

Girish Mishra, M.D., M.S., Series Editor

Pancreatic Cancer: Epidemiology and Pathology



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EPIDEMIOLOGY

Ductal Adenocarcinoma

Ductal adenocarcinoma is the most common form of pancreatic cancer and accounts for 85%–90% of all pancreatic neoplasms (1). In the United States, more than 32,000 people develop pancreatic adenocarcinoma each year (3,4). There is nearly equal incidence among men and women, with a reported male-to-female ratio of 1.3:1 (3, 5). The World Health Organization has also reported a ratio of 1.6 in developed countries to 1.1 in developing countries (1). The incidence of ductal adenocarcinoma is also higher in the black population than in whites, with 14.8 per 100,000 in black males compared to 8.8 per 100,000 in the general population (5). Eighty percent of cases

occur in patients that are 60–80 years of age, and ductal adenocarcinoma below the age of 40 is rare (1).

After a steady increase from 1930 to 1980, the incidence of pancreatic cancer has leveled off in both men and women over the past 15 to 25 years, making it the fourth leading cause of cancer death overall (1,3). Of the malignancies of the gastrointestinal tract, it is second only to colon cancer. Survival rates for pancreatic carcinoma is very low, and the incidence and mortality rate almost identical (1). Even for those people diagnosed with local disease, the 5-year relative survival rate is only 15% (3).

Cystic Neoplasms

Cystic lesions of the pancreas may be divided pathologically into simple cysts (related to development), pseudocysts (resulting from pancreatic inflammation and necrosis), and cystic neoplasms. Four types of cystic neoplasms of the pancreas have been described: serous cystic neoplasms, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms (mucinous duct ectasia) and solid and pseudopapillary cystic tumors (papil-

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lary cystic neoplasms). Solid and pseudopapillary cystic tumors are the least common of the pancreatic cystic neoplasms, and are not further discussed in this review.

Most serous cystic neoplasms of the pancreas are benign and account for 1%–2% of all pancreatic exocrine tumors. Microcystic and oligocystic forms have been recognized, with both types occurring most frequently in the 6th to 7th decade. While 70% of the microcystic form occurs in women, the oligocystic form has no gender predilection. Fifty to 75% of microcystic form occurs in the body and tail of the pancreas, while the oligocystic form localizes to the head and body and may therefore obstruct the pancreatic duct. While these lesions have a very low potential for malignant change, rare malignant cases (serous cystadenocarcinomas) have been reported (6).

Mucinous cystic neoplasms (MCN) of the pancreas occur almost exclusively in middle-aged women, and have been classified as adenoma, borderline (low-grade malignant) and non-invasive or invasive carcinoma (mucinous cystadenocarcinoma). MCN account for 2%–5% of all pancreatic exocrine tumors, with the majority arising in the region of the body and tail. Mucin-producing tumors that are malignant or have a high likelihood of undergoing malignant change can occur in a localized or diffuse form (7).

A ductal ectatic form of mucin-producing tumors also occurs (mucinous duct ectasia). These tumors, now termed intraductal papillary mucinous neoplasms (IPMN), account for 1%–3% of all pancreatic exocrine neoplasms, and have an incidence of less than 1 per 100,000 each year (7,8). Similar to MCN, intraductal papillary mucinous neoplasms (IPMN) of the pancreas are classified as adenoma, borderline and non-invasive or invasive carcinoma (intraductal papillary mucinous carcinoma (8)). The distinction of IPMN from MCN was not made until the last two decades, and it is likely that many IPMN were classified as MCN until approximately a decade ago (8). Unlike MCN, IPMN occurs more frequently in men (8).

