Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer

Author: Carlos Fernandez-del Castillo, MD
Section Editors: Kenneth K Tanabe, MD, Douglas A Howell, MD, FASGE, FACG, Tracy Jaffe, MD
Deputy Editors: Diane MF Savarese, MD, Kristen M Robson, MD, MBA, FACG

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INTRODUCTION

Cancer of the exocrine pancreas is a highly lethal malignancy. It is the fourth leading cause of cancer-related death in the United States and second only to colorectal cancer as a cause of digestive cancer-related death. (See "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer", section on 'Epidemiology'.)

Surgical resection is the only potentially curative treatment. Unfortunately, because of the late presentation, only 15 to 20 percent of patients are candidates for pancreatectomy. Furthermore, prognosis is poor, even after a complete resection. Five-year survival after margin-negative (R0) pancreaticoduodenectomy is approximately 30 percent for node-negative and 10 percent for node-positive disease (figure 1) [1]. (See "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis".)

The clinical presentation, diagnostic evaluation, and staging workup for pancreatic exocrine cancer will be reviewed here. Epidemiology and risk factors, pathology, surgical management, adjuvant and neoadjuvant therapy, and treatment of advanced pancreatic exocrine cancer, including palliative local management, are discussed elsewhere.

- (See "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer".)
- (See "Pathology of exocrine pancreatic neoplasms".)
- (See "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis".)
- (See "Treatment for potentially resectable exocrine pancreatic cancer".)
- (See "Initial chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable, exocrine pancreatic cancer".)
- (See "Supportive care of the patient with locally advanced or metastatic exocrine pancreatic cancer".)
- (See "Initial systemic chemotherapy for metastatic exocrine pancreatic cancer".)

PATHOLOGY

The commonly used term "pancreatic cancer" usually refers to a ductal adenocarcinoma of the pancreas (including its subtypes), which represents approximately 85 percent of all pancreatic neoplasms. Of the several subtypes of ductal adenocarcinoma, most have a similar poor long-term prognosis, with the exception of colloid carcinomas, which have a better prognosis, and adenosquamous cancers, which have a worse prognosis than other subtypes. In general, all are treated similarly. The more inclusive term "exocrine pancreatic neoplasms" includes all tumors that are related to the pancreatic ductal and acinar cells and their stem cells (including pancreatoblastoma), and is preferred. (See "Pathology of exocrine pancreatic neoplasms".)

More than 95 percent of malignant neoplasms of the pancreas arise from the exocrine elements. Neoplasms arising from the endocrine pancreas (ie, pancreatic neuroendocrine [islet cell] tumors) comprise no more than 5 percent of pancreatic neoplasms; their clinical manifestations, diagnosis, and staging is addressed elsewhere. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms".)

CLINICAL PRESENTATION

The most common presenting symptoms in patients with exocrine pancreatic cancer are pain, jaundice, and weight loss. In a multi-institutional series of 185 patients with exocrine pancreatic cancer diagnosed over a three-year period (62 percent involving the head of the gland, 10 percent body, 6 percent tail, and the remainder not determined), the most frequent symptoms at diagnosis were [2]:

- Asthenia – 86 percent

- Weight loss – 85 percent
- Anorexia – 83 percent
- Abdominal pain – 79 percent
- Epigastric pain – 71 percent
- Dark urine – 59 percent
- Jaundice – 56 percent
- Nausea – 51 percent
- Back pain – 49 percent
- Diarrhea – 44 percent
- Vomiting – 33 percent
- Steatorrhea – 25 percent
- Thrombophlebitis – 3 percent

The most frequent signs were:

- Jaundice – 55 percent
- Hepatomegaly – 39 percent
- Right upper quadrant mass – 15 percent
- Cachexia – 13 percent
- Courvoisier's sign (nontender but palpable distended gallbladder at the right costal margin) – 13 percent
- Epigastric mass – 9 percent
- Ascites – 5 percent

The initial presentation of pancreatic cancer varies according to tumor location. Approximately 60 to 70 percent of exocrine pancreatic cancers are localized to the head of the pancreas, while 20 to 25 percent are in the body/tail and the remainder involve the whole organ [3]. Compared with tumors in the body and tail of the gland, pancreatic head tumors more often present with jaundice, steatorrhea, and weight loss [2,4,5]. As an example, in the above noted series, jaundice was present in 73 percent of the 114 patients with a tumor located in the head of the pancreas, compared with 11 percent of 19 body lesions, and none of the 11 tail lesions [2]. Steatorrhea was present in 28 percent of the patients with pancreatic head lesions versus 11 percent of those with body, and none of those with tail lesions. Steatorrhea is attributable to loss of the pancreas's ability to secrete fat-digesting enzymes or to blockage of the main pancreatic duct.

Pain is one of the most frequently reported symptoms, even with small (<2 cm) pancreatic cancers [6,7]. The pain associated with pancreatic cancer is usually insidious in onset, and has been present for one to two months at the time of presentation. It has a typical gnawing visceral quality, and is generally epigastric, radiating to the sides and/or straight through to the back. It may be intermittent and made worse by eating or lying supine. It is frequently worse at night. Lying in a curled or fetal position may improve the pain. Severe back pain should raise suspicion for a tumor arising in the body and tail of the pancreas. Rarely, pain develops very acutely, as a result of an episode of acute pancreatitis due to tumoral occlusion of the main pancreatic duct [8]. (See "Etiology of acute pancreatitis".)

Jaundice, which is usually progressive, is most often due to obstruction of the common bile duct by a mass in the head of the pancreas, causing hyperbilirubinemia. Jaundice may be accompanied by pruritus, darkening of the urine, and pale stools. Hyperbilirubinemia is characteristically of the cholestatic type, with a predominant increase in the conjugated fraction of bilirubin. (See "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia" and "Classification and causes of jaundice or asymptomatic hyperbilirubinemia".)

Jaundice is a relatively early sign in tumors arising from the pancreatic head, and pancreatic tumors that present with painless jaundice have been ascribed a relatively more favorable prognosis compared with those that present with pain and obstructive jaundice [4,9]. Jaundice secondary to a tumor in the body or tail typically occurs later in the course of the disease and may be secondary to liver metastases.

A recent onset of diabetes mellitus [10-12] may be noted. Diabetes is common in the age group where pancreatic cancer occurs, but in up to 25 percent, the disease may be heralded by new-onset (two years or less) diabetes. Several studies have addressed whether earlier detection of nonspecific signs of an evolving pancreatic neoplasm (particularly in adults with new-onset diabetes mellitus) might improve resectability and overall outcomes, but the results are inconclusive. Screening for pancreatic cancer in adults with new-onset diabetes mellitus is discussed elsewhere. (See "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer", section on 'Diabetes mellitus, glucose metabolism, and insulin resistance'.)

Unexplained superficial thrombophlebitis, which may be migratory (classic Trousseau's syndrome) [13], is sometimes present and reflects the hypercoagulable state that frequently accompanies pancreatic cancer. There is a particularly high incidence of thromboembolic events (both venous and arterial), particularly in the setting of advanced disease, and clinicians should maintain a high index of suspicion. Multiple arterial emboli resulting from nonbacterial thrombotic endocarditis may occasionally be the presenting sign of a pancreatic cancer [14].

Thromboembolic complications occur more commonly in patients with tumors arising in the tail or body of the pancreas [15]. (See "Risk and prevention of venous thromboembolism in adults with cancer" and "Nonbacterial thrombotic endocarditis".)

Skin manifestations occur as paraneoplastic phenomena in some patients. As an example, both cicatricial and bullous pemphigoid are described, even as a first sign of disease [16]. (See "Cutaneous manifestations of internal malignancy", section on 'Paraneoplastic pemphigus'.)

Rarely, erythematous subcutaneous areas of nodular fat necrosis, typically located on the legs (pancreatic panniculitis), may be evident, particularly in patients with the acinar cell variant of pancreatic cancer (figure 2). It is hypothesized that the condition is initiated by autodigestion of subcutaneous fat secondary to systemic spillage of excess digestive pancreatic enzymes. The presence of this condition is not pathognomonic for an exocrine pancreatic cancer, as it has been described with pancreatic neuroendocrine tumors, intraductal papillary mucinous neoplasms, and in chronic pancreatitis. (See "Pathology of exocrine pancreatic neoplasms", section on 'Acinar cell carcinoma' and "Panniculitis: Recognition and diagnosis" and "Cutaneous manifestations of internal malignancy", section on 'Pancreatic panniculitis'.)

Signs of metastatic disease may be present at presentation. Metastatic disease most commonly affects the liver, peritoneum, lungs, and less frequently, bone. Signs of advanced, incurable disease include the following:

- An abdominal mass.
- Liver metastases.
- Ascites (image 1).
- Left supraclavicular lymphadenopathy (Virchow's node) (image 2).
- A palpable periumbilical mass (Sister Mary Joseph's node) (image 3) or a palpable rectal shelf are present in some patients with widespread disease. Pancreatic cancer is the origin of a cutaneous metastasis to the umbilicus in 7 to 9 percent of cases [17].

