treatment will certainly have a better prognosis than those in whom a surgical cure cannot be achieved.[80–83]

FUTURE DIRECTIONS

Researchers are working on targeting biologic agents in the signaling pathways that promote neoplastic growth. Potential biologic therapies may include inhibiting tumor invasion (epidermal growth factor receptor), angiogenesis (new blood vessel formation) with vascular endothelial growth factor inhibitors, and influencing programmed cell death (apoptosis). **HP**

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