

TOPIC HIGHLIGHT

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Less common neoplasms of the pancreas

Abby L Mulkeen, Peter S Yoo, Charles Cha

Abby L Mulkeen, Peter S Yoo, Charles Cha, Department of Surgery, Yale University School of Medicine, New Haven, CT and the VACT Healthcare System, West Haven, CT, 330 Cedar Street, LH 118, PO Box 208062, New Haven, CT, 06520-8062, United States
Correspondence to: Charles Cha, MD, Department of Surgery, Yale University School of Medicine, 330 Cedar Street, LH 118, PO Box 208062, New Haven, CT, 06520-8062, United States. charles.cha@yale.edu
Telephone: +1-203-7852380 Fax: +1-203-7852615
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Abstract

Recently, there has been an increased recognition of neoplasms of the pancreas other than ductal adenocarcinoma. Although not as well studied or characterized as pancreatic adenocarcinoma there are many distinct lesions which exhibit diverse biological behaviors and varying degrees of malignancy. These lesions include: endocrine neoplasms, cystic tumors, solid pseudopapillary tumors, acinar cell carcinoma, squamous cell carcinoma, primary lymphoma of the pancreas, and metastatic lesions to the pancreas. These less common neoplasms are being diagnosed more frequently as the number and sensitivity of diagnostic imaging studies increase. This review article discusses the clinical course, diagnosis, and treatment of these less common, but quite relevant, neoplasms of the pancreas.

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INTRODUCTION

Ductal adenocarcinoma is the most common of the various tumors that affect the pancreas. There are other distinctive neoplasms of the pancreas, however, which display a wide range of symptoms, biological behaviors, and outcomes. These include endocrine neoplasms, cystic tumors, solid pseudopapillary tumors, acinar cell carcinoma, squamous cell carcinoma, pancreatic lymphoma, and metastatic lesions of the pancreas. These tumors are becoming more

frequently documented in the literature and recognized more often, and at earlier stages, due to the increased sensitivity and utilization of diagnostic imaging. Therefore, the correct identification and treatment of these less common neoplasms of the pancreas is becoming increasingly important.

ENDOCRINE NEOPLASMS OF THE PANCREAS

Pancreatic endocrine tumors are far less prevalent than pancreatic adenocarcinomas. They occur in approximately 1 out of 100 000 people annually, and constitute 1%-2% of pancreatic tumors^[1]. These tumors frequently manifest as a constellation of symptoms associated with the hormones they produce (Table 1). Classification is based on hormone production and the functional pancreatic endocrine tumors include: insulinomas, gastrinomas, VIPomas, glucagonomas, somatostatinomas, adrenocorticotrophic hormone producing tumors, and growth hormone releasing factor secreting tumors. Additionally, there is a subset of non-functional pancreatic tumors which are clinically inert but produce neuroendocrine cell markers such as chromogranin-A and somatostatin receptors^[2]. Pancreatic endocrine tumors are also associated with several inherited syndromes, including multiple endocrine neoplasia type I (MEN-1) and von Hippel Lindau disease (vHL).

Insulinomas are the most common functional pancreatic neuroendocrine tumor and are most often associated with fasting hypoglycemia and neuroglycopenic symptoms but may present with cardiovascular symptoms as well. These tumors are frequently small (< 2 cm), predominantly benign, and may occur anywhere throughout the pancreas^[3]. The second most common functional pancreatic endocrine tumors are gastrinomas. These tumors produce gastrin and cause Zollinger-Ellison syndrome. Greater than 50% of gastrinomas are malignant at the time of diagnosis and many of these will have liver metastases^[4]. These patients commonly have peptic ulcer disease but diarrhea secondary to the increased gastric acid secretion is frequently a presenting symptom^[5]. Other less common functional neuroendocrine tumors of the pancreas include VIPomas which are frequently metastatic at the time of diagnosis^[6] (> 60%) and cause secretory diarrhea with subsequent electrolyte abnormalities. Glucagonomas are another rare functional pancreatic endocrine tumor. They are usually large (> 4 cm) tumors found almost exclusively within the body and tail of the pancreas and are symptomatically associated with the "4D's" (dermatitis, diabetes, deep venous thrombosis, and depression)^[7]. There are additional