Routine laboratory tests are often abnormal but are not specific for pancreatic cancer. Common abnormalities include an elevated serum bilirubin and alkaline phosphatase levels, and the presence of mild anemia.

Incidental finding — A solid pancreatic lesion is uncommonly found as an incidental finding on computed tomography (CT) scans done for another reason. In one report, 24 of the 321 patients with a solid pancreatic mass who were identified over an eight-year period had it incidentally discovered (7 percent); one-half of these were adenocarcinomas, while the remainder were pancreatic neuroendocrine tumors [18]. The majority of pancreatic lesions discovered on radiographic studies performed for another reason are cystic, and many of these represent intraductal papillary mucinous neoplasms, some of which will be a precursor lesion to exocrine pancreatic cancer. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Clinical presentation' and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Progression to pancreatic cancer'.)

DIFFERENTIAL DIAGNOSIS

The signs and symptoms associated with pancreatic cancer are often nonspecific, so the differential diagnosis is large. Three of the more common findings leading to suspicion for pancreatic cancer are jaundice, epigastric pain, and weight loss.

The positive predictive value (PPV) of these symptoms for the diagnosis of pancreatic cancer is low, with the possible exception of jaundice in an older patient. This was shown in a case-control study that examined the risk of pancreatic cancer based upon symptoms that were identified in the year before diagnosis in 21,624 patients seen in a primary care clinic [19]. The PPV of jaundice for pancreatic cancer in a patient aged 60 or older was 22 percent; it was <3 percent for all other single symptoms or pairs of non-jaundice symptoms, even in older individuals.

Jaundice — The differential diagnosis of the jaundiced patient is broad; a classification of jaundice according to the type of bile pigment and underlying mechanism of hyperbilirubinemia is presented in the table (table 1). Patients with biliary obstruction due to pancreatic cancer usually present with conjugated hyperbilirubinemia, and the differential diagnosis includes choledocholithiasis, biliary obstruction from other malignant tumors or adenomas, intrahepatic cholestasis, and acute or chronic hepatocellular injury (algorithm 1).

The diagnostic evaluation of a jaundiced patient with biliary obstruction is designed to eliminate benign tumors or gallstones from the differential and to establish the location and extent of tumor invasion and spread if a malignant bile duct obstruction is detected. (See "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia".)

Epigastric pain — The differential diagnosis of epigastric pain in adults is broad. Most patients with pancreatic cancer and abdominal pain have pain that has been present for more than three days, but not for many months. As such, they generally fall into the category of subacute pain, and the causes of both acute and chronic pain need to be included in the differential diagnosis. (See "Causes of abdominal pain in adults".)

The diagnostic approach generally depends on the history, location of the pain, tempo, and the general suspicion for benign versus malignant disease based upon associated symptoms such as weight loss. (See "Causes of abdominal pain in adults".)

Weight loss — Some of the causes of involuntary weight loss include malignancies, endocrinopathies, and psychiatric diseases. This is discussed in detail elsewhere. (See "Approach to the patient with unintentional weight loss".)

Pancreatic mass seen on an imaging study — Solid pancreatic masses may be detected incidentally on abdominal imaging studies. (See 'Incidental finding' above.)

The differential diagnosis of a pancreatic mass depends upon whether the mass is cystic or solid. Cystic pancreatic lesions include non-neoplastic cysts (eg, true cysts, retention cysts) (image 4A-B), pancreatic pseudocyst (image 5), and pancreatic cystic neoplasms (eg, intraductal papillary mucinous neoplasm of the pancreas (image 6 and image 7)), serous cystic tumors (image 8 and image 9), and mucinous cystic neoplasms (image 8 and image 10 and image 11). The classification and evaluation of cystic pancreatic lesions is discussed in detail elsewhere. (See "Classification of pancreatic cysts" and "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management".)

The differential diagnosis of a solid pancreatic mass seen on a radiographic imaging study includes a primary exocrine pancreatic cancer, a pancreatic neuroendocrine tumor, a solid pseudopapillary tumor (rare), lymphoma (rare) (image 12), metastatic cancer (rare), intrapancreatic accessory spleen, focal pancreatitis, and autoimmune pancreatitis.

Pancreatic neuroendocrine tumors are typically highly vascular with enhancement in the early arterial phase and washout in the early portal venous phase. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Computed tomography'.)

Although rare, the diagnosis of a pancreatic metastasis may be considered in a patient who has evidence of malignant disease in other sites. The most common primary sites for this are renal cell carcinoma and melanoma.

Clues suggesting the possibility of a primary pancreatic lymphoma include a lack of jaundice, constitutional symptoms (weight loss, fever, and night sweats), an elevated serum lactate dehydrogenase (LDH) or beta-2 microglobulin level, and a normal serum carbohydrate antigen 19-9 (CA 19-9) [20,21]. Primary pancreatic lymphomas are typically larger than 6 cm, and surrounding lymphadenopathy is common as with any lymphoma; however, neither of these features would exclude adenocarcinoma.

An endoscopic ultrasound (EUS)-guided biopsy may be recommended if a diagnosis of chronic or autoimmune pancreatitis is suspected on the basis of history (eg, extreme young age, history of alcohol use disorder, history of other autoimmune diseases), particularly if further imaging studies (either EUS, endoscopic retrograde cholangiopancreatography, CT, or magnetic resonance cholangiopancreatography [MRCP]) reveal multifocal biliary strictures (suggestive of autoimmune pancreatitis) or diffuse pancreatic ductal changes (suggestive of chronic pancreatitis).

Among patients who have a mass in the head of the pancreas or a malignant bile duct obstruction in the vicinity of the distal common bile duct, differentiating a primary exocrine pancreatic carcinoma from other less common periampullary malignancies (arising in the ampulla, duodenum, or bile duct) can be challenging (figure 3). Although the diagnosis may be evident after radiographic and endoscopic evaluation, it may not be possible to distinguish the tissue origin of a malignant periampullary neoplasm until resection and histopathologic evaluation of the entire surgical specimen is completed. (See "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging", section on 'Diagnostic evaluation'.)

DIAGNOSTIC APPROACH

It is not possible to reliably diagnose a patient with pancreatic cancer based on symptoms and signs alone. The lack of specificity for the diagnosis of pancreatic cancer when based on symptoms that are highly suggestive and sensitive for pancreatic cancer was shown in a landmark study in which 57 percent of such patients had other diagnoses, including non-pancreatic intra-abdominal cancers (13 percent), pancreatitis (12 percent), and non-pancreatic, non-cancerous disorders including irritable bowel syndrome (23 percent) and miscellaneous other conditions (10 percent) [22].

Awareness of risk factors (genetic predisposition, age, smoking, diabetes) may lead to an earlier and more aggressive evaluation for pancreatic cancer in patients who present with symptoms suspicious for the disease. (See "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer".)

In general, the diagnostic evaluation of a patient with suspected pancreatic cancer includes serologic evaluation and abdominal imaging. Additional testing is then directed based upon the findings of the initial testing as well as the patient's clinical presentation and risk factors.

Initial testing — All patients presenting with jaundice or epigastric pain should have an assay of serum aminotransferases, alkaline phosphatase, and bilirubin to determine if cholestasis is present. In addition, patients with epigastric pain should be evaluated for acute pancreatitis with a serum lipase. (See "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia", section on 'Initial laboratory tests' and "Causes of abdominal pain in adults".)

An additional test that can be useful is measurement of the tumor marker carbohydrate antigen 19-9 (CA 19-9). (See 'Carbohydrate antigen 19-9' below.)

The next step in the patient's evaluation is abdominal imaging, though the choice of test varies depending upon the patient's presenting symptoms.

Jaundice — For patients with jaundice, the initial imaging study is often transabdominal ultrasound (US). Transabdominal US has high sensitivity for detecting biliary tract dilation and establishing the level of obstruction. It also has high sensitivity (>95 percent) for detecting a mass in the pancreas, although sensitivity is lower for tumors <3 cm. (See 'Transabdominal ultrasound' below and "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia", section on 'Suspected biliary obstruction or intrahepatic cholestasis'.)

In other cases, CT of the abdomen and pelvis is the initial test ordered. CT has the advantage of providing information on potential resectability and the presence or absence of metastatic disease if a pancreaticobiliary neoplasm is suspected. (See 'Abdominal CT' below.)

Epigastric pain and weight loss — Abdominal CT is the preferred initial imaging test in patients presenting with epigastric pain and weight loss, but without jaundice. (See 'Abdominal CT' below.)

In practice, transabdominal US is commonly utilized as an initial screening technique for biliary-pancreatic disease in such patients because of to its low cost and wide availability [23,24]. However, while transabdominal US has high sensitivity for detecting tumors >3 cm, it is much lower for smaller tumors. (See 'Transabdominal ultrasound' below.)

Furthermore, if acute pancreatitis is in the differential, transabdominal US is not the preferred initial test. It is associated with a high frequency of incomplete examinations owing to overlying bowel gas from an ileus, and it cannot clearly identify necrosis within the pancreas; these important findings are best seen by contrast-enhanced CT scan.

