Pancreatic Cancer

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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Abstract

Pancreatic cancer remains one of the most feared cancer diagnoses due to the poor prognosis associated with the majority of cases. Most patients present with distant metastases, and 5-year relative survival rates have changed very little in the past 40 years (3%–6%). Complete surgical resection remains the only potential cure, but even this modality is associated with a 5-year survival rate of only 20%. Systemic chemotherapy, and in some cases radiotherapy, is the primary treatment option for patients with unresectable disease. The multidisciplinary management of patients with pancreatic cancer requires expert hepatobiliary surgeons, a gastroenterologist who specializes in endoscopic ultrasound and biliary stent placement, pathologists specializing in hepatobiliary diseases, interventional radiologists, radiation oncologists, medical oncologists, a full complement of operative, surgical, and oncology nurses, clinical dietitians, diabetic specialists, pain specialists, social services, and often wound and ostomy nurse specialists. The advanced practitioner in oncology is critical to the overall coordination of the multidisciplinary approach to treatment, as well as the complex symptom management associated with either treatment approach. The diagnostic evaluation, clinical presentation, and treatment selection—including surgery, radiation, and systemic treatment options—will be discussed, with an emphasis on supportive care throughout the continuum of care for the patient with pancreatic cancer.

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Pancreatic cancer remains one of the most feared cancer diagnoses due to the poor prognosis associated with the majority of cases. The incidence of pancreatic cancer is similar in men (21,370) and women (21,770), with a total of 43,140 new cases of pancreatic cancer reported in the United States in 2010. Pancreatic cancer is the fourth most common cause of cancer-related death, with 36,800 deaths reported in 2010. The majority of patients present with distant metastases (55%), with fewer cases of localized (15%) or regional metastatic disease (22%) (Jemal, Siegel, Xu, & Ward, 2010). Five-year relative survival rates have changed very little in the past 40 years, from 3% between 1975 and 1986 to 6% between 1999 and 2005. Complete sur-

gical resection remains the only potential cure but is associated with a 5-year survival rate of only 20% (Tempero et al., 2010).

Unfortunately more than 60% of patients have advanced disease at the time of diagnosis despite attempts to improve diagnostic technologies, surgical techniques, and systemic therapies (Tempero et al., 2010; Yip, Karapetis, Strickland, Steer, & Goldstein, 2009). This is due in part to the difficult physiological location of the pancreas, which is wedged between the stomach, liver, gallbladder, small bowel, spleen, and diaphragm (Figure 1). The region is rich in lymphatic tissue, vasculature, and nerves, often excluding surgical options due to encasement or penetration of these surrounding structures. There are currently no effective screening methods for pancreatic cancer and the symptoms associated with the disease are often vague and attributed to other more benign etiologies.

Given the complexity of the disease, the generally poor prognosis, and limited treatment options, patients with pancreatic cancer should be evaluated by a multidisciplinary team and undergo a comprehensive diagnostic evaluation prior to initiating therapy. Patients considered to have potentially resectable disease should be referred to an experienced hepatobiliary surgeon. The advanced practitioner plays a vital role in facilitating the diagnostic process, which may include multiple specialties. Patients considered to have resectable disease will proceed to surgery and a complex and life-changing postoperative recovery. For those patients with unresectable disease, systemic therapy and supportive care are the primary treatment strategies. Advanced practitioners (APs) in oncology play an integral role in the complex symptom management associated with either treatment approach. The diagnostic evaluation, clinical presentation, and treatment selection—including surgery, radiation, and systemic treatment options—will be discussed, with an emphasis on supportive care throughout the continuum of care for the patient with pancreatic cancer.

Etiology and Pathophysiology

Age is the leading risk factor for developing pancreatic cancer, with the majority of patients being over the age of 65 years (Jemal et al., 2010). The incidence is similar in men and women but 30% to 40% more common in African American men (Jemal et al., 2010). Additional environmental and genetic risk factors have been suggested, including mutations in the Kristen Rat sarcoma virus proto-oncogene (*KRAS*), insulin-like growth factor 1 receptor (IGF-1R), mitogen-activated protein kinase (MAPK), *TP53*, Hedgehog (Hh), Wnt-*B*, and *DPC4* (Table 1). The role of these genetic factors in the prognosis, clinical behavior, and as potential targets for treatment continues to be explored in clinical trials. The common mutation of *KRAS* limits the role of the epidermal growth factor receptor (EGFR) agents similar to limitations seen in colorectal cancers (Strimpakos, Syrigos, & Saif, 2010).

In a series of 76 autopsies conducted in patients who died of pancreatic cancer, 70% (53) died with metastatic disease with the liver (80%), peritoneum (48%), and lung (28%) being the most common metastatic sites, and organ failure and cachexia being the most common cause of death (Iacobuzio-Donahue et al., 2009). The remaining patients (30%) died as a result of complications of locally destructive disease. The most common genetic abnormalities found on tissue analysis in this population included

Table 1. Risk Factors for Pancreatic Cancer

Individual risk factors	**Genetic risk factors**
Age > 55 years	Mutant *KRAS* (74%–100%)
African American heritage	*P16INK4a* oncogene (27%–96%)
Male	*P53* tumor suppressor gene (43%–76%)
Ashkenazi Jew heritage	*DPC4* tumor suppressor gene (SMAD4) (50%)
High body mass index	*BRCA2* tumor suppressor gene (6%–17%)
Tobacco abuse	*FHIT* tumor suppressor gene (70%)
Diabetes	Familial atypical multiple mole melanoma syndrome
Chronic pancreatitis	Ataxia-telangectasia syndrome
Environmental risk factors	Peutz-Jeghers syndrome
Radiation tobacco exposure	Hereditary pancreatitis
Chemical exposure	Hereditary nonpolyposis colorectal cancer

Note. Information from Hodgin (2010), Iacobuzio-Donahue et al. (2009), Strimpakos et al. (2010), Yachida et al. (2010), Morris et al. (2010), van Lier et al. (2010).

