Early Identification of Pancreatic Cancer

Rosalyn Robinson, DNP, MSN, RN, APNP, FNP-BC

Because of the delayed presentation of definitive signs and symptoms of pancreatic cancer and the anatomic location of the pancreas, pancreatic tumors are rarely detected early. Typically in an advanced stage by the time of presentation, pancreatic cancer is associated with an extremely poor survival rate. It is important for clinicians to maintain an awareness of pancreatic cancer, including patient risk factors, diagnosis through appropriate imaging studies and laboratory testing, clinical presentation, and optimal treatment and management.

**Educational Objectives:**
- Discuss the options in diagnostic imaging (including computed tomography, magnetic resonance imaging, and endoscopic ultrasound) to palliate chemotherapy.
- List the components in the physical exam and associated history and physical examination findings, and strategies for the diagnosis, staging, and management of pancreatic cancer.
- Explain the respective roles of noninvasive precursor lesions, diabetes mellitus, and other risk factors, inherited or noninherited, for pancreatic cancer.
- Describe the presenting symptoms most often reported in patients with pancreatic cancer.
- Discuss the options in diagnostic imaging (including visualization and cytologic and histologic sampling) that contribute to the diagnosis and staging of pancreatic cancer.
- Explain management strategies for each of the clinical stages of pancreatic cancer, ranging from surgical interventions (and recommended follow-up) to palliative chemotherapy.

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**Accreditation Statement:**

**Physician Assistants**
This program has been reviewed and is approved for a maximum of 1.0 hour of American Academy of Physician Assistants (AAPA) Category 1 CME credit by the Physician Assistant Review Panel. Approval is valid for one year from the issue date of April 2012. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA’s CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs. Successful completion of the self-assessment is required to earn Category 1 CME credit. Successful completion is defined as a cumulative score of at least 70% correct.

**Nurse Practitioners**
This program has been approved by the Nurse Practitioner Association New York State (The NPA) for 1.0 contact hour.

**Disclosure of Conflicts of Interest:**
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n the United States in the year 2012, it has been estimated that some 43,920 patients will receive a new diagnosis of pancreatic cancer, and about 37,390 will die of the disease. Although it represents less than 2% of new cancer diagnoses, pancreatic cancer is the fourth leading cause of cancer-related deaths in both women and men. Because the anatomical location of the pancreas makes the disease difficult to diagnose at an early stage, pancreatic cancer has a median survival of less than six months after diagnosis, and a 4.6% survival rate at 5 years. The current focus on pancreatic cancer is to improve survival through earlier diagnosis—before the tumor has reached an advanced stage.

The incidence and mortality rates for pancreatic cancer have changed only minimally during the past 30 years. In recent decades, as reported in 2011 by the National Comprehensive Cancer Network (NCCN), the incidence of pancreatic cancer has increased steadily. Prevalence is greater in men than in women, and African-Americans have an increased incidence of pancreatic cancer, compared with whites. In the United States alone, the approximate medical costs associated with pancreatic cancer in 2006 amounted to nearly $1.9 billion.

According to data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database, derived from cases reported from 17 SEER regions between 1975 and 2009, the median patient age for a diagnosis of pancreatic cancer between 2004 and 2008 was 72 years. Prevalence of pancreatic cancer was greatest (28.6%) between ages 75 and 84, and age-adjusted incidence was reported at 12.0 per 100,000 men and women per year.

The US median age for pancreatic cancer–associated mortality between 2004 and 2008, as reported by SEER, was 73. Patients in the 75-to-84 age-group account for 30.5% of pancreatic cancer–related deaths. In terms of all patient deaths reported in the US between 2004 and 2008, the overall all-pancreatic cancer–associated age-adjusted death rate was 10.8 per 100,000 men and women per year.

In most cases, pancreatic cancer has a very unfavorable prognosis. It is estimated that 52% of all patients diagnosed with pancreatic cancer already have distant disease at the time of diagnosis; in 26%, cancer has already metastasized. According to data from the NCCN, survival rates for pancreatic cancer are 24% at one year after diagnosis, and 5% at five years. Treatment options eventually narrow down to palliative care.