Table 1 Classification of pancreatic endocrine tumours

Tumor	Hormone produced	Percent malignant	Clinical features	5 yr survival	Localization	Treatment
Insulinoma	Insulin proinsulin	10%	Hypoglycemia, neuroglycopenic symptoms	97%	EUS, intraoperative ultrasound	Surgical resection, chemotherapy, dextrose
Gastrinoma	Gastrin	60%-90%	Peptic ulcer disease, diarrhea	60%-70%	SRS, SPECT, EUS	Surgical resection, PPI, somatostatin
Glucagonoma	Glucagon	50%-90%	Necrolytic migratory erythema, diabetes, DVT, depression	50%-60%	CT w/contrast, EUS	Surgical resection, nutritional support, somatostatin, chemotherapy, insulin
VIPoma	Vasoactive intestinal peptide	40%-70%	Secretory diarrhea, hypokalemia, achlorhydria	50%	CT Scan, SRS	Somatostatin, correction of electrolytes, hydration, surgical resection
Somatostatinoma	Somatostatin	70%-80%	DM, cholelithiasis, steatorrhea	40%	CT, EUS, SRS	Surgical resection, chemotherapy, somatostatin
Non-functional tumors	Pancreatic polypeptide	60%-80%	Abdominal pain, weight loss, jaundice	50%	CT, MRI	Surgical resection

functional neuroendocrine tumors of the pancreas, each of which present with specific clinical symptoms related to the excess of hormone produced. However, approximately 15%-30% of pancreatic endocrine tumors are termed “nonfunctional”, as they may either produce elevated amounts of hormones which do not cause symptoms or may excrete small, clinically insignificant amounts of active hormones^[3]. These tumors are generally large, metastatic at the time of diagnosis, and may be distributed throughout the pancreas. Patients generally present with mechanical symptoms associated with the tumor itself, such as abdominal pain, weight loss, and jaundice^[8].

The treatment of endocrine tumors of the pancreas includes supportive medical treatment, surgery, both for cure and palliation, and nonsurgical cytoreduction. Frequently, these tumors require a combination of both surgical and medical treatment to best relieve the patients’ symptoms and offer the best prognosis. It is important to remember that endocrine neoplasms of the pancreas usually have metabolic derangements which must be corrected prior to further treatment. Patients with insulinomas should have their hypoglycemia controlled, aggressive preoperative nutritional support and anticoagulation is essential for those with glucagonomas, and dehydration and electrolyte abnormalities must be corrected when a VIPoma is diagnosed.

Complete surgical resection of endocrine neoplasms of the pancreas offers the only chance for cure, but patients can sometimes have metastases at the time of diagnosis making complete resection an impossibility. However, some authors have suggested that in patients with metastatic disease, aggressive surgery with debulking and resection of metastases will benefit patients symptomatically and improve survival^[9,10]. Combinations of non-surgical cytoreductive modalities and medical treatments are also used to enhance palliation and survival, including cryoablation, hepatic artery embolization, radio frequency ablation, somatostatin analogues, alpha interferon, chemotherapy, and radiotherapy^[11].

CYSTIC NEOPLASMS OF THE PANCREAS

The diagnosis of cystic lesions of the pancreas, which constitute less than 10 percent of pancreatic neoplasms^[12],

has become more commonplace due to the increased frequency and improved accuracy of imaging techniques. This has increased the need for a clear understanding of the diagnosis and management of these cystic lesions. Two of the more common cystic neoplasms are the serous cystadenomas and the mucinous cystic neoplasms. Serous cystadenomas occur predominantly in women, and are typically described as microcystic with a “honeycombed” appearance, although oligo-macrocytic variants do exist. All true serous cystadenomas are benign. However there are a few case reports in the literature of serous cystadenocarcinomas which are classified as malignant due to invasion of cells into surrounding tissues or metastatic spread^[13].