KRAS mutations (95%), *TP53* mutations (79%), and *DPC4* genetic mutations (63%). Clinical stage at presentation, treatment history, and histologic features did not correlate with metastatic disease in this population, whereas *DPC4* inactivation was highly correlated with widespread metastasis ($p = .007$).

Clinical Presentation and Diagnostic Evaluation

The most common presenting signs and symptoms of pancreatic cancer are often vague and attributed to other benign etiologies (Table 2). No clear early warning signs or symptoms have been identified. Presenting signs and symptoms vary according to the location of the primary tumor and extent of disease (Table 2). Abdominal pain (80%–85% of patients), weight loss, early satiety, anorexia, floating or acholic stools, dyspepsia, and nausea are the most common symptoms (Tempero et al., 2010; Hodgin, 2010). Jaundice resulting from biliary obstruction is present in approximately 90% of tumors in the head of the pancreas (Chu & Adler, 2010). Painful jaundice is more common in locally unresectable disease. The abrupt emergence of adult-onset type 2 diabetes may be an indication of underlying pancreatic cancer (Dokken & Kurtin, 2010). Unexplained thrombophlebitis, unprovoked thrombosis, or acute pancreatitis should also raise suspicion of underlying malignancy, including pancreatic cancer (Hodgin, 2010). Tumors in the pancreatic head often produce symptoms earlier than those in the body or tail of the pancreas due to the effects on surrounding structures (Figure 1).

Differential Diagnosis

Diagnosing pancreatic cancer is often challenging, as the presenting symptoms of pancreatic, hepatobiliary, and upper gastrointestinal cancers are similar. There are currently no general screening recommendations for pancre-

Table 2. Common Presenting Symptoms in Association With Tumor Location and Stage

Primary tumor location	Common presenting signs and symptoms	Clinical significance
All sites	Pain	Present in 80%–85% of patients with locally advanced or advanced disease Most often in the upper abdomen radiating through to the back May be exacerbated by eating or specific activities Often relieved by lying in a fetal position or leaning forward
	Jaundice	Common and often associated with pruritus, acholic stools, and dark urine Painful: present in approximately 50% of patients with unresectable disease Painless: present in approximately 50% of patients with locally resectable disease
	Weight loss	Often dramatic over a 6-month to 1-year period Result of increased resting energy expenditure, anorexia and malnutrition, fat malabsorption
	Ascites	Generally an indication of advanced disease
	Hyperglycemia	New onset of type 2 diabetes (within 60 months of diagnosis) is common
	Depression	Common in patients with pancreatic cancer and may affect treatment tolerance
Common clinical findngs associated with tumor location		
Pancreatic head	Weight loss, jaundice, pain, anorexia, diarrhea, dyspepsia, belching, depression	
Pancreatic body	Severe pain, palpable mass, early satiety, dyspepsia, vomiting, weight loss	
Pancreatic tail	Severe pain, dyspepsia, anorexia, weight loss, gastrointestinal bleeding, splenomegaly	
Carcinomatosis	Diffuse abdominal pain, ascites, constipation, or diarrhea	

Note. Information from Hodgin (2010) and Tempero et al. (2010).

atic cancer (Jemal et al., 2010). Screening and surveillance in patients with known risk factors such as Peutz-Jeghers syndrome or *BRCA2* mutations are being explored in prospective clinical trials (van Lier et al., 2010). A complete history, including a family history and a physical exam with scrutiny of hepatomegaly (30%–50% of patients), ascites, jaundice, or a palpable mass in the left upper quadrant is recommended (Hodgin, 2010; NCCN, 2011). Patients with symptoms suspicious for pancreatic cancer will be evaluated using standard laboratory evaluation, including a CA 19-9 level (NCCN, 2011). The CA 19-9 tumor marker has a sensitivity of 79% and a specificity of 82%, but may also be elevated in other gastrointestinal or hepatobiliary malignancies or in benign inflammatory states such as cholangitis; there is currently no US Food and Drug Administration–approved method for measurement (Chu & Adler, 2010; NCCN, 2011).

A diagnostic computed tomography (CT) scan using a pancreas protocol (triphasic cross-sectional imaging with thin slices through the pancreatic region) is the preferred imaging technique, as it allows for evaluation of the primary site and tumor involvement of important vascular or neural structures (Feig, Berger, & Fuhrman, 2006; NCCN, 2011). Due to the physiological complexity of the upper abdomen, CT imaging may not provide adequate diagnostic information; an endoscopic ultrasound may be used to clarify any questionable regional adenopathy or the site of the primary mass (NCCN, 2011). The use of positron emission tomography is generally reserved to further evaluate patients thought to have potentially resectable disease, but should not be used as the sole imaging technique (Hodgin, 2010). Pancreatic cancer arises in the head of the pancreas 60% to 70% of the time (Feig et al., 2006). The remaining lesions are located in the body or tail of the pancreas. Lesions located in the head of the pancreas most often cause symptoms such as pain or biliary obstruction and are more likely to be found in the earlier stages of the disease than lesions in the tail or body of the pancreas (Tempero et al., 2010).

Ultimately, a tissue diagnosis is required to confirm a pancreatic primary. The preferred method for biopsy is an endoscopic ultrasound–directed fine-needle aspiration of the primary mass to reduce the potential for peritoneal seeding associated with external CT-guided biopsies. Tissue testing for molecular abnormalities has become more common as a result of evolving technologies; however, clinical application of the findings is restricted primarily to the clinical trials setting. The majority (90%) of pancreatic tumors are adenocarcinomas (Sheikh, Walsh, Clynes, O'Connor, & McDermott, 2010).