Nevertheless, it is important for clinicians to be knowledgeable about pancreatic cancer, with an appreciation for the complexity of this disease. A clinical understanding of patients who are at high risk for pancreatic cancer may afford clinicians the opportunity to identify and treat pancreatic cancer earlier in the disease process.

### TABLE 1

<table>
<thead>
<tr>
<th>Role of Inherited Factors in Pancreatic Cancer</th>
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<tbody>
<tr>
<td>Levels of risk (expressed as standard incidence ratios) associated with reported risk factors for pancreatic cancer are shown, in addition to the associated genetic mutations and clinical clues.</td>
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<tr>
<td>Risk factor</td>
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<tr>
<td>Peutz-Jeghers syndrome</td>
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<tr>
<td>Hereditary pancreatic cancer</td>
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<td>Cystic fibrosis</td>
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<tr>
<td>Hereditary breast/ovarian cancer</td>
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<tr>
<td>Familial atypical multiple mole melanoma syndrome</td>
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<tr>
<td>Familial pancreatic cancer</td>
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<tr>
<td>Hereditary nonpolyposis colorectal cancer syndrome</td>
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### Abbreviation: GI, gastrointestinal.


### Role of Inherited Factors in Pancreatic Cancer

| Risk factor | Level of risk | Responsible gene | Clinical clues |
| Peutz-Jeghers syndrome | 132.0 | STK11/LKB1 | Benign polypos of GI tract; pigmented macules on lips, inner lining of cheeks, hands, and feet |
| Hereditary pancreatic cancer | 52.0 | PRSS1 | History of early pancreatic inflammation with no known cause |
| Cystic fibrosis | 31.5 | CFTR | History of cystic fibrosis |
| Hereditary breast/ovarian cancer | 23.1 | BRCA1, BRCA2 | History of breast and/or ovarian cancer |
| Familial atypical multiple mole melanoma syndrome | 13.1 | CDK2NA/p16 | Multiple melanomas, with or without history of pancreatic malignancy |
| Familial pancreatic cancer | 6.4 – 32.0 | BRCA2, CDK2NA/p16, STK11, PRSS1 | Family history of pancreatic cancer |
| Hereditary nonpolyposis colorectal cancer syndrome | < 6.0 | MLH1 | Personal/family history of early colorectal cancer |

### Abbreviation: GI, gastrointestinal.


### The Development of Pancreatic Cancer

The progression from normal ductal epithelium to pancreatic ductal adenocarcinomas occurs through noninvasive precursor lesions (usually pancreatic intraepithelial neoplasias [PanINs]) that undergo clonally chosen genetic and epigenetic changes in the process. PanINs represent the most commonly identified neoplastic precursor to invasive ductal adenocarcinomas, which account for at least 90% of all pancreatic tumors and are considered one of the most lethal among all solid malignancies. PanINs measure less than 5.0 mm in diameter and cannot ordinarily be detected on pancreatic imaging. PanINs can store somatic genetic changes identified in invasive pancreatic cancers; these changes increase at the same rate that cytologic and architectural atypia develop in the precursor lesions. The genetic and epigenetic variations associated with pancreatic cancer may help explain the rapid progression of the tumor to an advanced stage.

### Pancreatic Cancer and Diabetes

The correlation between diabetes mellitus and pancreatic cancer has been acknowledged for many years; patients with type 1 or type 2 diabetes have an increased risk for...
Pancreatic cancer—by 40% to 100% in patients with long-term diabetes. In nearly one-third of patients who develop “late-onset diabetes,” this condition may be an effect (and thus, a “harbinger”) of pancreatic cancer. In the recently diagnosed diabetic patient, the risk for pancreatic cancer is increased by four- to sevenfold, and 1% to 2% of patients diagnosed with diabetes at age 50 or older will develop pancreatic cancer. In the recently diagnosed diabetic patient, the risk for pancreatic cancer and can develop the disease 20 years earlier than those with the associated genetic mutation who do not smoke. Among the germline mutations associated with cancer, BRCA2 mutations have been reported in 12% to 17% of patients with familial pancreatic cancer.