Mucinous cystic neoplasms (MCNs) have an epithelial lining made of columnar mucin-producing epithelium that has an ovarian-type stroma and stains positively for estrogen and progesterone receptors^[14]. Unlike the honeycombed appearance of serous neoplasms, most mucinous tumors are unilocular and although uncommon, a finding of peripheral calcification on CT is predictive of a malignant MCN^[15]. Series have found that from 8% to 33% of these tumors contain invasive carcinoma^[16]. MCNs are generally found in the body and tail of the pancreas and more commonly affect females in the 5th decade of life. With both neoplasms, patients often present with nonspecific complaints such as abdominal pain and weight loss, though they may be asymptomatic^[17]. Of note, in a recent review of 106 patients with serous adenomas, 47% of tumors were found in asymptomatic patients as part of the workup of an unrelated problem^[18]. It is this type of patient with an incidentally found lesion that presents a challenge in both diagnosis and treatment. Given the risk of invasive cancer the treatment of mucinous cystic neoplasms should be surgical resection. The treatment of serous cystic lesions is more controversial. A recent paper from the Massachusetts General Hospital describing their experience with serous cystadenomas proposes a selective approach towards resection, based on tumor size and the ability to accurately diagnosis the lesion^[18]. If radiographic imaging is equivocal, endoscopic ultrasound with fine needle aspiration is performed and markers such as mucin-like antigen and carcinoembryonic antigen (CEA) levels, which are both low in serous tumors and high in

mucinous lesions, are evaluated^[16]. If based on this workup the diagnosis of a serous cystadenoma of < 4 cm in an asymptomatic patient is made, expectant management with serial CT scans is recommended^[18]. However, due to the difficulty in unequivocally differentiating between benign versus malignant cystic tumors preoperatively, some feel that an aggressive surgical approach should be used for all patients presenting with a cystic pancreatic neoplasm^[19,20].

INTRADUCTAL PAPILLARY MUCINOUS TUMORS

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are defined as intraductal mucin-producing neoplasms with tall, columnar, mucin-containing epithelium with or without papillary projections. Typically, these tumors involve the main pancreatic duct but recently, a distinction has been made between those tumors which involve the main duct and those which predominantly involve the branches of the ductal system (branch-duct IPMNs). Some have suggested that the branch duct variant of IPMN is more indolent and has a lesser incidence of malignancy than the main duct IPMN^[21,22]. IPMNs display a histological range from adenoma, to IMPN with dysplasia, to carcinoma in situ, to invasive carcinoma which seems to mimic the adenoma-carcinoma sequence seen in colorectal cancer. A review of recent reports found that approximately 50% of resected specimens contained invasive carcinoma^[23]. Patients generally present in their 60's, but several recent studies have shown that those patients with invasive IPMNs are 5-6 years older than those patients with benign disease^[24,25]. Patients are often symptomatic at presentation with complaints of abdominal pain, weight loss, and diarrhea^[26]. Thin cut CT scan, which is the radiological test of choice, will often reveal a mass in the head of the pancreas and if diagnostic uncertainty is present, endoscopic ultrasound with fine needle aspiration may be preformed. Treatment of IPMN consists of surgical resection, often a pancreaticoduodenectomy, of all gross disease with an attempt to achieve negative surgical margins. A comparison of recent reports showed a 5 year survival rate from 77%-100% in noninvasive IPMNs compared to 43%-65% in those patients with invasive disease^[23-27]. Recurrent disease has been shown to occur both in the pancreatic remnant and at distant sites and therefore close follow-up with frequent imaging has been recommended.