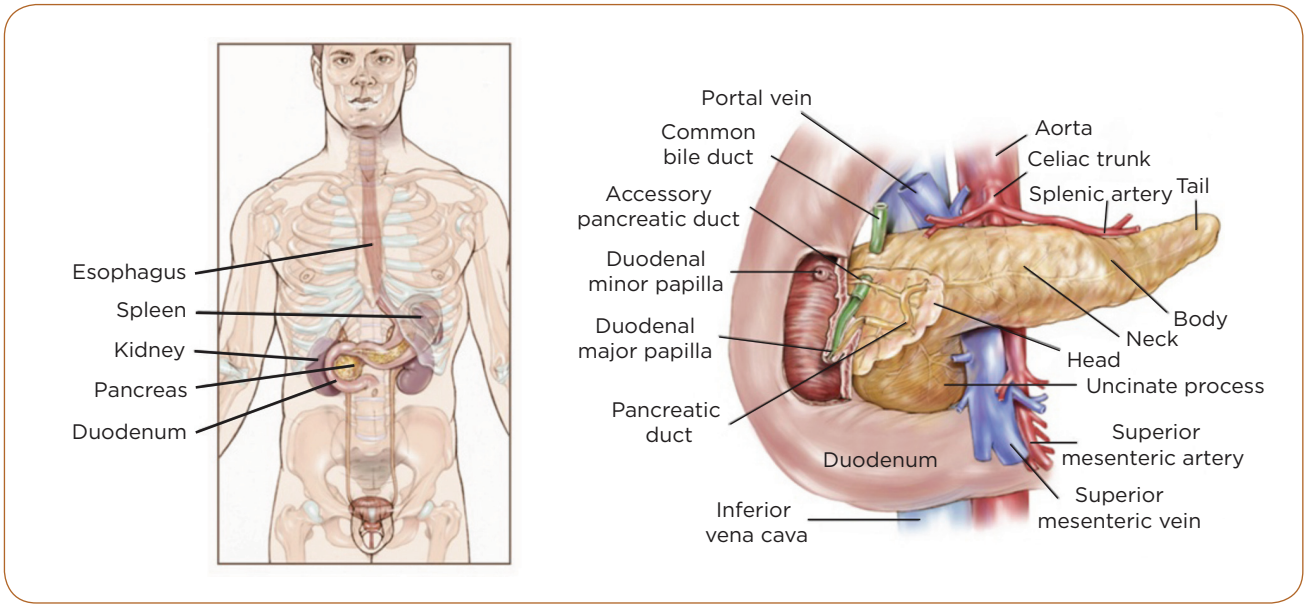

Figure 1. Physiological location of the pancreas with respect to surrounding organs. Reprinted with permission from the American Society of Clinical Oncology.

Treatment Selection

Due to the complex physiology and variable constellation of presenting symptoms, multidisciplinary review of newly diagnosed pancreatic cancer thought to be potentially resectable is the best approach to selecting patients who may benefit from this aggressive approach (NCCN, 2011). Given the high probability of recurrence after resection and the common eventual mortality due to the disease, avoiding unnecessary aggressive surgical interventions requires careful and thoughtful evaluation. Consideration will be given to estimated preoperative stage of disease, performance status, and presence of comorbidities. Fit patients (good performance status and limited or controlled comorbidities) with resectable disease will be considered for more aggressive therapies, including surgical resections and chemoradiotherapy. Importantly, 1 in 10 patients thought to have resectable disease preoperatively are determined to be unresectable during surgery (Tempero et al., 2010). A technically skilled and experienced surgeon is critical to recognizing unresectable disease to avoid unnecessarily aggressive resection.

Perhaps as important as the disease-specific criteria for aggressive treatment approaches is consideration of the self-care capabilities of the patient as well as available caregiver support. Given the limited potential for curative surgery, a full discussion with the patient regarding recovery period and the potentially reversible vs. permanent lifestyle changes and symptoms (insulin dependence, dietary changes) is critical to informed consent. Patients undergoing more aggressive surgical or combined-modality treatment will require continued support of the multidisciplinary team. The multidisciplinary management of patients with pancreatic cancer requires expert hepatobiliary surgeons, a gastroenterologist specialized in endoscopic ultrasound and biliary stent placement, pathologists specializing in hepatobiliary diseases, interventional radiologists, radiation oncologists, medical oncologists, a full complement of operative, surgical, and oncology nurses, clinical dietitians, diabetic specialists, pain specialists, social services, and often wound and ostomy nurse specialists.

The AP in oncology is critical to overall coordination of the multidisciplinary approach to treatment. This requires a working knowledge of each specialty area to reduce the incidence and severity of potential adverse events, and to improve the quality of life for the patient with pancreatic cancer. In addition, the AP plays an important role in the education and support of the family/caregiver, also critical to optimal outcomes.

Surgical Management of Pancreatic Cancer

Surgical resection is currently the only chance for cure of this very aggressive disease. The best chance for survival is a complete R0 (margin-negative) resection. The median survival of resected patients ranges from 15 to 19 months and the 5-year survival rate is approximately 20% (Tempero et al., 2010). In addition to R0 resection, the tumor histology and the absence of positive lymph nodes at the time of surgery are the best prognostic predictors of long-term survival (Tempero et al., 2010). Radiologic baseline staging with a triphasic CT scan is the preferred modality to assess for potential resectability. Patients who present with metastatic disease outside the pancreas at the time of initial presentation should not be considered surgical candidates.

There are five recognized surgical techniques used to resect pancreatic cancer. These include the standard pancreaticoduodenectomy (Whipple procedure), pylorus-preserving pancreaticoduondenectomy, total pancreatectomy, regional pancreatectomy, and what is known as the MD Anderson extended resection (Feig et al., 2006). The most common approaches are the pancreaticoduodenectomy (Whipple) and the regional pancreatectomy (see Figures 2 and 3). Total pancreatectomy is generally avoided unless positive margins are found at the time of surgery, or if pancreatic anastomosis is not possible. Patients who undergo total pancreatectomy will require lifelong insulin (Feig et al., 2006). Prior to proceeding with resection of a pancreatic lesion, laparoscopic evaluation may be recommended to rule out disseminated disease (Feig et al., 2010).