As of 2010-2011, the US Preventive Services Task Force (USPSTF) recommended against routine screening (ie, abdominal palpation for organomegaly, serologic markers, or ultrasonography) for pancreatic cancer in asymptomatic adults; the USPSTF has not yet reviewed the effectiveness of screening patients with hereditary pancreatitis, even though they “may have a higher lifetime risk for developing pancreatic cancer.” Screening for pancreatic cancer is usually reserved for patients with a lifetime pancreatic cancer risk of at least 5%; it begins with a genetic analysis to detect mutations associated with pancreatic cancer.

Imaging may follow, with the intent to detect precursor lesions or early pancreatic cancers.

**CLINICAL PRESENTATION**

Clinically silent in its early stages, pancreatic cancer usually presents after the tumor has metastasized to distant organs or has invaded adjacent tissues. Typically, patients with pancreatic cancer have undergone abdominal CT for evaluation of other clinically indicated reasons before receiving this diagnosis.

The presenting symptoms for pancreatic cancer include, but are not limited to, abdominal pain, midback pain, jaundice, loss of appetite and weight loss, floating stools, dyspepsia, nausea, and depression (see Figure 1). Reprinted from Clin Gastroenterol Hepatol, 2004;2(6). Holly et al. Signs and symptoms of pancreatic cancer: a population-based case-control study in the San Francisco Bay area, page 513. Copyright (2004), with permission from Elsevier.

**Other Risk Factors for Pancreatic Cancer**

Cigarette smoking and family history (ie, at least one first-degree relative affected by the disease) are the predominant risk factors for pancreatic cancer. In addition to smoking, significant avoidable or reversible risk factors include alcohol abuse, obesity, a sedentary lifestyle, a diet high in fats and meats and low in vegetables and folate, and certain environmental exposures (eg, solvents used in dry cleaning, gasoline-related particles, nickel). Risk factors that are unavoidable or irreversible include advancing age, male gender, African-American ethnicity, a non–O blood group type, and a history of radiation treatment.

Analyses of risk factors for pancreatic cancer appear in Table 1 and Table 2 (inherited risk factors). It has been estimated that 20% to 25% of pancreatic tumors are attributable to cigarette smoking, and individuals who smoke carry more cancer-related genetic mutations than do nonsmokers.

Additionally, patients with hereditary pancreatitis who smoke are at double the risk for pancreatic cancer and can develop the disease 20 years earlier than those with the associated genetic mutation who do not smoke. Among the germline mutations associated with cancer, BRCA2 mutations have been reported in 12% to 17% of patients with familial pancreatic cancer. As of 2010-2011, the US Preventive Services Task Force (USPSTF) recommended against routine screening (ie, abdominal palpation for organomegaly, serologic markers, or ultrasonography) for pancreatic cancer in asymptomatic adults; the USPSTF has not yet reviewed the effectiveness of screening patients with hereditary pancreatitis, even though they “may have a higher lifetime risk for developing pancreatic cancer.”

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Case Patient: Woman, 66, with Left-side Abdominal Pain and Weight Loss

An African-American woman, age 66, presented with a 5-month history of continuous abdominal pain. She reported nausea without vomiting, whether or not she had eaten recently, and denied any associated contributing factors (ie, constipation, diarrhea, bloody stools). She described the abdominal pain as cramping in nature and generalized to the left side of her abdomen; she rated the pain at 7 on a 10-point pain scale. Increased activity, she noted, aggravated her symptoms.

The patient reported a lack of appetite as a result of her abdominal pain and a weight loss of about 10 lb over the previous 2 months. Additionally, intermittent low back pain, which she described as a “pulling” sensation, had begun during the previous 2 to 3 months, although she denied any injury or trauma to explain this.