RISK FACTORS

Several risk factors have been identified or implicated in the development of pancreatic neoplasms, with many risk factors associated with ductal adenocarci-

noma. Cigarette smoking is the most significant modifiable risk factor for pancreatic ductal adenocarcinoma, with 30% of cases thought to result directly from cigarette smoking (3). There is a 2–3 fold relative risk attributed to cigarette smoking, which increases with number of pack-years (1). Since this close association exists, the decline incidence of ductal adenocarcinoma has been attributed to the decline in smoking rates (3). Other modifiable risk factors in the development of ductal adenocarcinoma include diet high in meats and fat, occupational exposure to certain pesticides, dyes, and chemicals related to gasoline, and obesity, with very overweight people 20% more likely to develop pancreatic cancer (3). Older studies suggesting that coffee and alcohol consumption might increase risk have not been confirmed.

Non-modifiable risk factors include age, gender, and race. The risk of developing cancer of the pancreas increases with age, with almost all patients older than 50 years. Men are 20% more likely to develop cancer of the pancreas than are women, and African Americans are 40% to 50% more likely to develop cancer of the pancreas than whites. Family history, which may be a factor in as many as 10% of cases, is another non-modifiable risk factor. Patients with the BRCA2 gene mutation have a higher rate of ductal adenocarcinoma, which may account for 10% to 20% of familial pancreatic cancers. Other inherited cancer syndromes such as inherited colorectal cancer may also be associated with pancreatic cancer. Patients with an inherited tendency for melanoma can also have a higher rate of pancreatic cancer (3).

Certain diseases and conditions may also predispose to ductal adenocarcinoma. Pancreatic cancer is more common in patients with diabetes mellitus type II, while only slightly higher than average risk for type I (3). The risk is highest within 5 years of the diagnosis of those with type II diabetes (3). Chronic pancreatitis is also associated with an increased risk of pancreatic cancer, with recent studies suggesting this association may be related to this subset of patients having other risk factors such as smoking. Familial forms of chronic pancreatitis are due to an inherited genetic mutation and appear to have a high lifetime risk in the range of 40% to 75% for developing pancreatic cancer (3).

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Risk factors for developing cystic lesions of the pancreas are largely related to non-modifiable reasons such as age and gender. With the exception of IPMN, most cystic neoplasms occur in women, usually middle-age (2,6,8,9). Cigarette smoking has been implicated in the development of IPMN. In one study, most patients with IPMN were cigarette smokers, but due to low incidence of this lesion, etiologic factors have been difficult to determine (8).

CLINICAL PRESENTATION

Ductal Adenocarcinoma

Ductal adenocarcinomas have a mean diameter of 2.5 cm and usually arise in the head of the pancreas (Figure 1). Abdominal pain and weight loss may be presenting symptoms. Diabetes mellitus is present in 70%, with a diabetes history in many of less than two years (1). These tumors may cause mass effect on or directly invade the common bile duct or main pancreatic duct and cause stenosis or complete obstruction, leading to clinical symptoms related to chronic obstructive pancreatitis such as jaundice and pruritus. CA19-9 and CEA are released by pancreatic tumor cells and can be detected by blood tests. Testing for CA19-9 is sometimes used after treatment for pancreatic cancer to monitor recurrence (3). At resection most pancreatic adenocarcinomas have spread beyond the pancreas, either by direct extension, lymphatic and or hematogenous spread, head carcinomas usually spread via perineural sheaths and primarily involves the retroperitoneal soft tissue (1).

Cystic Neoplasms

Serous cystadenomas may be quite large and produce symptoms as a result of organ displacement. Seventy-five percent of serous cystic neoplasms of the microcystic variety occur in the body and tail of the pancreas. Approximately two thirds of patients have symptoms of abdominal pain, weight loss, and nausea and vomiting (2). The oligocystic variety occurs in the head and body, and may obstruct the pancreatic duct and may cause clinical symptoms of abdominal pain and jaundice as well as steatorrhea. Pancreatic serum