For these reasons, and because of the greater amount of staging information that can be obtained, CT is preferred in this setting, particularly for patients who have symptoms other than epigastric pain that raise suspicion for pancreatic cancer (eg, weight loss, recent diagnosis of atypical diabetes mellitus, jaundice) [25-29]. (See 'Clinical presentation' above.)

Subsequent testing if initial imaging is positive — If a pancreatic mass is seen on transabdominal US, an abdominal CT scan is typically next obtained to confirm the presence of the mass and to assess disease extent; in other cases, a CT may have been done as the initial test. In either case, if a pancreatic cancer is suspected, a "pancreatic protocol" (ie, multi-phase contrast-enhanced, helical) CT of the abdomen and pelvis is the next step. If the CT appearance is typical for a pancreatic cancer, enough information is provided to assess resectability, and the patient is fit for a major operation, additional testing (including biopsy) may be unnecessary before surgical intervention. On the other hand, if the diagnosis is in doubt, resectability is uncertain, or if a therapeutic intervention is needed, additional procedures may be indicated. (See 'Staging system and the staging workup' below and 'Diagnostic algorithm and need for preoperative biopsy' below and 'Abdominal CT' below.)

In some institutions, magnetic resonance imaging (MRI) is preferred over CT, with very similar sensitivity and specificity regarding identification of the mass and metastatic spread.

ERCP is indicated if biliary decompression is required; in such cases, diagnostic sampling can also be performed. However, not all patients with biliary obstruction from pancreatic cancer require decompression, and stent placement should be avoided in patients who have not yet undergone CT because a stent may cause artifact in the pancreatic head that can mask the lesion, and the trauma of stent insertion may induce inflammatory changes that might be indistinguishable from tumor. (See 'Endoscopic retrograde cholangiopancreatography' below and "Endoscopic stenting for malignant biliary obstruction" and "Surgical resection of lesions of the head of the pancreas", section on 'Preoperative biliary drainage' and "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis", section on 'Role of preoperative biliary drainage'.)

MRCP is an alternative for patients who cannot undergo ERCP (eg, those with a gastric outlet obstruction), but it lacks therapeutic capability. (See 'Magnetic resonance cholangiopancreatography' below.)

Endoscopic ultrasound (EUS)-guided or percutaneous biopsies of a pancreatic mass can be obtained if histologic confirmation is needed, though this is not always required in patients who appear to have potentially resectable disease and who have typical imaging findings. EUS may also be used as an alternative to contrast-enhanced multi-phase helical CT for the staging of pancreatic cancer. (See 'Endoscopic ultrasound' below and 'Biopsy and establishing the diagnosis' below.)

Subsequent testing if initial imaging is negative — For patients who are strongly suspected of having pancreatic cancer but whose initial imaging is negative, further testing may be indicated. If an abdominal CT scan has not yet been done, that is the next step.

For patients with cholestasis who have no additional findings on US or CT, ERCP is indicated. MRCP is an alternative for patients who cannot undergo ERCP (eg, those with a gastric outlet obstruction). (See 'Jaundice' above and 'Magnetic resonance cholangiopancreatography' below.)

If these tests are negative, additional testing is typically not required and an alternative cause for the patient's symptoms should be sought. However, if the suspicion for pancreatic cancer remains high (eg, in a patient with profound weight loss or who has risk factors for pancreatic cancer, such as hereditary pancreatitis or chronic pancreatitis), an EUS is a reasonable next step to exclude a small pancreatic cancer (algorithm 2). (See "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer", section on 'Risk factors'.)

Any lesions that are visible only on EUS should be biopsied to confirm the diagnosis prior to surgical exploration. EUS-guided fine-needle aspiration (FNA) biopsy is the best modality for obtaining a tissue diagnosis, even if the tumor is poorly visualized by other imaging modalities. In a series of 116 patients suspected of having pancreatic cancer, but with inconclusive findings on CT scan, EUS with FNA had a sensitivity and specificity for diagnosing a pancreatic malignancy of 87 and 98 percent, respectively [30]. Independent risk factors associated with EUS detection of pancreatic ductal adenocarcinoma included pancreatic ductal dilation on CT scan (odds ratio [OR] 4.1, 95% CI 1.5-11) and tumor size detected by EUS of ≥1.5 cm (OR 8.5, 95% CI 2.0-35).

Specific tests used in the initial evaluation

Transabdominal ultrasound — The initial study in patients who present with obstructive jaundice, or epigastric pain and weight loss is often transabdominal US. Transabdominal US has high sensitivity for detecting biliary tract dilation and establishing the level of obstruction. (See "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia", section on 'Suspected biliary obstruction or intrahepatic cholestasis'.)

On US, a pancreatic carcinoma typically appears as a focal hypoechoic hypovascular solid mass with irregular margins. Dilated bile ducts may also suggest the presence of a pancreatic tumor.

Support for the utility of first-line abdominal US for the diagnosis of a pancreatic tumor in patients who present with symptoms of pancreatic cancer comes from a prospective cohort study of 900 patients who underwent transabdominal US to work up painless jaundice, anorexia, or unexplained weight loss [31]. The sensitivity for detection of all tumors in the pancreas was 89 percent (124 of 140), including 90 percent for detection of exocrine pancreatic cancer (79 of 88 patients). Among the 779 patients who were followed over time and established not to have developed a pancreatic tumor, 9 had false-positive US findings (specificity 99 percent).

While the reported sensitivity for US in diagnosing pancreatic cancers arising in the head and neck of the pancreas is 95 percent for tumors >3 cm, it is much less for smaller tumors [23,31,32]. Sensitivity is also dependent upon the expertise of the ultrasonographer and the presence or absence of bile duct obstruction. Ultrasound is of little utility for evaluation of pancreatic tail masses as this region is usually obscured by bowel gas.

Abdominal CT — A mass within the pancreas is the most common CT finding of pancreatic cancer, although enlargement of the whole gland is sometimes seen [27,33]. Sensitivity of CT for pancreatic cancer depends on technique and is highest (89 to 97 percent) with a multi-phase contrast-enhanced, helical multidetector row CT [34]. This "pancreatic protocol" type of CT is often not the initial study for a patient without a known diagnosis of pancreatic cancer.

As expected, sensitivity is higher for larger tumors; in one study, the sensitivity was 100 percent for tumors >2 cm, but only 77 percent for tumors ≤2 cm in size [35]. (See 'Technique' below and 'Initial testing' above.)

The typical CT appearance of an exocrine pancreatic cancer is an ill-defined hypoattenuating mass within the pancreas (image 13), although smaller lesions may be isoattenuating, making their identification difficult. Intravenous contrast is required to detect most pancreatic malignancies.

Secondary signs of a pancreatic cancer (which are seen with many small isoattenuating cancers) include a pancreatic duct cutoff, dilatation of the pancreatic duct or common bile duct, parenchymal atrophy, and contour abnormalities as well as a soft tissue cuff around the superior mesenteric artery (image 14) [36]. Dilation of both the pancreatic duct and the common bile duct, commonly referred to as the "double duct sign" is present in approximately 62 to 77 percent of cases of pancreatic cancer (picture 1), but is not diagnostic for a pancreatic head malignancy [37,38]. Approximately 50 percent of ampullary carcinomas have a double duct sign [39], and it can also occasionally be seen with benign adenomas and autoimmune pancreatitis [40]. (See "Autoimmune pancreatitis: Clinical manifestations and diagnosis".)

Endoscopic retrograde cholangiopancreatography — ERCP is a highly sensitive tool for visualization of the biliary tree and pancreatic ducts. (See "Endoscopic methods for the diagnosis of pancreatobiliary neoplasms", section on 'Endoscopic retrograde cholangiopancreatography'.)

An early meta-analysis found a sensitivity of 92 percent and specificity of 96 percent for diagnosing cancer of the pancreas by ERCP [41]. Findings suggestive of a malignant tumor within the head of the pancreas include superimposable strictures or obstruction of the common bile and pancreatic ducts (the "double duct" sign), a pancreatic duct stricture in excess of 1 cm in length, pancreatic duct obstruction, and the absence of changes suggestive of chronic pancreatitis (picture 1).

Furthermore, ERCP provides an opportunity to collect tissue samples (forceps biopsy, brush cytology) for histologic diagnosis. However, the sensitivity for detection of malignancy (approximately 50 to 60 percent) is lower than that of EUS-guided FNA (sensitivity 92 percent). (See "Endoscopic methods for the diagnosis of pancreatobiliary neoplasms", section on 'Tissue sampling during ERCP' and 'Endoscopic ultrasound-guided biopsy' below.)

Other limitations of ERCP are that parenchymal abnormalities can only be detected by inference; tumors can be missed in the uncinate process, accessory duct, and tail; and the need for intraductal contrast administration. Direct visualization of the pancreatic duct is possible during ERCP using pancreatoscopy. Pancreatoscopy uses a miniature endoscope that is passed through the duodenoscope (image 15) to visualize the pancreatic duct and to obtain targeted biopsies of pancreatic duct strictures. However, the procedure is not widely available. (See "Cholangioscopy and pancreatoscopy".)