Observation revealed a patient with a nonjaundiced appearance. The abdominal exam revealed a soft and round, nondistended abdomen with no hepatosplenomegaly and no ascites. Marked tenderness of the epigastric region was noted, as well as left-side pain with no fluid wave.

The patient was referred to a gastroenterologist for further evaluation of her abdominal pain and appropriate treatment. Eventually, after multiple diagnostic tests (see “Noteworthy Findings From Diagnostic Studies,” below), abdominal/pelvic CT findings led to a diagnosis of locally advanced pancreatic cancer.

Further imaging was performed to determine the staging of the pancreatic mass. Endoscopic ultrasonography revealed three enlarged peripancreatic lymph nodes and cholelithiasis; concern for malignant involvement was raised as a result of these and other endosonographic criteria. Results of biopsy of the three enlarged lymph nodes were positive for malignancy, consistent with adenocarcinoma (tumor staging, T4 N1 MX).

Noteworthy Findings from Diagnostic Studies

**Laboratory results**
The only abnormal finding was blood urea nitrogen (BUN), which measured low at 6.0 mg/dL (normal range, 7.0 to 20.0 mg/dL).

**Imaging**
- Colonoscopy. Diffuse diverticulosis, left- greater than right-sided. Internal and external hemorrhoids. Two hyperplastic sigmoid polyps.
- Abdominal ultrasound. Poorly visualized liver. Underlying liver lesion cannot be excluded. No gallstones detected. Thickening of pericholecystic fluid with an unremarkable pancreas.
- Abdominal/pelvic CT. Nonspecific mass encasing the superior mesenteric artery. Differential considerations include inflammatory tissue relative to vasculitis versus an infiltrative surrounding mass, such as a sarcoma/lymphoma. No other significant finding (eg, adenopathy).
- Pelvic ultrasound. Markedly limited, uterus surgically absent, ovaries not seen.
- Upper endoscopy. Numerous erosions, some measuring 6 mm to 7 mm, located in the antrum and the distal body of the stomach. Linear erosions, duodenitis, normal-appearing esophagus.

**Diagnosis**

It is critical to explore the many differential diagnoses for abdominal pain; the history and physical examination should guide the evaluation. Characterizing the pain according to location, chronology, severity, aggravating and alleviating factors, and associated symptoms can be most helpful. Pregnancy should be excluded in all women of childbearing age who present with abdominal pain.

When pancreatic cancer is suspected, the differential diagnosis should include a malignant obstruction of the common bile duct, gastric cancer, cholangitis, cholelithiasis, cholelithiasis, cholecystitis, a choledochal cyst, duodenal or gastric ulcers, and acute or chronic pancreatitis.

Additionally, conditions whose symptoms can mimic those of pancreatic cancer include abdominal aortic aneurysm, intestinal ischemia, and stricture of the bile duct. Symptoms associated with pancreatic ductal adenocarcinoma may also occur in patients with tumors of the bile duct, pancreatic lymphoma, gastric lymphoma, ampullary carcinoma, or hepatocellular carcinoma.

**Laboratory Workup**

Testing should include a complete metabolic panel, lipase, amylase, and a complete blood count with differential. These will reveal abnormalities in the total bilirubin and/or liver enzymes, and possible elevation of lipase and/or amylase, which could indicate acute, chronic, or hereditary pancreatitis—all of which are implicated in pancreatic cancer.

No distinct tumor markers for pancreatic cancer have yet been identified. Though low in specificity for pancreatic cancer, the serum marker cancer antigen 19-9 (CA 19-9) is elevated in most patients when pancreatic cancer is diagnosed. Also, postsurgical levels of CA 19-9 are effective in evaluating patients’ response to neoadjuvant therapy and determining patient prognosis.

**Diagnostic Imaging**

Because it is noninvasive and relatively inexpensive, abdominal ultrasound (US) is often used first to investigate abdominal pain or jaundice; results suggestive of pancreatic cancer might include low echogenic mass or dilatation of the pancreatic duct or of the common bile duct. However, conventional US is only 50% to 70% accurate for a diagnosis of pancreatic tumor.