Recent studies have suggested that mortality rates for patients who undergo pancreaticoduodenectomy in low-volume centers are significantly higher than those who undergo surgery in high-volume centers. Low-volume centers were considered institutions that performed less than five pancreaticoduodenectomies per year (Tempero et al., 2010). In 2002, a study per-

formed by Birkmeyer and colleagues reviewed the mortality rate of Medicare patients that had complex surgical procedures at high-volume vs. low-volume centers. The study demonstrated that the adjusted mortality rate for patients having pancreatic resection at low-volume centers was 12.5% higher than that for patients having surgery at very high-volume centers (16.3% vs. 3.8%) (Birkmeyer et al., 2002).

Postoperative Care

Pancreatic surgery is very complex. However, with advances in surgical techniques and training, the current mortality rate is < 5% (Feig et al., 2006). Patients may experience complications that are common in routine surgeries, such as bleeding, intrabdominal abscess, and infection, as well as complications that are unique to pancreatic surgery (Morrison, 2010); see Table 3. Preoperative education and counseling of the patient, family, and caregivers regarding potential adverse events, postoperative care, and long-term lifestyle changes such as insulin dependence and reliance on oral digestive enzymes is necessary prior to proceeding with surgery.

Familiarity with common postoperative adverse events will allow for prompt diagnosis and effective management of these potentially serious complications. The formation of a pancreatic fistula, communication between the

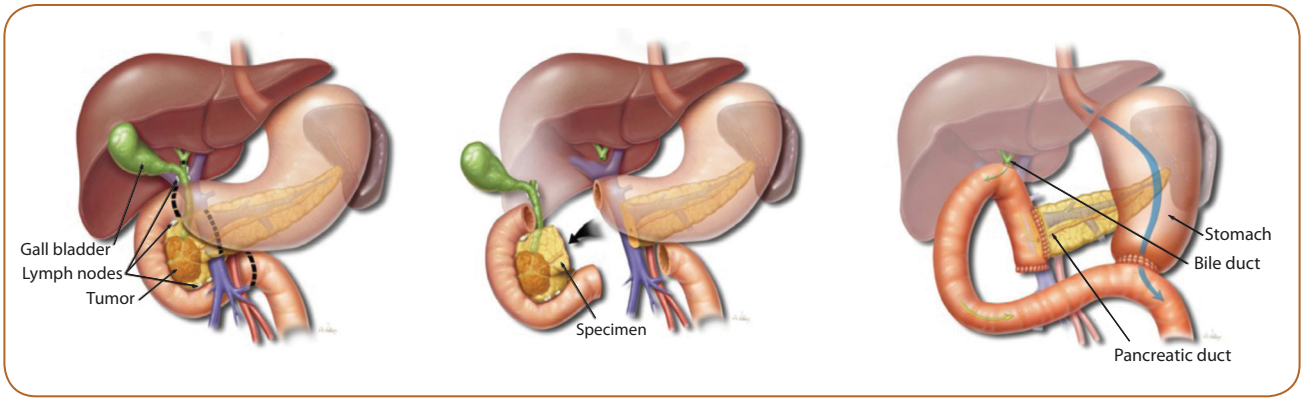

Figure 2. The Whipple procedure. Also called a pancreaticoduodenectomy, the Whipple procedure is a surgery in which the head of the pancreas, gallbladder, stomach and part of the small intestine, and the bile duct are removed. Enough of the pancreas is left to produce digestive juices and insulin. Reprinted with permission from the Elkins Pancreas Center.

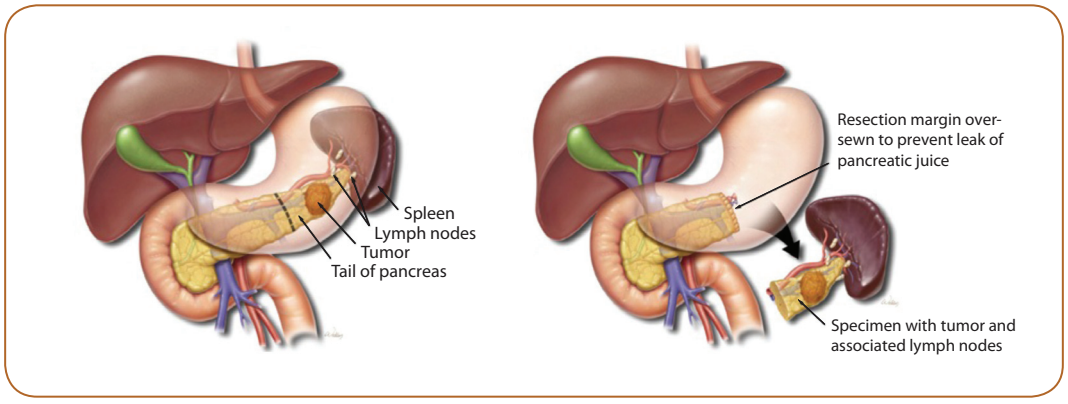

Figure 3. Distal pancreatectomy and splenectomy. A distal pancreatectomy is the removal of the end of the pancreas while leaving the pancreatic head attached. When the disease affects the splenic artery or vein, the adjacent spleen is often removed. The remaining portion of the pancreas functions normally by producing and releasing digestive enzymes and hormones. Reprinted with permission from the Elkins Pancreas Center.

pancreas and other internal structures or vessels, may occur in the early postoperative period (Morrison, 2010). As a result, digestive enzymes can leak into the peritoneal and pleural cavities, resulting in postoperative fever, ascites, chest pain, abdominal distension, escalating abdominal pain, or bleeding. An urgent CT scan, CT-guided drainage including insertion or reinsertion of an intra-abdominal drainage tube is often very effective in managing this complication when combined with supportive therapies (Feig et al., 2006; Morrison, 2010). Angiography may need to be performed in the event of bleeding to ensure there is not an arterial-enteric fistula (Feig et al., 2006).

Postoperative gastric ileus typically presents with early satiety, constipation, and postprandial nausea and vomiting. Gastric ileus is often a temporary problem due to surgical trauma and perioperative medications (Morrison, 2010). Management of gastric ileus may involve a temporary liquid diet, medications to stimulate gastric emptying such as metaclopramide, and possible gastric decompression with a nasogastric tube.