ERCP is superior to transabdominal US and CT for the detection of extrahepatic biliary obstruction and is the procedure of choice when there is high suspicion for choledocholithiasis. However, it is also more expensive than US or CT, and as an invasive procedure, it is associated with a finite rate of mortality (0.2 percent) and complications such as pancreatitis, bleeding, and cholangitis. As a result, the role of ERCP in patients with suspected pancreatic cancer is evolving into a mainly therapeutic modality for patients who present with cholestasis due to tumor obstruction of the biliary system and require placement of a biliary stent. (See "Endoscopic stenting for malignant biliary obstruction" and "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia", section on 'Suspected biliary obstruction or intrahepatic cholestasis'.)

However, preoperative stenting is not always necessary in a patient with a potentially resectable pancreatic cancer. Furthermore, preferably, stenting should not be performed before CT scanning to assess resectability, as the stent may cause artifact in the pancreatic head that can mask the lesion, and the trauma of stent insertion may induce inflammatory changes that might be indistinguishable from tumor. The indications and controversies surrounding the risks and benefits of preoperative stent placement are discussed elsewhere. (See "Endoscopic stenting for malignant biliary obstruction", section on 'Indications' and "Surgical resection of lesions of the head of the pancreas", section on 'Preoperative biliary drainage' and "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis", section on 'Role of preoperative biliary drainage'.)

Magnetic resonance cholangiopancreatography — MRCP uses magnetic resonance technology to create a three-dimensional image of the pancreaticobiliary tree, liver parenchyma, and vascular structures. MRCP is better than CT for defining the anatomy of the biliary tree and pancreatic duct, has the capability to evaluate the bile ducts both above and below a stricture, and can also identify intrahepatic mass lesions. It is most often performed in conjunction with an MRI of the pancreas or liver, and has the benefit of seeing both the duct and the soft tissue mass within the pancreas. Gadolinium-based intravenous contrast is administered for the MRI component of the examination. MRCP is at least as sensitive as ERCP in detecting pancreatic cancers [42,43], and unlike conventional ERCP, it does not require contrast material to be administered into the ductal system. Thus, the morbidity associated with endoscopic procedures and contrast administration is avoided.

Although MRCP has not yet replaced ERCP in the patients suspected of having pancreatic cancer in most centers (algorithm 2), MRCP may be preferred in specific settings:

- Patients who have gastric outlet or duodenal stenosis or who have had surgical rearrangement (eg, Billroth II) or ductal disruption, resulting in ducts that are difficult to assess successfully by ERCP.
- To detect bile duct obstruction occurring in the setting of chronic pancreatitis. (See "Overview of the complications of chronic pancreatitis".)
- For patients in whom attempted ERCP either is unsuccessful or provides incomplete information because of pancreatic duct obstruction [44].

Role of tumor markers — Several serum markers for pancreatic cancer have been evaluated, the most useful of which is CA 19-9 (also called cancer-associated antigen 19-9).

Carbohydrate antigen 19-9 — The reported sensitivity and specificity rates of CA 19-9 for pancreatic cancer range from 70 to 92, and 68 to 92 percent, respectively [45-50]. However, sensitivity is closely related to tumor size. CA 19-9 levels are of limited sensitivity for small cancers [45,51-54]. Furthermore, CA 19-9 requires the presence of the Lewis blood group antigen (a glycosyl transferase) to be expressed. Among individuals with a Lewis-negative phenotype (an estimated 5 to 10 percent of the population), CA 19-9 levels are not a useful tumor marker [53,55].

CA 19-9 levels also have low specificity, especially in jaundiced patients. Bile duct obstruction causing hyperbilirubinemia raises CA 19-9 levels, and thus CA 19-9 as a tumor marker is typically unhelpful in jaundiced patients. CA 19-9 is frequently elevated in patients with cancers other than pancreatic cancer and various benign pancreaticobiliary disorders (table 2) [51-53,56,57]. One study found that serum concentrations above 37 units/mL represented the most accurate cutoff value for discriminating pancreatic cancer from benign pancreatic disease, but the

sensitivity and specificity for pancreatic cancer at this level were only 77 and 87 percent, respectively [56]. Furthermore, the positive predictive value (PPV) is low, particularly among asymptomatic individuals. In a large series of over 70,000 asymptomatic individuals, the PPV of a serum CA 19-9 level >37 units/mL was only 0.9 percent [58]. As a result, CA 19-9 is not recommended as a screening test for pancreatic cancer. Even among symptomatic individuals (epigastric pain, weight loss, jaundice), the sensitivity, specificity, and positive predictive value of an elevated CA 19-9 >37 units/mL level are only approximately 80, 85, and 72 percent [52,59].

The specificity and PPV for the diagnosis of pancreatic cancer can be improved by using higher cutoff levels (100 or even 1000 units/mL), but at the expense of sensitivity [52]. Importantly, there is a very broad range of CA 19-9 levels that can be seen in benign disease, and there are no specific cutoff values (even beyond 10,000 units/mL) that are seen only in patients with malignant disease [48,56,60].

Serum levels of CA 19-9 do have some value as prognostic markers and also as an indicator of disease activity in patients with initially elevated levels:

- The degree of elevation of CA 19-9 (both at initial presentation and in the postoperative setting) is associated with long-term prognosis [61-66].
- Among patients who appear to have potentially resectable pancreatic cancer, the magnitude of the preoperative CA 19-9 level can also help to predict the presence of radiographically occult metastatic disease, the likelihood of a complete (R0) resection, and long-term outcomes [61,67-71]. As examples:
  - In a report of 491 patients undergoing staging laparoscopy for a radiographically resectable pancreatic adenocarcinoma, CA 19-9 values above 130 units/mL were a significant predictor of finding radiographically occult unresectable disease [67]. The rates of unresectable disease among all patients with a CA 19-9 level ≥130 units/mL versus <130 units/mL were 26 and 11 percent, respectively. Among patients with tumors in the body/tail of the pancreas, more than one-third of those who had a CA 19-9 level ≥130 units/mL had unresectable disease.
  - In another report of consecutive patients who underwent resection for a primary pancreatic cancer, data from 1543 patients with preoperative detectable serum levels of CA 19-9 showed a correlation between resectability and survival rates with preoperative CA 19-9 values (table 3) [72].
- While high levels of CA 19-9 may help surgeons to better select patients for staging laparoscopy [68], CA 19-9 alone should not be used as an indicator of resectability [73]. Furthermore, while a year 2016 Clinical Practice Guideline on management of potentially curable pancreatic cancer from the American Society of Clinical Oncology (ASCO) suggested that chemotherapy could be used before surgery for patients who had anatomically resectable but high-risk tumors (for both distant metastatic disease and positive surgical margins, as judged by elevated levels of CA 19-9), there was no recommendation for a specific cutoff value of CA 19-9 to select patients for neoadjuvant therapy [73]. (See 'Staging laparoscopy' below and "Treatment for potentially resectable exocrine pancreatic cancer", section on 'Approach to the patient'.)
- Serial monitoring of CA 19-9 levels (once every one to three months) is useful to follow patients after potentially curative surgery and for those who are receiving chemotherapy for advanced disease. Rising CA 19-9 levels usually precede the radiographic appearance of recurrent disease, but confirmation of disease progression should be pursued with imaging studies and/or biopsy. (See "Initial systemic chemotherapy for metastatic exocrine pancreatic cancer", section on 'Response assessment'.)

Other markers — Although several marker candidates have emerged from preclinical and early clinical studies that might have better sensitivity than CA 19-9 alone, particularly for early stage disease [74-78], none has either replaced or supplemented CA 19-9 to date.

Newer studies examining combinations of tumor-specific circulating proteins (including CA 19-9) plus metabolites, and circulating proteins plus mutations in cell-free DNA in the blood show promise for early detection of potentially resectable pancreatic cancers compared with protein marker panels alone, but additional studies are needed to validate test characteristics, particularly in high-risk cohorts, such as those with underlying pancreatitis [79-81]. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Blood tests'.)

Biopsy and establishing the diagnosis — Histologic confirmation is required to establish a diagnosis of pancreatic cancer. (See "Pathology of exocrine pancreatic neoplasms".)

Following the initial evaluation, some patients may have a biopsy-proven diagnosis of pancreatic cancer, typically because they presented with jaundice and underwent an ERCP. (See 'Endoscopic retrograde cholangiopancreatography' above.)

However, in many cases, the diagnosis will not yet be histologically confirmed. Once pancreatic cancer is suspected on initial imaging studies, the next step in the workup is generally a staging evaluation to establish disease extent and resectability rather than biopsy. Patients who are fit for major surgery and who appear to have potentially resectable pancreatic cancer after the staging evaluation is complete do not necessarily need a preoperative biopsy confirming the diagnosis of a pancreatic cancer before proceeding directly to surgery. However, the increased

recognition of chronic or autoimmune pancreatitis, which can closely mimic pancreatic cancer, has altered this paradigm in certain populations. A preoperative biopsy may be recommended if a diagnosis of chronic or autoimmune pancreatitis is suspected on the basis of history (eg, extreme young age, history of alcohol use disorder, history of other autoimmune diseases), particularly if imaging studies (EUS, ERCP, or MRCP) reveal multifocal biliary strictures (suggestive of autoimmune pancreatitis) or diffuse pancreatic ductal changes (suggestive of chronic pancreatitis). These issues are discussed in more detail below. (See 'Diagnostic algorithm and need for preoperative biopsy' below.)