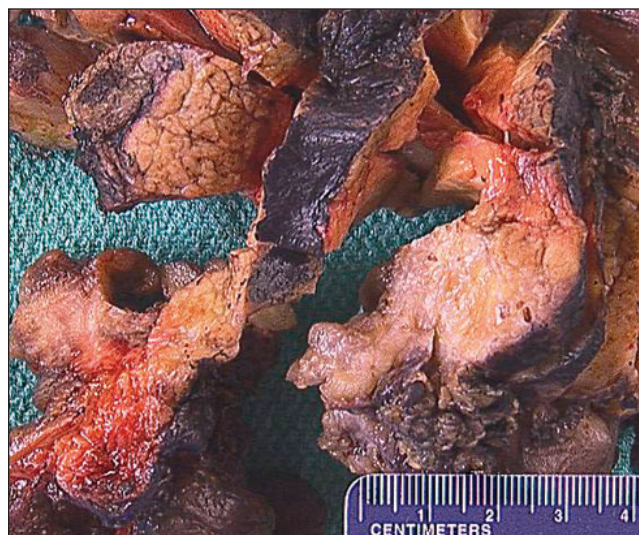


Figure 1. Pancreatic head mass, surgical resection specimen, gross photograph. The pancreaticoduodenectomy specimen has been inked black to denote the margins of surgical resection, placed in fixative, and sectioned in the region of the pancreatic head. Cut section reveals the normal tan-yellow lobulated parenchyma of the pancreas (arrow) and the yellow-white solid lesion in the pancreatic head (arrowhead). The color and consistency of this lesion is typical of pancreatic ductal adenocarcinoma. The lesion also appears to extend to the duodenum, raising suspicion of invasion of the duodenal wall (double arrowhead).

markers are usually normal. Radiographic studies show a well-circumscribed multilocular cyst with central stellate scar and sunburst type calcification. Serous cystadenocarcinomas may have clinical findings related to bleeding from gastric varices due to tumor invasion of the stomach wall and splenic vein (2).

The majority of mucinous cystic neoplasms (MCN) of the pancreas occur in the body and tail and show no communication with the pancreatic ductal system (Figure 2). Thus obstructive jaundice is uncommon with this lesion. The association with diabetes mellitus is frequent (6). Increased serum level of CEA and CA 19-9 with low serum amylase are suggestive of MCN (6). US and CT show sharply demarcated hypoechoic mass with one or more large cysts with irregular thickenings and papillary excrescences suggestive of malignant transformation.

Intraductal papillary mucinous neoplasms (IPMN) arise in the main pancreatic duct or its branches, usu-

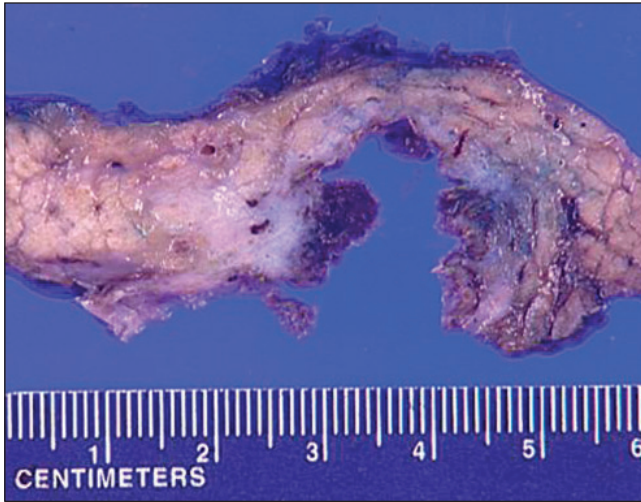


Figure 2. Pancreatic body cystic mass, surgical resection specimen, gross photograph. The distal pancreatectomy specimen has been placed in fixative and sectioned. Cut section reveals the normal tan-yellow lobulated appearance of the pancreas (arrow) and a cystic cavity with surrounding hemorrhage and fibrosis of the pancreatic parenchyma (arrowhead). Histological features, including benign appearing low cuboidal to columnar epithelium and ovarian-type subepithelial stroma, classified this lesion as a mucinous cystadenoma.

ally located in the head of the gland, and can reach 1–8 cm in maximum dimension (8). Epigastric pain, pancreatitis, weight loss, diabetes, and jaundice are typical (8). Patients with IPMN can present with repeated episodes of acute pancreatitis, presumably triggered by intermittent duct obstruction caused by viscous mucous plugs. Increased serum amylase and lipase are present. Radiographic studies may show a dilated pancreatic duct, but definitive diagnosis requires surgical removal and extensive histologic sampling.