Endocrine insufficiency is common in patients with extensive pancreatic resection (Morrison, 2010). Consultation with a diabetic specialist and close scrutiny of postoperative blood glucose levels will allow early identification of insulin-dependent diabetes (Dokken & Kurtin, 2010). Exocrine insufficiency following pancreatic surgery can result in a constellation of symptoms including postprandial diarrhea and malnutrition due to lack of fat absorption and weight loss. Pancreatic enzyme replacement prior to meals, in addition to medications for diarrhea, often helps alleviate this problem (Morrison, 2010).

Another possible complication is biliary reflux. Patients may present with symptoms of chronic acid reflux, tooth enamel decay, halitosis, and nausea with bilious emesis. These patients often require long-term acid suppressants such as proton pump inhibitors in combination with antiemetics (Morrison, 2010). Since many of the postoperative complications are lifelong, regular patient education and counseling will be extremely important. Adherence to medications such as pancreatic enzymes and insulin will have a significant positive impact on postsurgical management and quality of life, but may require continued reinforcement by the multidisciplinary team.

Neoadjuvant Therapy

Patients with unresectable pancreatic cancer have a median survival of 10 to 14 months (Bikenbach et al., 2011). An estimated 1 in 4 patients who undergo pancreatic resection do not recover sufficiently from their surgery to allow administration of systemic chemotherapy (Feig et al., 2010). The role of neoadjuvant chemoradiotherapy has been evaluated in recent clinical trials. Thirty-six patients with stage III disease thought to be initially unre-

Table 3. Surgical Interventions for Pancreatic Cancer and Potential Adverse Events

Surgical Procedure	Description	Potential postoperative complications
Pancreaticoduodenectomy (Whipple procedure) Mortality rate: 3% Cancer in the head, neck, or uncinate process of the pancreas	Resection of the diseased portion of the head of the pancreas as well as a segment of the duodenum, antrectomy, cholecystectomy, choledochectomy with reconstruction via pancreaticojejunostomy, choledochojejunostomy, and gastrojejunostomy	Pancreaticojejunal anastamotic leak Pancreatic endocrine/exocrine insufficiency Intra-abdominal abscess Bleeding Arterial-enteric fistula Gastric ileus Biliary reflux
Distal pancreatectomy Mortality rate 1%–3% Cancer in the body or the tail of the pancreas	Removal of the distal portion of the pancreas as well as the spleen due to high probability of splenic artery involvement	Asplenia Pancreatic fistula Bleeding Pancreatic endocrine/exocrine insufficiency

Note. Information from Morrison (2010) and Feig et al. (2006).

sectable based on vascular invasion received either neoadjuvant chemotherapy (42%) or chemoradiotherapy (58%). At a median postoperative follow-up of 13 months (range: 2–44 months), the median overall survival (OS) was 25 months from resection and 30 months since treatment initiation (Bikenbach et al., 2011). These patients with stage III unresectable disease experienced similar survival compared to patients with stage I or II disease. A similar study investigated the use of gemcitabine, infusional 5-FU, oxaliplatin, and radiation therapy in 29 patients with borderline resectable pancreatic cancer (Lin, Kos, Sasson, Meza, & Grem, 2011). Nine patients (31%) had adequate downstaging of their disease with subsequent R0 or R1 resection. Interestingly, patients with a persistently elevated CA 19-9 level (> 90) had a significantly shorter progression-free survival (PFS) and OS (Lin et al., 2011).

Postoperative Adjuvant Therapy

Adjuvant chemotherapy, which is recommended for patients who have undergone pancreatic resection, should be initiated within 4 to 8 weeks following surgery in patients who have adequately recovered from pancreatic resection (Tempero et al., 2010; Feig et al., 2010). The CONKO-001 trial, a randomized phase III trial, assigned 368 treatment-naive patients who had undergone complete pancreatic resection to an observation arm vs. adjuvant gemcitabine. Median OS was significantly improved for patients who received gemcitabine (22.8 vs. 20.2 months; p = .005), with the median disease-free survival being 13.4 vs.6.9 months (Neuhaus et al., 2008). A large prospective randomized trial known as ESPAC-3 compared the use of bolus 5-FU/leucovorin vs. gemcitabine following pancreatic resection. The results demonstrated no significant difference in OS when the groups were compared (23.0 and 23.6 months, respectively) (Neoptolemos et al., 2010).

The impact of adjuvant chemoradiation has also been studied. A phase II study performed by the Radiation Therapy Oncology Group (RTOG 97-04) compared pre- and post-chemoradiation with 5-FU vs. pre- and post-chemoradiation with gemcitabine. The patients were given 3 weeks of chemotherapy prior to chemoradiation; a total of 50.4 Gy of radiation was given in both arms, followed by 3 months of chemotherapy. This trial demonstrated a non–statistically significant increase in OS in the gemcitabine arm (20.5 vs. 16.9

Table 4. NCCN Guidelines for Treatment of Metastatic Pancreatic Cancer V1.2011

Front-line setting	**Level of evidence**
Gemcitabine 1,000 mg/m^2 IV given over 30 min on days 1, 8, 15 on a q28d schedule	Category 1
FOLFIRINOX	Category 1
Gemcitabine 600 mg/m^2 IV given over 60 min on days 1, 8, 15 on a q28d cycle (fixed-dose gemcitabine schedule)	Category 2B
Gemcitabine and nab-paclitaxel	Category 2B
Gemcitabine 1,000 mg/m^2 IV given over 30 min + cisplatin 30 mg/m^2 IV on days 1 and 8 on a q21d cycle	Category 2B
Fixed-dose-rate gemcitabine with docetaxel + capecitabine (GTX regimen)	Category 2B
Second-line setting	
Second-line therapy may consist of a gemcitabine-based combination if not used in the front-line setting	
Capecitabine 1,000 mg/m^2 po bid on days 1–14 on a q21d cycle	
Continuous infusion 5-FU/leucovorin	
XELOX: Capecitabine 1,000 mg/m^2 po bid on days 1–14 and oxaliplatin 85 mg/m^2 IV given on day 1 on a q21d cycle	

Note. Information from NCCN (2011).

months), although there was a statistically significant difference seen in patients (388 out of 451) who underwent resection of lesions of the pancreatic head (Regine et al., 2008). Common adjuvant chemotherapy regimens include gemcitabine, 5-FU/leucovorin, and capecitabine (Xeloda)-based regimens. Gemcitabine has a more favorable side-effect profile, and is often the treatment of choice. Following the completion of 6 months of adjuvant therapy, routine surveillance should occur every 3 to 6 months for 2 years, and then annually. Each follow-up visit should include a history and physical with a review of systems evaluating symptoms of possible recurrent disease, CA 19-9 levels, CBC, serum chemistries, and CT scan imaging (Tempero et al., 2010).