In many trials of imaging options for early detection and
staging of pancreatic cancer, endoscopic US (EUS) has been deemed an effective modality for defining local T and N staging and for evaluating the potential for vascular involvement; CT has been pronounced effective for defining distant metastasis. For an algorithm detailing evaluation of the patient with a suspected pancreatic tumor, see Figure 2.

All patients with suspected pancreatic cancer should be evaluated initially using CT or MRI. Multidetector row CT (MDR-CT) is the most commonly used imaging modality for the detection and staging of pancreatic carcinoma. On contrast-enhanced CT, pancreatic adenocarcinoma commonly appears as a low-density area. EUS-guided fine-needle aspiration is an appropriate option for making a diagnosis with tissue samples. Triphasic pancreatic protocol CT provides about 90% accuracy for predicting resectability of a pancreatic tumor; EUS is comparably effective.

MR cholangiopancreatography (MRCP) is a useful tool for visualizing the pancreas and the bile duct, while endoscopic retrograde cholangiopancreatography (ERCP) combines endoscopy and x-ray to visualize the pancreas and biliary tree. In one prospective, controlled study comparing these two modalities, MRCP and ERCP had 84% and 70% sensitivity, respectively, and 97% and 94% specificity, respectively, for diagnosis of pancreatic cancer (in cases actually diagnosed by histologic findings following surgical or fine-needle biopsy). Although ERCP makes it possible to obtain cytology and histology samples and to perform biliary stenting in patients with obstructive jaundice, it can miss tumors in the uncinate process, the accessory duct, and the tail of the pancreas.

Tumor Staging for Pancreatic Cancer

Pancreatic tumors can develop from various pancreatic cell lines; they are defined by appearance, hormonal function, and origin cell type. The staging system for pancreatic exocrine cancer continues to evolve. In the seventh edition of the American Joint Committee on Cancer’s AJCC Staging Manual (2011), the AJCC bases the preoperative clinical staging of pancreatic cancer on the results of high-quality cross-sectional imaging, through which local resectability and the absence or presence of distant disease are determined (see Table 3).

Clinical staging categories for the pancreatic tumor are:

- Resectable
- Borderline resectable
- Locally advanced, and
- Metastatic disease.

The significance of tumor staging extending past resectable versus unresectable is currently unknown, as treatment has had little effect on survival. Cancers involving the pancreas are typically described according to the location of involvement within the organ: the head, the body, or the tail. The uncinate process.

Confirming the presence of ductal adenocarcinoma by histology and cytology is essential; long-term survival may be increased in patients treated for other forms of pancreatic cancer (eg, ampullary or periampullary carcinomas; mucinous cystadenocarcinomas) or even benign lesions.

TREATMENT AND MANAGEMENT

One reliable evidence-based clinical resource is the NCCN publication Clinical Guidelines in Oncology for Pancreatic Adenocarcinoma. A multidisciplinary approach to resectable or borderline resectable pancreatic cancer is the best management strategy and should involve a consulting gastroenterologist, a primary care provider, a surgeon, a medical oncologist, and a radiation oncologist, if one is needed.

In patients with locally advanced or metastatic pancreatic cancer, a
Surgery

Currently, the only known curative therapy for pancreatic cancer is surgical resection of the tumor and its surrounding tissue. The anatomic location and position of the tumor will guide the choice among surgical options:

- **Classic pancreaticoduodenectomy** (the Whipple procedure), recommended for tumors involving the head, neck, and uncinate process of the pancreas.
- **Pylorus-preserving pancreaticoduodenectomy** (section of the head, neck, uncinate process, and transection of the duodenum)
- **Extended or radical pancreaticoduodenectomy** (treatment, as for periampullary malignancies, that may involve resection of the head, neck, and uncinate process of the pancreas; the duodenum, gastric antrum and pylorus, common bile duct, and gallbladder; extensive dissection of retroperitoneal tissue and lymph nodes; possible vascular resection)
- **Total pancreaticoduodenectomy**, an option to treat a multicentric tumor or diffuse carcinoma of the entire gland; and
- **Distal pancreatectomy**, for adenocarcinomas in the body and tail of the pancreas.