When it is indicated, biopsy of a pancreatic mass can be accomplished either percutaneously or via EUS.

Percutaneous biopsy — Percutaneous FNA biopsy of a pancreatic mass can be performed using either US or CT guidance (picture 2). The sensitivity and specificity of this procedure for the diagnosis of pancreatic cancer depends upon tumor size and operator expertise; values in the range of 80 to 90 and 98 to 100 percent, respectively, are reported [82].

A theoretical concern is that percutaneous FNA biopsy of the pancreas may disseminate tumor cells intraperitoneally or along the needle path in patients who are believed to be candidates for potentially curative resection. However, the risk appears to be quite low or absent. In one study of 41 patients undergoing resection for primary pancreatic adenocarcinoma, 21 of 32 patients without preoperative open biopsies had undergone preoperative CT or fluoroscopically guided FNA [83]. There was no increase in positive peritoneal washings, peritoneal failure rate, or median survival in these patients. Nevertheless, concern persists, and in practice, we try to avoid percutaneous FNA in patients with resectable masses.

A transduodenal EUS-guided FNA biopsy or ERCP sampling reduces these risks [84-86]. (See 'Endoscopic retrograde cholangiopancreatography' above.)

Endoscopic ultrasound-guided biopsy — EUS-guided FNA is the best modality for obtaining a tissue diagnosis, even if the tumor is poorly visualized by other imaging modalities. This procedure is less likely to cause intraperitoneal spread of the tumor since the biopsy is obtained through the bowel wall rather than percutaneously. EUS-guided FNA has a sensitivity of approximately 90 percent and specificity of 96 percent for the diagnosis of a pancreatic cancer. (See "Endoscopic ultrasound in the staging of exocrine pancreatic cancer", section on 'Accuracy'.)

The addition of molecular genetic analysis (eg, assay for K-ras or p53 gene mutations by reverse transcriptase polymerase chain reaction [RT-PCR]) to cytologic examination may improve sensitivity, especially in patients with small primary tumors. At present, however, molecular analysis is not a routine component of the diagnostic evaluation for pancreatic masses. EUS-guided FNA is addressed in detail elsewhere. (See "Endoscopic ultrasound in the staging of exocrine pancreatic cancer", section on 'EUS with tissue sampling'.)

If FNA specimens are inadequate or nondiagnostic, EUS-guided fine-needle (core) biopsy (using a needle designed to acquire larger "core" specimens) may be considered, where local expertise is available. At some institutions, an EUS-guided fine-needle biopsy may be preferred over FNA for the evaluation of solid pancreatic mass lesions that are accessible from the stomach, in the absence of a contraindication (inaccessible target, presence of intervening structures prohibiting biopsy, uncorrectable coagulopathy or thrombocytopenia). EUS-guided fine-needle biopsy for evaluating lesions in the gastrointestinal tract is discussed separately. (See "Endoscopic ultrasound-guided fine needle biopsy in the gastrointestinal tract".)

STAGING SYSTEM AND THE STAGING WORKUP

The preferred staging system for all pancreatic cancers (exocrine and neuroendocrine) is the tumor, node, metastasis (TNM) system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC); the current version (eighth edition) is outlined in the table (table 4) [87]. Compared with the seventh edition, there are prominent changes to both the definitions of the T stages, which are based on data demonstrating differences in overall survival according to the size of the primary tumor, and in the subdivision of N1 versus N2 disease based upon the number of involved lymph nodes (figure 1) [1]. The definitions of regional lymph nodes depends on the primary site [87]:

- The standard regional nodal basins for tumors arising in the head or neck of the pancreas include lymph nodes along the common bile duct, common hepatic artery, portal vein, pyloric, posterior, and anterior pancreatoduodenal arcades, and along the superior mesenteric vein and right lateral wall of the superior mesenteric artery.
- For cancers located in the body or tail of the pancreas, regional nodal basins include lymph nodes along the common hepatic artery, celiac axis, splenic artery, and splenic hilum.
- Tumor involvement of other nodal groups is considered to represent distant metastases.

Survival curves for resected pancreatic cancer according to the eighth edition prognostic stage groupings from a Surveillance, Epidemiology, and End Results (SEER) database analysis of 8960 patients are provided in the figure (figure 4); median survival durations for patients with stage IA, IB, IIA, IIB, and III disease were 38, 24, 18, 17, and 14 months, respectively [88].

Similar outcomes were noted in an international validation cohort of 1525 patients with resected pancreatic cancer; five-year survival rates stratified according to stage grouping were as follows [89]:

- Stage IA – 39 percent
- Stage IB – 34 percent
- Stage IIA – 28 percent
- Stage IIB – 21 percent
- Stage III – 11 percent

Notably, at least in the United States, the prognosis for resected stage IA disease appears to be improving over time. In an analysis of data from the National Cancer Institute Surveillance, Epidemiology, and End Results database, the incidence of stage IA pancreatic cancer increased significantly between 2004 and 2016 (annual percentage change 14.5), and their average age at diagnosis decreased by 3.5 years overall; these changes were accompanied by a near doubling of five-year survival (from 45 percent in 2004 to 84 percent in 2012) [90]. These trends were attributed to improved early diagnosis and detection, although screening for early detection is currently limited to high-risk individuals who have familial syndromes predisposing them to pancreatic cancer. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients".)

The goal of the staging workup is to delineate the extent of disease spread and identify patients who are eligible for resection with curative intent.

Imaging studies — Imaging studies play an important role in the staging and management of pancreatic cancer.

Abdominal computed tomography — A "pancreatic protocol" (multi-phase, contrast-enhanced thin-slice) CT of the abdomen and pelvis is used to assess disease extent and resectability.

Technique — The reliability of CT as a staging tool for pancreatic cancer is highly dependent upon technique. Multi-phase, contrast-enhanced thin-slice (multidetector row) helical computed tomography (MDCT) with three-dimensional reconstruction is the preferred method to diagnose and stage pancreatic cancer. Helical CT scanners with multiple rows of detectors permit imaging of larger volumes of tissue while acquiring both arterial and venous phases in shorter periods of time [91,92]. This has improved the evaluation of the main pancreatic duct and, thus, the detection of small tumors [93].

For comprehensive imaging of a suspected pancreas cancer, the patient is usually scanned in several dynamic phases of contrast injection (termed a "pancreas protocol") [94]:

- The arterial phase of enhancement, which corresponds to the first 30 seconds after the start of the contrast injection, provides excellent opacification of the celiac axis, superior mesenteric artery (SMA), and peripancreatic arteries. The use of this phase is variable amongst different institutions, as the arterial structures can be well delineated in the pancreatic phase that follows.
- An attenuation difference between tumor and normal pancreas, which increases lesion conspicuity, is best achieved after peak enhancement of the aorta in the arterial phase but before peak enhancement of the liver, which occurs in the portal venous phase. This is sometimes termed the "pancreatic phase" [95,96].
- The portal venous phase, which is obtained at 60 to 70 seconds after the start of the contrast injection, provides better enhancement of the superior mesenteric vein (SMV), splenic and portal veins. In addition, peak hepatic enhancement, which optimizes the detection of hepatic metastases, also occurs in the portal venous phase [97].

Assessing resectability — Complete surgical resection is the only potentially curative modality of treatment for pancreatic cancer. An initial assessment of resectability is typically made based upon the preoperative multi-phase staging contrast-enhanced CT scan. In general, pancreatic cancers are categorized on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases (figure 5) [98]. Local unresectability is usually (but not always) due to vascular invasion (figure 6).

Definitions of unresectable and borderline resectable disease — In general, pancreatic cancers can be categorized along a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases (figure 5) [98]. A pancreatic cancer is categorically unresectable if distant metastases are present in the liver, peritoneum, omentum, extraregional lymph nodes, or any extra-abdominal site.

Local unresectability is usually (but not always) due to vascular invasion, particularly of the SMA (figure 6). Although practice is variable across institutions, many surgeons would consider a pancreatic cancer to be locally advanced and unresectable if it is associated with encasement (more than one-half of the vessel circumference) of the SMA or celiac artery, or if there is occlusion of the SMV or SMV-portal vein confluence without suitable vessels above and below the tumor to allow for reconstruction.

We follow the consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) [99], which are largely based upon a consensus statement from the Society of Abdominal Radiology/American Pancreatic Association [100] and define the following characteristics as indicating unresectability:

- Head of pancreas/uncinate lesions:
  - Solid tumor contact with the SMA >180 degrees
  - Solid tumor contact with the celiac axis >180 degrees
  - Solid tumor contact with the first jejunal SMA branch
  - Unreconstructable SMV or portal vein due to tumor involvement or occlusion (can be due to tumor or bland thrombus)
  - Contact with the most proximal draining jejunal branch into the SMV
- Body and tail lesions:
  - Solid tumor contact of >180 degrees with the SMA or celiac axis
  - Solid tumor contact with the celiac axis and aortic involvement
  - Unreconstructable SMV or portal vein due to tumor involvement or occlusion (can be due to tumor or bland thrombus)
- For all sites:
  - Distant metastases
  - Metastases to lymph nodes beyond the field of resection

Most of these patients will be managed with initial chemotherapy, with or without chemoradiotherapy. If a sufficient downstaging response is obtained, subsequent surgical exploration can be considered. (See "Initial chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable, exocrine pancreatic cancer", section on 'Criteria for unresectability'.)