Chemoradiation for the Pancreatic Cancer Patient

The role of chemoradiation in pancreatic cancer remains controversial (Ko & Crane, 2010). Chemoradiation has been used in the neoadjuvant and adjuvant settings and may also be given with palliative intent for local control of metastatic disease (Ko & Crane, 2010). Preoperative chemotherapy and chemoradiation may promote downstaging of borderline resectable disease with consideration of surgical resection following systemic treatment (Tempero et al., 2010). Four months of neoadjuvant therapy using gemcitabine is recommended prior to starting chemoradiation (NCCN, 2011). Primary definitive chemoradiation is delivered to a dose of 50 to 60 Gy with concomitant infusional 5-FU (Tempero et al., 2010). A commonly accepted regimen is continuous infusion 5-FU given at 300 mg/m^2/day, Monday through Friday on the days of radiation. Other potential radiosensitizers include oral capecitabine or gemcitabine. Gemcitabine has been shown to be the superior proven systemic therapy, but when combined with radiotherapy it has more gastrointestinal mucosa toxicities (Ko & Crane, 2010). For patients who have unresectable pancreatic lesions and no distant metastasis, a strategy of gemcitabine-based systemic chemotherapy for 2 to 6 months followed by consolidation with chemoradiation is one that has produced some favorable median survival durations of 14.4 to 18.8 months (Ko & Crane, 2010).

Medical Management for Patients With Metastatic Disease

More than 80% of patients diagnosed with pancreatic cancer will not be candidates for a potentially curable resection and a large number of patients (approximately 80%) who were able to have pancreatic resection will develop metastases within 2 to 3 years of their surgery. Systemic chemotherapy is the preferred treatment for these patients. (See Table 4 for highlights from the NCCN Guidelines for the treatment of metastatic disease.) The goal of treatment in this setting is to prolong OS and provide palliation of symptoms such as pain and biliary obstruction. Evaluation of the patient's performance status, medical history, and current symptoms should be conducted prior to determining what chemotherapeutic agents are given. Patients who have an Eastern Cooperative Oncology Group (ECOG) performance status of between 0 and 2 should be considered candidates for systemic chemotherapy. Patient preference regarding important issues such as quality of life and treatment schedules should also be considered. If possible, enrollment on a clinical trial is highly recommended, especially in the front-line setting, when a patient's performance status tends to be better. Pretreatment staging of disease with a CT of the chest, abdomen, and pelvis, and well as pertinent laboratory analysis including a CA 19-9 level prior to the initiation of systemic chemotherapy, is necessary to provide comparison after an interval of treatment to assess for response.

Gemcitabine was established as the standard of care in the treatment of pancreatic cancer in the late 1990s based on an important trial comparing weekly gemcitabine at 1,000 mg/m^2 IV to weekly 5-FU bolus. The patients who received gemcitabine had a statistically significant benefit in OS of 5.65 vs. 4.41 months with bolus 5-FU. Gemcitabine monotherapy (1,000 mg/m^2 IV over 30 minutes weekly for 3 weeks every 28 days) is recommended as the standard front-line chemotherapy for metastatic disease (Tempero et al., 2010). Gemcitabine as a single agent is generally well tolerated and may improve symptoms associated with the disease. The most common side effects of gemcitabine are myelosupression, fatigue, and nausea.

FIXED-DOSE-RATE GEMCITABINE

The way gemcitabine is administered has been the subject of investigation. When gemcitabine is

given at a fixed dose rate (10 mg/m²/min) it is felt to maximize intracellular concentrations of phosphorylated forms of gemcitabine (Tempero et al., 2003). The ECOG 6201 was a phase III trial that randomized patients with advanced pancreatic cancer to receive gemcitabine at a fixed-dose-rate vs. gemcitabine at a higher dose over 30 minutes. The median survival was increased in the group receiving the fixed dose rate gemcitabine (6.2 vs. 4.9 months; p =.04) (Tempero et al., 2003). Patients who received fixed-dose-rate gemcitabine had more myelosupression, but a tolerable side-effect profile overall.

GEMCITABINE IN COMBINATION WITH OTHER AGENTS

Numerous chemotherapeutic agents have been evaluated in clinical trials in combination with gemcitabine, including cisplatin, oxaliplatin, capecitabine, 5-FU, and irinotecan. Although the regimens of gemcitabine + cisplatin and gemcitabine + oxaliplatin vs. gemcitabine alone have been shown to have favorable response rates and clinical benefit, they have not been found to improve OS (Tempero et al., 2010). Gemcitabine has also been studied in combination with targeted agents such as bevacizumab (Avastin) and cetuximab (Erbitux), and these combinations did not correlate with improved OS when compared to single-agent gemcitabine (Tempero et al., 2010). However, in a randomized phase III trial in patients with metastatic disease evaluating gemcitabine alone vs. gemcitabine + erlotinib (inhibitor of EGFR tyrosine kinase), patients who received gemcitabine + erlotinib had more favorable results. The study was well powered (N = 569), and it demonstrated that the patients randomized to the combination arm had a statistically significant improvement in OS and PFS. Median survival was 6.24 vs. 5.91 months, and 1-year survival was 23% vs. 17% (Moore et al., 2007).