In patients with borderline resectable pancreatic cancer, the risk for positive surgical margins is high because tumors are likely to be involved with adjacent tissue (eg, nerve plexus, portal vein). This risk can be reduced, and prognosis improved, through neoadjuvant treatment regimens that combine gemcitabine-based chemotherapy and chemoradiotherapy.

Palliative Chemotherapy

The stated purpose of palliative therapy, according to the NCCN, is to optimize quality of life by relieving cancer-related pain and other symptoms associated with biliary obstruction or gastric outlet obstruction. For patients with locally advanced, resectable or metastatic disease, NCCN recommendations (category 1 or 2A) for appropriate first-line therapy include:

- Gemcitabine, standard infusion (ie, 1,000 mg/m² over 30 min, once per week for three weeks every 28 days), though not considered effective for certain pancreatic carcinomas
- Gemcitabine plus cisplatin
- Gemcitabine plus erlotinib
- Gemcitabine plus capcitabine

In 2011, researchers in France reported results of a phase III trial comparing gemcitabine with the combination chemotherapy regimen FOLFIRINOX (oxaliplatin, irinotecan, 5-fluorouracil, and leucovorin). According to Conroy et al, patients randomized to receive FOLFIRINOX experienced a survival advantage (median progression-free survival, 6.4 months vs 3.3 months) and delayed degradation of quality of life, but they were more likely to experience toxicity (eg, febrile neutropenia, thrombocytopenia) than patients in the gemcitabine group.

NCCN-recommended second-line therapies include gemcitabine monotherapy (for patients who have not previously received this agent); capcitabine monotherapy; 5-fluorouracil combined with leucovorin and oxaliplatin; or oxaliplatin plus capcitabine.

FOLLOW-UP

The primary care provider should initiate supportive care at the time the patient receives a diagnosis of pancreatic cancer, including information about prognosis and treatment options (particularly palliative care). The clinician should continue to follow the patient’s clinical course throughout treatment for advanced disease. Pain management should be a priority, particularly identifying and addressing its precise cause.

As with other cancers, pancreatic cancer poses a considerable risk for recurrence after surgical resection and/or chemoradiation. Ongoing follow-up physical exams, routine laboratory studies (including screening for CA 19-9 every one to three months), and imaging studies should be ordered and results reviewed periodically (for example, CT at least every six months).

Anticipatory Guidance for At-Risk Patients

Counseling patients at high risk for pancreatic cancer, targeting prevention and early detection, is key to reducing the incidence of this lethal disease. It is important to educate patients regarding the risk factors associated with pancreatic cancer—particularly smoking, the most reversible risk factor for pancreatic cancer. Patients who present with chronic pancreatitis and who consume excessive amounts of alcohol should be warned about the association between chronic pancreatitis and pancreatic cancer.
Counseling should also focus on healthy eating, with a diet high in fruits and vegetables, routine physical activity, weight management, and an increased dietary intake of vitamin D (> 600 IU/d). Genetic counseling and testing options should be explored with at-risk patients and their families. These patients should be advised to seek immediate medical attention for abdominal pain, unexplained weight loss, and/or jaundice, and to return for further evaluation if symptoms persist despite initial treatment.

The greater the clinician’s clinical understanding of the various pancreatic syndromes and their management, the better prepared he or she will be to evaluate each patient’s genetic risk and to provide high-quality clinical care.

CONCLUSION

Making a diagnosis of pancreatic cancer early enough to make effective treatment possible continues to challenge both researchers and clinicians. Current treatment modalities are not sufficiently effective, as evidenced by the high mortality rate associated with pancreatic cancer. Until clinical research provides increased insight into detecting this lethal disease and generating more effective therapies, it is up to the primary care clinician to routinely explore the family and social history of at-risk patients and to recognize the risk factors and symptomatology associated with pancreatic cancer. Early detection, followed by the most effective treatment options available, may lead to a more hopeful prognosis.