There is less consensus on the definition of "borderline" resectable pancreatic cancer [101-103]. Some reserve the term "borderline resectable" for cases where there is focal (less than one-half of the circumference) (image 16) tumor abutment of the visceral (superior mesenteric, celiac) arteries or short-segment occlusion of the SMV or SMV-portal vein confluence or hepatic artery. (See "Initial chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable, exocrine pancreatic cancer", section on 'Borderline resectable'.)

Encasement (more than one-half of the vessel circumference) (image 16) or occlusion/thrombus of the SMV or the SMV-portal vein confluence (figure 6) used to be universally considered an indicator of unresectability. However, many centers have demonstrated the feasibility of SMV reconstruction, and this is now considered by many to represent borderline resectable disease (figure 5) [104]. If venous occlusion is present, a suitable segment of portal vein (above) and SMV (below the site of venous involvement) must be present to allow for venous reconstruction. However, in most centers, surgery will be preceded by some form of neoadjuvant treatment for patients with venous occlusion. (See "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis", section on 'Vascular resection' and "Initial chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable, exocrine pancreatic cancer", section on 'Borderline resectable'.)

The NCCN [99] formally defines the category of borderline resectable pancreatic cancer, which is largely based upon a consensus statement from the Society of Abdominal Radiology/American Pancreatic Association [100], as follows:

- For tumors of the head or uncinate process:
  - Solid tumor contact with the SMV or portal vein of >180 degrees with contour irregularity of the vein or thrombosis of the vein, but with suitable vessel proximal and distal to the site of involvement, allowing for safe and complete resection and vein reconstruction.
  - Solid tumor contact with the inferior vena cava.
  - Solid tumor contact with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction.
  - Solid tumor contact with the SMA ≤180 degrees.
  - Solid tumor contact with variable anatomy (eg, accessory right hepatic artery, replaced right hepatic artery, replaced common hepatic artery, and the origin of replaced or accessory artery), and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning.
- For tumors of the body/tail:
  - Solid tumor contact with the celiac axis of ≤180 degrees.

- Solid tumor contact with the celiac axis >180 degrees without involvement of the aorta and with an intact and uninvolved gastroduodenal artery, thereby permitting a modified Appleby procedure (although some members of the consensus committee preferred this criterion to be in the unresectable category).

Most patients with borderline resectable disease are referred for neoadjuvant therapy prior to surgical exploration. (See "Initial chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable, exocrine pancreatic cancer".)

The entire concept of a "borderline resectable" pancreatic cancer is problematic for centers trying to accurately stage and treat patients according to the AJCC staging system. The seventh edition of the AJCC staging criteria uses the T4 category (tumor involves the celiac axis or the SMA) to designate an unresectable primary tumor, with T3 designating a tumor that extends beyond the pancreas but without involvement of the celiac axis or mesenteric artery. However, as noted above, involvement of a focal area of the visceral arteries may be considered a borderline resectable situation. One study of 257 patients with stage III pancreatic cancer (all T4 lesions based upon infiltration of the celiac axis or SMA) found that 30 percent could undergo a successful complete (R0) resection after chemoradiation or chemotherapy alone [105]. The eighth edition revision to the AJCC staging system no longer classifies T4 disease as categorically unresectable. However, they do not use the term "borderline resectable" to classify any clinical stage of disease. (See 'Staging system and the staging workup' above.)

Accuracy of computed tomography

- **Primary tumor** – The sensitivity of multi-phase helical CT for pancreatic adenocarcinoma is high, 89 to 97 percent [34]. As expected, sensitivity is higher for larger tumors; in one study, the sensitivity was 100 percent for tumors >2 cm, but only 77 percent for tumors ≤2 cm in size [35]. However, most small isoattenuating pancreatic cancers have secondary signs such as a pancreatic duct cutoff or dilated main pancreatic duct [106].

- **Metastatic disease** – Contrast-enhanced CT is the modality of choice to detect distant metastases (image 17). The sensitivity for hepatic metastases is high, particularly using the pancreatic protocol technique. In one study of 43 patients with pancreatic cancer, the sensitivity, specificity, positive predictive value, and negative predictive value of contrast-enhanced multidetector row helical CT for detection of liver metastases were 88, 89, 92 and 84 percent, respectively [107]. Lower sensitivity rates (53 and 69 percent) are reported by others and may be related to the size of the hepatic metastases [108,109].

  Peritoneal involvement may be detected indirectly by the presence of ascites, mesenteric nodules/carcinomatosis, or mesenteric lymph nodes. However, the sensitivity of CT for peritoneal dissemination is not sufficiently high to eliminate the need for diagnostic laparoscopy in equivocal cases [110-112]. (See 'Staging laparoscopy' below.)

  For tumors of the head and neck of the pancreas, regional lymphatic tumor spread usually occurs around the celiac axis and the peripancreatic and periportal areas (figure 7). For tumors arising in the tail, regional nodal basins are located along the common hepatic artery, celiac axis, splenic artery and splenic hilum.

  The sensitivity and specificity of CT for detecting involvement of lymph nodes are low, leading some to suggest that in a patient who has a presumed pancreatic cancer that is considered resectable, the finding of peripancreatic nodes on CT should not prevent exploration [113]. However, the presence of extensive peripancreatic lymphatic involvement and nodal involvement beyond the peripancreatic tissues is generally considered to represent unresectable disease. (See 'Definitions of unresectable and borderline resectable disease' above.)

- **Vascular invasion** – CT criteria for vascular invasion include arterial embedment in the tumor mass or venous obliteration, tumor involvement exceeding one-half the circumference of the vessel, vessel wall irregularity, vessel caliber stenosis, or a "teardrop" sign of the SMV [114]. Most radiologists use a standard template to describe the relationship and degree of contact between the tumor and blood vessels, which are needed to define resectability [100]. (See 'Assessing resectability' above.)

  In general, multi-phasic contrast-enhanced helical multidetector row CT (MDCT) has a high predictive value for unresectability (90 to 100 percent) [115-118], but the predictive value for resectability is slightly lower (range 64 to 90 percent) [117,119,120]. The accuracy of MDCT for assessing vascular invasion was addressed in a systematic review and meta-analysis of 18 studies [121]. The pooled sensitivity and specificity for diagnosing vascular invasion were 77 and 81 percent, respectively, but when the analysis was limited to the five most recent studies conducted since 2004, and presumably using the most advanced CT technology, sensitivity and specificity rates were 85 and 82 percent, respectively.

  An important exception is that classic CT criteria for vascular involvement, particularly arterial involvement, are not reliable in patients who have undergone neoadjuvant therapy with a highly active chemotherapy combination such as FOLFIRINOX and are undergoing radiographic restaging to assess resectability. In such cases, surgical exploration may be the only method to assess true resectability. (See "Initial chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable, exocrine pancreatic cancer", section on 'FOLFIRINOX'.)

Other studies — A variety of other imaging modalities, including endoscopic ultrasound (EUS), MRI, fludeoxyglucose (FDG) positron emission tomography (PET), and staging laparoscopy, may be required to assess resectability in some circumstances.

Endoscopic ultrasound — Due to the small distance between the echoendoscope and the pancreas through the gastric or duodenal wall, EUS provides much higher resolution than transabdominal ultrasound. Pancreatic cancer on EUS appears as a hypoechoic mass, typically with dilation of the proximal pancreatic duct. The border of the lesion may have an irregular contour, and the echo pattern of the mass may be homogenous or inhomogeneous. (See "Endoscopic ultrasound in the staging of exocrine pancreatic cancer".)

Multiple studies comparing EUS with other imaging modalities for initial diagnosis and staging of pancreatic cancer concluded that EUS may be more accurate for smaller tumors, for local T and N staging, and for predicting vascular invasion. However, although EUS may detect metastatic disease in the liver or mediastinal lymph nodes, it is inferior to CT for evaluation of distant metastases. In addition, the specificity of EUS for excluding vascular invasion in small tumors is limited, particularly when inflammatory changes are present. EUS is also operator-dependent; as a result, its value varies with locally available expertise. Finally, the development of modern MDCT has markedly improved the sensitivity of CT for the detection of smaller tumors and the presence of vascular invasion, reaching values that are comparable with those obtained by EUS by an experienced endoscopist. However, head-to-head studies comparing the two modalities are lacking. (See "Endoscopic ultrasound in the staging of exocrine pancreatic cancer", section on 'Vascular invasion' and "Endoscopic ultrasound in the staging of exocrine pancreatic cancer", section on 'Comparison of EUS with other imaging techniques'.)

Equally uncertain is whether EUS adds information on tumor resectability to the results of preoperative modern MDCT [122].