BIOPSY

When the patient's history and physical examination suggest the presence of pancreatic neoplasm, radiographic imaging follows with endoscopic imaging techniques such as retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). With the use of EUS, biopsy of the lesion via fine-needle aspiration technique can be performed. With FNA,

cells and fluid can be removed for direct microscopic examination. A combination of radiographic imaging, biopsy and tumor marker studies can achieve accuracy rates of greater than 95%, especially for ductal adenocarcinoma (1).

Distinguishing among pseudocysts and serous and mucinous adenomas and carcinomas is a challenge on fine needle aspiration cytology. In some cases, however, preoperative diagnosis may not be possible. False negative cytology is not unusual, and mucous-secreting cells can be found in the normal pancreatic duct lining (7). In the absence of a history of recent pancreatitis, a neoplastic cyst should be suspected. The American Society of Gastrointestinal Endoscopy has issued a guideline: EUS findings by themselves are not accurate enough to definitively diagnose the type of cystic lesion of the pancreas or to determine its malignant potential (10). Further discussion on the use of radiographic techniques, with a focus on EUS, will be featured in the next segment in the series on pancreatic neoplasms.

CLINICAL MANAGEMENT

Ductal Adenocarcinoma

Pancreaticoduodenectomy is the standard operation for pancreatic cancer within the head or uncinate process of the pancreas. This procedure, also called the "Whipple procedure," involves removal of the pancreatic head, duodenum, a segment of proximal jejunum, common bile duct, and gallbladder. Modifications of the standard Whipple procedure have been developed in an attempt to minimize the morbidity associated with this procedure (11). Surgical resection of cancers located in the body or tail of the pancreas consists of a distal subtotal pancreatectomy, usually combined with splenectomy.

Despite extensive surgical resection, patients still have a relatively poor prognosis. Adjuvant therapies, such as chemotherapy and radiation therapy have been investigated in effort to improve the cure rate achieved with surgery alone (12). The rationale for combined modality therapy is provided by recurrence after surgical resection in more than one-half of patients (13). Despite several randomized trials evaluating postoper-

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ative combined chemoradiotherapy or a combination of preoperative plus postoperative treatment in patients with resected pancreatic cancer, its benefit remains unclear and controversial (12).

Cystic Neoplasms

Further management of a serous cystadenoma is determined by clinical symptoms, progression and location of the lesion. Observation is appropriate for symptomatic and non-enlarging serous cystadenomas since the risk of malignant change is small. Symptomatic or enlarging serous cystadenomas should be resected. A mucinous cystadenoma should be resected because of the high potential for malignant change. Patients with intraductal papillary mucinous neoplasms (IPMN) are subject to intermittent obstruction and recurrent episodes of pancreatitis. These patients should undergo resection to remove the mucous-secreting abnormal portion of the pancreas. Similar to mucinous cystadenoma, those with IPMN should undergo resection even if asymptomatic because of the significant risk of progression to invasive cancer. In general, distal pancreatectomy is performed for lesions in the body or tail, and pancreaticoduodenectomy for lesions in the pancreatic head.

While surgical management is indicated in the majority of pancreatic cystic neoplasms, management of these lesions has not been standardized and is evolving (14). Further discussion on clinical management and the use of adjuvant modalities in the treatment of pancreatic ductal adenocarcinoma and cystic neoplasms will be featured in a future segment in the series on pancreatic neoplasms.

HISTOLOGIC FINDINGS

Ductal Adenocarcinoma

Ductal adenocarcinomas are usually well to moderately differentiated lesions. Well differentiated tumors show large duct structures with a papillary or cribriform pattern and medium-sized neoplastic glands with mild cellular atypia embedded in a desmoplastic fibrous stroma (accounting for the firm gross consistency). There is usually significant mucin production (1). Benign ducts and residual acini may be present.