SECOND-LINE THERAPY

While many patients will benefit from front-line chemotherapy, progression of disease is expected after a varied interval of time. A number of patients will have a good performance status and be considered for second-line therapy. If at all possible, participation in a clinical trial is recommended. If a patient did not receive gemcitabine in the front-line setting, treatment with gemcitabine would be indicated. The general accepted second-line therapy is a 5-FU–based regimen with or without oxaliplatin. Oral capecitabine given at 1,000 mg/m² twice daily on days 1 through 14 on a 21-day cycle is also a good potential option. The phase III CONKO-003 study was important in making FOLFOX the routine approach to second-line therapy. The patients enrolled in this study were fluoropyrimidine naive. Patients who received FOLFOX had improvements in PFS when compared with 5-FU/leucovorin (20 vs. 13 weeks; p = .14) (Pelzer et al., 2008).

The European Study Group for Pancreatic Cancer's ESPAC-3 trial enrolled 1,088 patients from 159 cancer centers throughout Europe and Asia who had undergone pancreatic resection between July 2000 and July 2007. These patients were randomized to receive standard gemcitabine or 5-FU plus folinic acid. There was no difference in OS between patients receiving gemcitabine (23.6 months) and patients receiving 5-FU and folinic acid (23 months) (Neoptolemos et al., 2010). Serious adverse events were more common in the 5-FU/folinic acid patients (14%) compared to the gemcitabine group (7.5%), but no differences in PFS or global quality of life were found.

More recently, the phase III study PRODIGE 4/ACCORD 11 evaluated the combination of oxaliplatin, 5-FU, leucovorin, and irinotecan in patients with metastatic pancreatic cancer and good performance status. This regimen is also known as FOLFIRINOX. A planned interim analysis showed improvement in PFS (6.4 vs. 3.3 months; p < .0001) and median OS (11.1 vs. 6.8 months; p < .001) in the patients receiving FOLFIRINOX compared to those receiving standard gemcitabine therapy (Conroy et al., 2010). Serious adverse events were more common in the FOLFIRINOX arm. Fatigue (25%), neutropenia (46%), and febrile neutropenia (5.4%) were the most common grade 3/4 adverse events, making this regimen difficult to use on a regular basis in many metastatic pancreatic cancer patients who have limited overall performance status and complex comorbidities.

The Current Role of Targeted Therapy

Molecularly targeted therapies have been investigated in recent clinical trials for pancreatic adenocarcinoma. Unfortunately, the EGFR tyrosine kinase inhibitor erlotinib has been the only agent to demonstrate a modest benefit in OS

(Tempero et al., 2010). The response demonstrated to erlotinib is perplexing due to evidence that 74% to 100% of patients with pancreatic cancer have the *KRAS* mutation (Strimpakos, Syrigos, & Saif, 2010). The EGFR inhibitor cetuximab has been shown to have activity in pancreatic cancer, yet the phase III Southwest Oncology Group–directed Intergroup trial S0205 demonstrated that there was no significant difference in objective responses and overall survival for patients who received gemcitabine plus cetuximab when compared to the patients who received gemcitabine alone (Philip et al., 2010). Among the patients who were tested for EGFR tumor expression, 90% were positive, and no treatment benefit was seen in this subset (Philip et al., 2010).

Further dismal results were seen using sorafenib (Nexavar), a multitargeted kinase inhibitor that has demonstrated activity in other solid tumors. A recent phase II study was performed evaluating the role of sorafenib vs. sorafenib in combination with gemcitabine in patients with advanced pancreatic adenocarcinoma. Median PFS and OS in the group receiving sorafenib alone were 2.9 and 4.3 months, respectively. One partial response was seen in the combination arm, with a PFS and OS of 2.9 and 6.5 months, respectively. The study was closed at a mid-interim analysis due to lack of response (El-Khoueiry et al., 2011).

Additional molecular targets being investigated are vascular endothelial growth factor inhibitors. Between June 2004 and April 2006 the Cancer and Leukemia Group B conducted a randomized, double-blind, phase III clinical trial comparing the use of gemcitabine plus the VEGF inhibitor bevacizumab and gemcitabine plus a placebo in patients with untreated metastatic pancreatic adenocarcinoma. The median OS for gemcitabine plus bevacizumab was 5.8 months and that for gemcitabine plus placebo was 5.9 months; the investigators concluded that there was no benefit in adding the VEGF inhibitor bevacizumab to gemcitabine (Kindler et al., 2010).

New Therapies on the Horizon

Despite some small advances in the treatment of pancreatic cancer, new therapies are desperately needed in the treatment of this fatal disease. One of the more promising therapies under investigation is nab-paclitaxel. Nab-paclitaxel uses endogenous pathways via binding of the albumin to secreted protein acid rich in cystine (SPARC) (Moss & Lee, 2010). Pancreatic stellate cells have demonstrated the ability to produce substances that contribute to the invasion of pancreatic cancer cells. The level of SPARC produced from pancreatic stellate cells has been found to be inversely proportional to survival (Moss & Lee, 2010). In a phase II clinical trial for front-line therapy in metastatic pancreatic cancer, nab-paclitaxel and gemcitabine were given on days 1, 8, and 15 using a 28-day cycle. One patient had a complete response to therapy, 24% of patients had partial responses, and 41% of patients had stable disease (Von Hoff et al., 2009). Median PFS was 4.2 months for SPARC-negative patients and 6.2 months for SPARC-positive patients (Von Hoff et al., 2009). Although the trial had a small number of participants (N = 53), the results are encouraging and future investigation is warranted.

Another area of investigation is the hedgehog signaling pathway. It has been demonstrated that ligand-dependent activation by the hedgehog pathway occurs in the tumor microenvironment of pancreatic cancer cells (Kelleher, 2011). There have been in vivo and in vitro studies using treatment with cyclopamine (an oral inhibitor of the hedgehog pathway) that demonstrated activity in reducing pancreatic cancer metastasis (Kelleher, 2011). The use of oral hedgehog inhibitors is now in the early stages of clinical trials for pancreatic cancer.