Nevertheless, the role of EUS in the preoperative staging of pancreatic cancer is evolving, and there are several points in the diagnostic evaluation where this modality may be of benefit, particularly for patients whose CT evaluation does not demonstrate a defined mass lesion (algorithm 2). (See 'Subsequent testing if initial imaging is negative' above and "Endoscopic ultrasound in the staging of exocrine pancreatic cancer".)

In addition, EUS-guided fine-needle aspiration biopsy (FNA) is the best modality for obtaining a tissue diagnosis, even if the tumor is poorly visualized by other imaging modalities. (See 'Endoscopic ultrasound-guided biopsy' above.)

Concerns for biopsy tract or peritoneal seeding from EUS-guided FNA have not been borne out [123].

Magnetic resonance imaging — Although pancreatic adenocarcinomas are easily visualized on MRI (image 18), there is no evidence that MRI offers a significant diagnostic advantage over multi-phase contrast-enhanced pancreatic helical multidetector row CT (MDCT) for the local staging evaluation [124-128]. One potential benefit of MRI is its increased sensitivity for the detection of small liver metastases compared with CT [108,109,129,130]. Combining CT and MRI offers little that cannot be achieved with one alone. Thus, the choice of MRI or CT depends upon the level of locally available expertise and the clinician's comfort with one or the other radio-imaging technique. We prefer MDCT.

Chest computed tomography — CT of the chest may be used as a staging tool to detect lung metastases. However, although routine chest CT is recommended in NCCN [99] staging guidelines, many centers do not perform a routine staging chest CT for patients suspected of having pancreatic cancer who have no symptoms to suggest pulmonary metastases. Many of these studies will show indeterminate small lung nodules, the impact of which on prognosis or treatment of the primary tumor is unclear [131]; furthermore, among patients with radiographic suspicion for lung metastases, the primary tumor is usually unresectable for another reason [132].

Positron emission tomography scanning — PET scanning with the tracer FDG relies on functional activity to differentiate metabolically active proliferative lesions such as cancers, most of which are FDG-avid, from benign masses. Most benign lesions do not accumulate FDG, with the exception of inflammatory lesions such as chronic pancreatitis [133].

The utility of PET scans in the diagnostic and staging evaluation of suspected pancreatic cancer, particularly whether PET provides information beyond that obtained by contrast-enhanced MDCT, has been controversial. In uncontrolled studies and meta-analyses, the sensitivity of integrated PET/CT (which has better spatial resolution as compared with PET alone) in the initial diagnosis of pancreatic cancer has ranged from 73 to 94 percent, while specificity ranges from 60 to 89 percent [134-142]. One possible benefit of PET is enhanced detection of small-volume metastatic disease, which is often missed by CT. Unfortunately, the available data are conflicting, with some studies suggesting that PET is useful for identifying metastatic disease that is missed by CT (image 19) [136,138,143-145] and others noting that PET often misses small-volume (subcentimeter) metastases within the peritoneum and elsewhere, including the liver [133,134,146]. False-negative PET scans can also occur in hyperglycemic patients; false-positive results can be seen in various inflammatory states, such as pancreatitis, infected pseudocyst, or local inflammation caused by placement of a biliary stent.

The clinical impact of adding integrated FDG PET/CT to modern contrast-enhanced MDCT in patients with suspected pancreatic cancer was addressed in a prospective multicenter trial conducted in the United Kingdom [147]. Of the 589 enrolled patients with suspected pancreatic cancer who underwent FDG PET/CT after MDCT, 550 had complete data (including resection or sufficient clinical follow-up to determine the

actual diagnosis) and in-range PET/CT (within two weeks of MDCT), and they formed the study population. In a preliminary report presented at the 2016 annual meeting of the American Society of Clinical Oncology (ASCO), the following were noted:

- The sensitivity (93 versus 89 percent), specificity (76 versus 71 percent), positive predictive values (78 versus 73 percent), and negative predictive values (92 versus 87 percent) for diagnosing pancreatic cancer all favored PET/CT over MDCT alone.
- There was a significant incremental benefit of adding PET, both in patients with a positive MDCT and in those with a negative CT:
  - Among patients with a positive MDCT, a positive PET/CT increased the odds of diagnosing pancreatic cancer by 55 percent, and a negative PET/CT decreased the odds of diagnosing pancreatic cancer by 95 percent.
  - Among patients with a negative MDCT, a positive PET/CT increased the odds of diagnosing pancreatic cancer by 538 percent, while a negative PET/CT decreased the odds of diagnosing pancreatic cancer by 46 percent.
- Of the 290 patients who were initially planned for resection following MDCT, 61 (21 percent of the total) did not ultimately undergo resection, 58 because of findings on PET/CT. The reason for not proceeding with resection was metastases in 41, while 17 had suspected-benign lesions not requiring resection.
- Pancreatic ductal adenocarcinoma was diagnosed in 261 patients (47 percent). Among this subgroup, PET/CT corrected the staging of the cancer (as indicated by MDCT) in 56 (14 percent of the entire study population). A smaller proportion had a change to an incorrect stage or maintained an incorrect stage based upon the MDCT (n = 22, 6 percent of the entire cohort). In approximately one-half of the cases in which the staging was corrected by PET/CT, patients were upstaged to stage IV disease.
- The addition of PET/CT to MDCT was cost-effective at current costs of PET/CT in the United Kingdom National Health System, and it was most cost effective for patients with suspected pancreatic cancer who were being considered for resection.

While these data seem promising, they have only been presented in preliminary form and have not been subject to rigorous peer-review. While we await formal publication of these results, the data remain insufficient to conclude that PET or integrated PET/CT provides useful information above that provided by modern contrast-enhanced CT in a sufficient number of patients to warrant a change in practice. Consensus-based guidelines for staging of pancreatic cancer from the NCCN [99] and the European Society for Medical Oncology (ESMO) [148] do not recommend routine use of PET/CT for staging of pancreatic cancer.

Staging laparoscopy — We suggest a selective approach to staging laparoscopy to maximize yield by limiting the procedure to those with the highest likelihood of occult metastatic disease. This includes patients with a tumor of the body or tail of the pancreas who appear to have potentially resectable disease by CT scan, large (>3 cm) primary tumors, advanced vascular involvement (but not encasement of occlusion of an adjacent vessel), any patient for whom high-quality imaging is in any way suggestive of occult metastatic disease, and those with a high initial carbohydrate antigen 19-9 (CA 19-9) level (eg, >100 units/mL).

Accurate staging drives proper treatment of patients with pancreatic cancer, particularly when selecting patients for surgical resection. Because most have unresectable disease at presentation, a key goal is to avoid a futile laparotomy whenever possible.

Currently available imaging techniques are highly accurate at predicting unresectable disease, but they fall short in predicting resectable disease, mainly because of limited sensitivity for small-volume metastatic disease. Radiographically occult subcentimeter metastases on the surface of the liver or peritoneum that are rarely visible by CT, MRI, PET, or transabdominal US may be visualized laparoscopically. Studies have consistently shown that up to one-third of patients thought to be resectable by state of the art imaging will be found to be unresectable based upon laparoscopic findings [110,149-153].

However, the value of staging laparoscopy is not universally accepted. While hospital operating room utilization is improved, and patient stay, cost, and morbidity are reduced when an unnecessary open laparotomy is avoided for unresectable or metastatic disease, there are no controlled studies demonstrating a benefit for this procedure in patients who have undergone radiographic staging evaluation using modern high-quality imaging such as MDCT [154]. This issue was not addressed in a 2016 Cochrane review on the subject, and given that 7 of the 16 trials were undertaken in the 1980s and 1990s, it is unlikely that modern CT techniques were used [152]. (See 'Technique' above.)

We limit the procedure to those with the highest likelihood of occult metastatic disease [155,156]. This includes patients with a tumor of the body or tail of the pancreas who appear to have potentially resectable disease by CT scan (one-half of whom will have occult peritoneal metastases [157,158]). (See "Overview of surgery in the treatment of exocrine pancreatic cancer and prognosis", section on 'Tumors in the body or tail' and 'Carbohydrate antigen 19-9' above.)

We also use staging laparoscopy in patients with advanced vascular involvement (but not yet complete encasement or occlusion of the major vessels). Other indications for a staging laparoscopy prior to open laparotomy include a high preoperative CA 19-9 level (although the optimal threshold is not established [67,68,70,159]; we use >1000 units/mL) and high-quality imaging that is in any way suggestive of occult metastatic disease. At some institutions, diagnostic laparoscopy is performed if neoadjuvant therapy is to be recommended.

Importance of peritoneal cytology — Peritoneal washings are often obtained at the time of laparoscopy. While it would seem intuitive that patients who have positive peritoneal washings would be unlikely to benefit from radical resection of the pancreatic primary tumor, it has not been conclusively demonstrated that positive peritoneal cytology as an isolated finding is an independent adverse prognostic factor [160-162]. In general, most patients who have cytologically positive washings have other findings that suggest advanced disease and unresectability such as ascites and/or the presence of metastases in the liver, pelvis, or omentum [160,163,164]. If these are absent, most pancreatic surgeons do not rely upon the results of peritoneal washings obtained at the time of laparoscopy to guide decision-making regarding resectability. However, prognosis is worse in these cases, even in the absence of ascites [165], and the AJCC staging system considers positive peritoneal washings to represent distant metastatic (M1) disease (table 4) [87].