SOLID PSEUDOPAPILLARY TUMORS OF THE PANCREAS

These rare pancreatic neoplasms tend to affect young women and have characteristic histological features, including a combination of solid and cystic components and the presence of pseudopapillae. Interestingly, unlike ductal adenocarcinoma, solid pseudopapillary tumors of the pancreas (SPTs) are not associated with abnormalities in *K-ras*, *p53*, or *DPC4* genes but like colon cancer, do demonstrate genetic abnormalities in the *APC/B-catenin* pathway^[28]. Presenting symptoms are frequently non-spe-

cific in nature and often include abdominal pain, increased abdominal girth, and the presence of a palpable mass. A review of 718 patients with solid pseudopapillary tumors of the pancreas found a 10:1 ratio of affected women to men, a mean age of 22 years, the presence of metastases in 20% of the patients, and a cure rate greater than 95%^[29]. Surgery is the treatment of choice for these tumors, with pancreaticoduodenectomy performed for lesions in the head of the pancreas and distal pancreatectomy for those lesions in the body or tail. Metastatic or locally invasive disease is not necessarily a contraindication to surgery, and improved longterm survival has been demonstrated with aggressive surgical resection^[30,31]. There have been reports of some success with radiotherapy or chemotherapy in cases deemed unresectable^[29]. Although the majority of these tumors are considered to be of low malignant potential, a recent report of two cases of aggressive SPTs noted death of the patients at 6 and 16 mo after diagnosis. In these cases a high mitotic index and extensive tumor necrosis was noted^[32]. These findings might help distinguish a more virulent form of SPT and lead to a more aggressive post-operative treatment course.

ACINAR CELL CARCINOMA

Acinar cell carcinoma of the pancreas accounts for approximately 1% of pancreatic cancers. These tumors exhibit expression of pancreatic enzymes such as trypsin, lipase, chymotrypsin and amylase. Similar tumors with primarily acinar differentiation include mixed acinar-endocrine carcinomas, which exhibit both acinar and endocrine cellular differentiation, and pancreatoblastomas which are usually found in children. Patients most frequently present with abdominal pain and bloating and these tumors may be associated with hypersecretion of lipase which leads to subcutaneous nodules and ectopic fat necrosis^[33]. On CT or MRI it presents as an exophytic, hypovascular, and well marginated mass^[34]. Unlike typical pancreatic adenocarcinoma the genetic mutations in *K-ras*, *p53*, and *Smad* are uncommonly found but there seem to be alterations in the adenomatous polyposis coli-*b-catenin* pathway which are similar to colorectal cancer^[35].

A retrospective review from the Memorial Sloan-Kettering Cancer Center evaluated 39 patients with acinar cell carcinoma^[36]. They noted that these lesions were found equally throughout the pancreas, approximately half the patients had metastatic disease at time of presentation, and that the median survival was 19 mo. This median survival (19 mo) falls between that of ductal adenocarcinoma (6 mo) and endocrine neoplasms of the pancreas (40-60 mo). In these patients the stage of disease correlated with survival (14 mo in patients with metastases vs 38 mo in patients with localized disease). Patients who were amenable to surgery had a 36 mo median survival as opposed to 14 mo in patients who did not receive surgery. Despite the improved survival in the surgical patients, there was a high recurrence rate (72%) which the authors felt may have been indicative of the presence of micrometastases and may imply the need for adjuvant therapy. Many of these patients who recurred experienced a distant rather than lo-

cal recurrence which suggests the need for better systemic therapy. Case reports have demonstrated some success with concurrent chemotherapy (capecitabine or irinotecan, FU and leucovorin) and radiotherapy which will likely be further elucidated as more data is obtained^[36,37].