Supportive Care and Quality of Life

Given the limited prognosis for the majority of patients with pancreatic cancer, with as many as 90% of patients dying within 1 year of diagnosis, supportive care strategies and quality-of-life considerations are a mainstay of treatment (Hodgin, 2010). The advanced practitioner in oncology plays a critical role in the continued monitoring of disease- and treatment-related symptoms common to this population, including biliary obstruction, ascites, gastric outlet obstruction, pain management, depression, pancreatic insufficiency, diabetes, thromboembolic events, and diabetes (Table 5). Adverse events can appear suddenly and unexpectedly in patients with metastatic disease. Ongoing discussion with the patient and family to include reportable signs and symptoms will promote early identification and prompt intervention for these potentially life-threatening events. End-of-life discussions and

Table 5. Common Disease- and Treatment-Related Adverse Events Associated With Pancreatic Cancer

Adverse event	Underlying cause(s)	Clinical findings	Strategies for clinical management
Nutritional deficits	Pancreatic insufficiency GERD	Anorexia Weight loss Early satiety	Nutritional consult Placement of a percutaneous enteral gastrostomy (PEG) tube Nutritional supplements rich in calories and proteins Small frequent meals Pancreatic enzymes
Gastrointestinal toxicities	Delayed gastric emptying Pancreatic insufficiency Chemotherapy Radiation	Nausea and vomiting Constipation Diarrhea Steatorrhea Early satiety	Premedication for chemotherapy and radiotherapy Institute bowel regimen for either constipation or diarrhea Consider effect of concomitant medications and comorbidities as contributing factors to bowel irregularities Medical nutritional management
Diabetes	Pancreatic insufficiency	Hyperglycemia Elevated HgA1C	Medical nutritional management Exercise Medications
Depression	Many	Anorexia Somnolence Insomnia	Referral to social services, clinical psychology, or psychiatry Antidepressants Effective treatment of pain and other symptoms
Pain	Increased intrahepatic pressure Pancreatic ischemia Fibrosis Neurogenic inflammation Perineural invasion Biliary obstruction Splanchnic nerve compression	Insomnia Pain—define type and location Anorexia	Opioids and nonopioid adjuvant agents Celiac plexus block Treatment of underlying symptoms (ascites, delayed gastric emptying, gastroesophageal reflux, constipation)
Coagulopathy	Acute onset of dyspnea, chest pain Unilateral lower extremity swelling, pain, erythema Episodic, severe, right upper quadrant pain	Pulmonary emboli Deep-vein thrombosis Thrombosis of splanchnic, mesenteric vein	Low-molecular-weight heparin Coumadin Low-molecular-weight heparin, particularly for patients taking capecitabine due to often severe supratherapeutic INR when administered concurrently Low-dose ASA Surveillance for thromboembolism
Fluid retention	Hypoalbuminemia Carcinomatosis Hepatic failure Gemcitabine	Ascites Hypoalbuminemia Abdominal bloating Lower extremity edema	Diuretics Paracentesis Percutaneous peritoneal drain Compression stockings Medical nutritional management
Pancreatic insufficiency	Surgical resection of the pancreas Extensive pancreatic disease	Diarrhea Belching Flatus Acholic stools Wasting syndrome	Enzyme replacement Medical nutritional management
Hemolytic uremic syndrome	Gemcitabine (rare)	Hematuria Bloody diarrhea Back pain Fever Lethargy	Early identification of symptoms Laboratory monitoring for acute renal failure, anemia, thrombocytopenia

Continued

Table 5. Common Disease- and Treatment-Related Adverse Events Associated With Pancreatic Cancer (cont.)

Adverse event	Underlying cause(s)	Clinical findings	Strategies for clinical management
Pneumonitis	Gemcitabine Oxaliplatin Radiation	Cough Dyspnea Fever Ground glass opacities on spiral CT of the chest	Early identification of symptoms CT of the chest for differential diagnosis of PE vs. pneumonitis High-dose corticosteroids
Palmar-plantar erythoderma	Capecitabine	Painful swelling of the palmar and plantar surfaces Desquamation	Early identification of symptoms Avoidance of friction, heat Emollient creams Dose modification or delay
Alopecia	Irinotecan and nab-paclitaxel (complete) Gemcitabine (partial)	Hair loss	Prepare the patient for hair loss Select cranial prosthesis (wig) prior to starting therapy
Peripheral neuropathy	nab-paclitaxel Oxaliplatin	Paresthesias Dysesthesias Pain Ataxia Constipation	Baseline and ongoing assessment of neuropathy Recognize symptoms may be exacerbated by concurrent diabetes
Biliary obstruction	Tumor compression of the biliary duct Adhesions	Jaundice Pain Fever Dark urine Pruritus Confusion	Stent exchange—frequency determined by plastic vs. metal stent Coordination of care with interventional radiology or gastroenterology Percutaneous biliary drains Dressing changes, bag changes, and skin care Monitoring for site infections, cholangitis Use of prophylactic antibiotics

Note. ASA = acetyl salicylic acid; INR = international normalized ratio; GERD = gastroesophageal reflux disease; PE = pulmonary embolism. Information from Dokken & Kurtin (2010), Bratton & Kurtin (2010), Hodgin (2010), Tempero (2010), Chu & Adler (2010), Ko & Crane (2010), Morrison (2010).

palliative care for symptom control are necessary when there is evidence of declining performance status or continued wasting, or in the presence of sentinel events such as biliary obstruction not amenable to decompression, rapidly recurring ascites, gastric outlet obstruction in poor surgical candidates, or end-organ failure.

Summary

Clinical advances in the diagnosis and treatment of pancreatic cancer have been limited in the past 40 years. More recent developments in the molecular analysis of this disease, the refinement of surgical and diagnostic techniques, and the development of specialized multidisciplinary teams and treatment centers have provided improved patient outcomes. Despite these advances, the overall prognosis for most patients remains dismal, and continued clinical trial enrollment is necessary to develop new strategies for treatment. The advanced practitioner in oncology plays a critical role in the coordination of patient care, monitoring and management of the complex constellation of symptoms seen in this patient population, and the facilitation of ongoing education and support of the patient and family.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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