Mitotic activity is low, which increases with glandular atypia as lesions become less well differentiated. Varying degrees of differentiation can be seen in the same lesion. This makes distinction of malignant cells from normal cells or from cells distorted by pancreatitis difficult in some cases. Numerous variants of ductal adenocarcinomas exist, and are classified according to their histologic components. Extension to lymph nodes occurs at an early stage and is associated with a poor prognosis (1,4).

Cystic Neoplasms

Serous cystic adenomas of the pancreas are epithelial neoplasms composed of cysts lined by glycogen-rich ductular type epithelium. This epithelium produces a watery fluid similar to serum. No mitoses or cytologic atypia are present. Microcystic serous cystadenomas are well-circumscribed with numerous small cysts and have central stellate fibrous scar. Oligocystic serous cystadenomas are composed of a few relatively large cysts that may extend into surrounding pancreatic parenchyma, and are poorly demarcated on histologic evaluation. Serous cystadenocarcinomas are also composed of small cysts lined by glycogen-rich cells, but the epithelium exhibits atypia with mitotic figures and is often denuded, making the diagnosis difficult (2).

Mucinous cystic neoplasms of the pancreas are epithelial neoplasms composed of columnar mucin-producing epithelium, supported by an ovarian type stroma. These lesions are classified as adenoma, borderline (low-grade malignant) and non-invasive or invasive carcinoma (mucinous cystadenocarcinoma) (6). Histologically, two distinct components are present, with an inner epithelial layer and an outer densely cellular layer composed of ovarian-type stroma. While mucinous cystadenomas have a slight increase in basally oriented nuclei and no mitoses, MCN of borderline potential typically have papillary projections with nuclear pseudostratification (crowding of slightly enlarged nuclei) and mitoses (6). Mucinous cystadenocarcinoma is a high grade intraepithelial lesion, showing severe nuclear atypia and frequent mitoses, with invasive forms extending into the surrounding stroma. The lining epithelium, which is often partially denuded, may contain benign-appearing columnar

cells to frankly malignant mucin-producing cancer cells. Calcifications in the cyst wall may be seen.

Intraductal papillary mucinous neoplasms of the pancreas are composed of tall columnar mucin-containing epithelial cells forming papillary structures. The production of viscous mucin causes dilation of neoplastic ducts, and may also dilate duct segments lined by normal appearing epithelium. Goblet and Paneth cells may be present as a result of intestinal metaplasia in the neoplastic epithelium. Sclerosing pancreatitis may also be present secondary to duct obstruction. Adenomas show tall columnar mucin-containing cells with slight or no dysplasia. Borderline lesions have moderate dysplasia with loss of polarity, nuclear crowding, nuclear enlargement, stratification, and nuclear hyperchromatism. IPM carcinoma shows severe dysplastic epithelial change even in absence of invasion. With IPMN lesions, even if the initial lesion is benign, it has a high potential for malignant change (8).

Precursor Lesions

Precursor lesions to ductal adenocarcinoma have been recognized. It has been suggested that the term Pancreatic Intraepithelial Neoplasia (PanIN) lesions be adopted for precursor lesions within the pancreatic duct (1,15). The normal ductal and ductular epithelium is a cuboidal to low-columnar epithelium with amphophilic cytoplasm. Mucinous cytoplasm, nuclear crowding and atypia are not seen. PanIN duct lesions are those that involve the smaller caliber ducts (15). They do not involve the main pancreatic duct, and they generally are too small to be seen grossly or by radiologic imaging. The PanIN lesions range from PanIN-1A, -1B, II and III, with advancing degrees of architectural change (from flat epithelium composed of tall columnar cells to papillary and cribriform epithelium) and atypia (from small round basally located nuclei to nuclear irregularities and prominent nucleoli) (1,15). ■

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