DIAGNOSTIC ALGORITHM AND NEED FOR PREOPERATIVE BIOPSY

Our suggested diagnostic approach to the patient with suspected pancreatic cancer is outlined in the algorithm (algorithm 2). (See 'Biopsy and establishing the diagnosis' above.)

A diagnostic biopsy of a suspected pancreatic malignancy may be indicated if there is evidence of systemic spread of disease, if there is local evidence of unresectability on staging studies, if the patient is unfit for major surgery, if neoadjuvant treatment is being contemplated (eg, for a borderline resectable lesion), or if alternative diagnoses need to be excluded (eg, metastatic disease to the pancreas). (See "Initial chemotherapy and radiation for nonmetastatic, locally advanced, unresectable and borderline resectable, exocrine pancreatic cancer", section on 'Role of surgery'.)

However, a preoperative diagnostic biopsy may not be needed in a fit patient with a potentially resectable pancreatic lesion that is highly suspected of malignancy. While a positive biopsy can confirm the suspected diagnosis, a benign sample will not exclude the presence of malignancy. In one systematic review of 53 studies addressing this issue, the negative predictive value of percutaneous and endoscopic ultrasound (EUS)-guided biopsies was only 60 to 70 percent [166]. Attempts to make a preoperative tissue diagnosis may in fact be detrimental if tumor cells are disseminated during percutaneous biopsy.

Thus, if a patient is a reasonable surgical candidate, and if the clinical presentation and imaging are typical for a resectable adenocarcinoma after the staging evaluation has been completed, it is reasonable to proceed to surgery without a tissue diagnosis. (See 'Staging system and the staging workup' above.)

However, it must be recognized by both the clinician and the patient that uncertainty regarding the diagnosis in these instances persists and that some patients with benign lesions may be subjected to the radical resections used for malignant lesions. These cases comprise between 5 and 11 percent of patients who undergo surgery for a presumed cancer [167-171]. The frequency of radical resection for benign disease may be reduced when this approach is combined with additional imaging, including EUS-guided transduodenal biopsy. (See 'Endoscopic ultrasound-guided biopsy' above.)

Focal chronic pancreatitis and autoimmune pancreatitis are the two benign processes that are most commonly mistaken for pancreatic malignancy on CT or US. Serologic testing for IgG4 or EUS-guided biopsy may be recommended if a diagnosis of chronic or autoimmune pancreatitis is suspected on the basis of history (eg, extreme young age, prolonged ethanol abuse, history of other autoimmune diseases), particularly if further imaging studies (either EUS, endoscopic retrograde cholangiopancreatography [ERCP] or magnetic resonance cholangiopancreatography [MRCP]) reveal multifocal biliary strictures (suggestive of autoimmune pancreatitis) or diffuse pancreatic ductal changes (suggestive of chronic pancreatitis). (See "Chronic pancreatitis: Clinical manifestations and diagnosis in adults" and "Autoimmune pancreatitis: Clinical manifestations and diagnosis".)

For jaundiced patients who have no involvement or minimal involvement of the major vessels according to CT or EUS and no evidence of distant metastases on helical CT or EUS, we proceed directly to an attempt at surgical resection. For non-jaundiced patients (particularly with body or tail tumors), or those with major but incomplete involvement of the vascular structures (tumor contiguous to less than one-half of the vessel circumference [117,119]), we perform preoperative laparoscopy to exclude tiny metastases that might have been overlooked by CT. If the laparoscopy is negative, we then embark on a radical surgical resection. (See 'Staging laparoscopy' above.)

ASSESSING RISK FOR HEREDITARY SYNDROMES

Between 4 and 20 percent of patients with pancreatic cancer have germline mutations in known cancer predisposition genes. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Inherited cancer susceptibility syndromes'.)

A provisional clinical opinion from the American Society of Clinical Oncology (ASCO) suggests that all patients diagnosed with pancreatic cancer undergo assessment of their risk of a familial predisposition to cancer with a detailed personal and family cancer history [172]. Germline genetic testing should be performed in individuals with a family history of pancreatic cancer meeting criteria for familial pancreatic cancer,

those with three or more diagnoses of pancreatic cancer in the same side of the family, and individuals meeting criteria for other genetic syndromes associated with increased risk for pancreatic cancer. Germline genetic testing may also be offered to patients with pancreatic cancer who lack a personal or family history suggestive of an associated genetic syndrome if an informative result could directly benefit the patient or his or her family members. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Referral for genetic evaluation'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pancreatic cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Pancreatic cancer (The Basics)")
- Beyond the Basics topics (see "Patient education: Pancreatic cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Clinical presentation** – The most common presenting symptoms in patients with exocrine pancreatic cancer are pain, jaundice, and weight loss. Compared with tumors in the body and tail of the gland, pancreatic head tumors more often present with jaundice, steatorrhea, and weight loss. (See 'Clinical presentation' above.)
- **Our recommended diagnostic approach** – Our general diagnostic approach, as detailed in the following sections, is summarized in the algorithm (algorithm 2).
- **Initial evaluation**
  - Most patients presenting with symptoms worrisome for pancreatic cancer (jaundice, epigastric pain, weight loss), undergo CT of the abdomen, or in the case of jaundice a right upper quadrant transabdominal ultrasound (US). If a pancreatic mass is seen on transabdominal US, an abdominal CT scan is needed to confirm the presence of the mass and assess disease extent. (See 'Initial testing' above.)
  - Given the limited sensitivity and specificity, the serum tumor marker carbohydrate antigen 19-9 (CA 19-9) should not be used as a diagnostic test for pancreatic cancer. Serum levels of CA 19-9 do have some value as prognostic markers and also as an indicator of disease activity in patients with initially elevated levels. (See 'Carbohydrate antigen 19-9' above.)
- **Staging workup and assessing resectability**
  - **Multi-phase contrast-enhanced CT** – When a mass lesion of the pancreas is detected on initial CT or US, a pancreatic protocol (multi-phase, contrast-enhanced helical multidetector row CT [MDCT]) is needed to assess disease extent and resectability, if not already done. Local unresectability is usually (but not always) due to vascular invasion. (See 'Abdominal computed tomography' above.)

    In general, pancreatic cancers can be categorized on the basis of MDCT findings on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases (figure 5). Although practice is variable, most surgeons would consider a pancreatic cancer to be categorically unresectable if any of the following are present (see 'Definitions of unresectable and borderline resectable disease' above):
    - Extensive peripancreatic lymphatic involvement, nodal involvement beyond the peripancreatic tissues, and/or distant metastases.

- Direct involvement of the superior mesenteric artery (SMA), inferior vena cava, aorta, celiac axis, or hepatic artery, as defined by the absence of a fat plane between the low-density tumor and these structures on CT scan (figure 6).

- Encasement (more than one-half of the vessel circumference) or occlusion/thrombus of the superior mesenteric vein (SMV) or the SMV-portal vein confluence used to be universally considered an indicator of unresectability. However, many centers have demonstrated the feasibility of SMV reconstruction, and this is now considered by most experienced centers to represent borderline resectable disease; in practice, most of these patients are referred for neoadjuvant therapy prior to surgery. (See 'Definitions of unresectable and borderline resectable disease' above.)

- **Other radiographic studies** – The utility of PET scans, chest CT, and MRI in the staging workup of suspected pancreatic cancer, particularly whether any of these imaging studies provide information beyond that obtained by MDCT, remains uncertain, and we do not routinely order these tests. (See 'Positron emission tomography scanning' above and 'Chest computed tomography' above and 'Magnetic resonance imaging' above.)

- **Role of diagnostic laparoscopy** – If upfront resection is being considered, we limit the use of diagnostic laparoscopy to individuals with a tumor of the body or tail of the pancreas who appear to have potentially resectable disease by cross-sectional imaging, large (>3 cm) primary tumors, advanced vascular involvement (but not encasement of occlusion of an adjacent vessel), any patient for whom high-quality imaging is equivocal for the presence of peritoneal metastases, and those with a high initial CA 19-9 level (eg, >100 units/mL). (See 'Staging laparoscopy' above.)

- **Histologic confirmation** – Histologic confirmation is required to establish a diagnosis of pancreatic cancer. Tissue diagnosis is mandatory for patients who are unfit to undergo a major resection, for those with a high suspicion of metastatic disease, and for any patient being considered for neoadjuvant therapy rather than upfront surgery. However, if the patient is a reasonable candidate for upfront surgery, and the imaging results are typical for a resectable adenocarcinoma, it is reasonable to proceed to surgery without a tissue diagnosis. (See 'Diagnostic algorithm and need for preoperative biopsy' above.)

- **Assessing risk for hereditary syndromes** – Assessment of risk for hereditary syndromes is an important component of the initial evaluation, given that between 4 and 20 percent of patients with pancreatic cancer have germline mutations in known cancer predisposition genes. (See 'Assessing risk for hereditary syndromes' above.)

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