SQUAMOUS CELL CARCINOMA OF THE PANCREAS

Although not normally present in the pancreas, squamous metaplastic cells may present during periods of inflammation^[38]. These cells may then transform to squamous cell carcinoma of the pancreas which is a rare and unusual cancer. The reported incidence is 0.5% to 2% of pancreatic malignancies and a recent case report found 61 cases, including 36 autopsy/registry cases, in the English literature^[39]. Their review of these cases found a mean age of 62 years, common presenting symptoms of abdominal/back pain, weight loss, and anorexia, tumor size of 7.8 cm, and equal distribution of the lesion in the head, body, or tail^[39]. Given the rarity of this neoplasm, in cases in which squamous cell carcinoma of the pancreas is diagnosed it is important to perform a thorough search for a possible alternate primary location. Patients with squamous cell carcinoma of the pancreas have a poor prognosis, with a median survival of 7 mo for patients undergoing curative resection and 3 mo for those not undergoing a curative resection^[39,40]. There are several reports of the use of chemotherapy in unresectable cases, but the prognosis remains poor.

PRIMARY LYMPHOMA OF THE PANCREAS

Primary lymphoma of the pancreas is rare disease and in one study was shown to comprise 1.3% of 1050 pancreatic fine needle aspirations^[41]. Patients generally range from 58-66 years old and frequently present with abdominal pain, weight loss, and an abdominal mass, while only 25% present with jaundice^[42]. The head of the pancreas is the most common location for these tumors but the entire gland may be affected. The majority of primary pancreatic lymphoma displays a B-cell phenotype, although a Japanese report found that 21% of cases were T-cell lymphomas and cases of anaplastic large cell lymphoma and Hodgkin lymphoma of the pancreas have been reported^[43-46]. Diagnosis of this rare cancer is critical and requires adequate samples for tissue typing. Fine needle aspiration (FNAs) with flow cytometry has been advocated by some to be an accurate diagnostic tool which then obviates the need for invasive surgery to only those patients with non-diagnostic FNAs^[47]. The primary treatment of pancreatic lymphoma consists of chemotherapy and radiotherapy using non-Hodgkin's lymphoma protocols and survival ranges from to 2-6.5 years^[42]. For patients undergoing surgery, biliary and gastric bypass may be beneficial to relieve jaundice and prevent obstructive fibrosis in the common bile duct following chemotherapy and radiation. A review of those patients undergoing surgery found that 35% of patients underwent biopsy alone, 27.5% had a biliary bypass, 15% had a gastric bypass, and 7.5% had pancreatic resection^[42].

METASTATIC LESIONS OF THE PANCREAS

Although uncommon, the pancreas may serve as a site for distant metastases and when these metastases present as an isolated pancreatic mass, questions regarding diagnosis and treatment may arise. Almost any tumor type may metastasize to the pancreas but in an analysis of a surgical and autopsy database, the majority of tumors found in the surgical database were lymphomas, carcinomas of the stomach, kidney, and lung whereas in the autopsy database metastasis was most commonly from the lung, followed by the GI tract and kidney^[48]. A review of resection for metastases to the pancreas found renal cell carcinoma to be the most frequent primary histopathology (62%), followed by non-small cell lung cancer, melanoma, and sarcoma^[49]. In this series, postoperative morbidity was 25%, mortality was 6%, and the overall actuarial survival rate for 2 and 5 years was 62% and 25%, which indicates that resection of metastatic disease to the pancreas is safe and may offer some survival benefit in select patients. The prolonged disease free interval between the initial cancer and pancreatic recurrence can be quite prolonged (median 2.6-7.5 years)^[48-51]. Hiotis *et al* found that approximately one-third of the metastatic tumors evaluated were clinically suspected to be primary pancreatic neoplasms^[49]. These findings demonstrate the difficulty in diagnosing pancreatic metastases and emphasize the need to consider metastatic disease to the pancreas in the workup of any pancreatic tumor and particularly in patients with a history of prior malignancy.

In conclusion, the most common neoplasm affecting the pancreas is ductal adenocarcinoma but there are a host of less common pancreatic neoplasms with distinct clinical and biological behaviors. Although relatively rare, more of these lesions will be seen as diagnostic imaging continues to become more frequent and sensitive. Accurate and timely identification of a pancreatic neoplasm coupled with a knowledge of its biological behavior and therapy will be essential in order to offer patients the optimal therapy.

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