Pancreatic neuroendocrine tumors in British Columbia: A review

Given the nuances in evaluating patients with pancreatic neuroendocrine tumors, referral for specialty consultation is advised.

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ABSTRACT: Pancreatic neuroendocrine tumors are neoplasms arising from the endocrine cells of the pancreas. Although these lesions are neoplastic, there are significant differences in prognosis and management depending on tumor characteristics; thus, they present a diagnostic challenge to the clinician and can create confusion for patients. Most lesions can be worked up with appropriate imaging. Endoscopic ultrasound is a sensitive modality for tissue diagnosis, risk stratification, and may play an evolving role in management. Given the nuances in evaluating patients with pancreatic neuroendocrine tumors, referral for specialty consultation is advised.

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BC Cancer estimates the average-risk patient's lifetime risk of pancreas ductal adenocarcinoma at 1.3%. In contrast, pancreatic neuroendocrine tumors (NETs) are rare. The pancreatic NET incidence was less than 1 case per 100 000 population per year,[1,2] and pancreatic NETs account for only 1% to 2% of all pancreatic neoplasms.[3,4] However, clinicians should be aware of these lesions because of increasing incidence, attributed to improved access to cross-sectional imaging.[5,6] One in five incidental pancreatic lesions on CT are pancreatic NETs.[7]

The nomenclature of pancreatic NETs has changed over time. Prior to the 1990s, these lesions were called "islet cell tumors" or "carcinoids." The World Health Organization recommended the standardized terminology "endocrine tumor"[8] and then "neuroendocrine tumor." Medical school curricula tend to highlight the hereditary syndromes of multiple endocrine neoplasia type 1, von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis type 1; however, 90% of pancreatic NETs are sporadic and are not associated with an inherited syndrome.[9]

Pathology and classification

Pancreatic NETs show expression of both epithelial markers (keratins) and neuroendocrine markers, such as chromogranin A and synaptophysin.[10,11] Hormone-producing pancreatic NETs with symptoms are called functional tumors.[12] Less than 20% of pancreatic NETs are functional.[13] Functional pancreatic NETs include insulinomas, gastrinomas, vasoactive intestinal peptide–secreting tumors (VIPomas), glucagonomas, pancreatic NETs producing carcinoid syndrome, and somatostatinomas.[10,14]

Pancreatic NETs can be divided into well-differentiated NETs (grades 1 to 3),[13] neuroendocrine carcinomas (small cell or large cell), and mixed neuroendocrine–nonneuroendocrine neoplasms **[Table]**. Mixed lesions have both neuroendocrine and nonneuroendocrine components.[11] The most common nonneuroendocrine component is adenocarcinoma.[11] Histologically, well-differentiated NETs are monomorphic neoplastic proliferations with salt-and-pepper chromatin most often arranged in trabeculae and nests **[Figure 1]**. These lesions also have a Ki-67 proliferation

TABLE. Pancreatic neuroendocrine tumor classification, features, and prognosis.

	Well-differentiated neuroendocrine tumors	Neuroendocrine carcinoma
Pathologic features	Well-differentiated morphology Lower proliferative index	High-grade morphology High proliferative index
Prognosis	Slowly progressive Prognosis based on size, resectability, and World Health Organization grade (1 to 3)	Rapidly progressive Poor prognosis

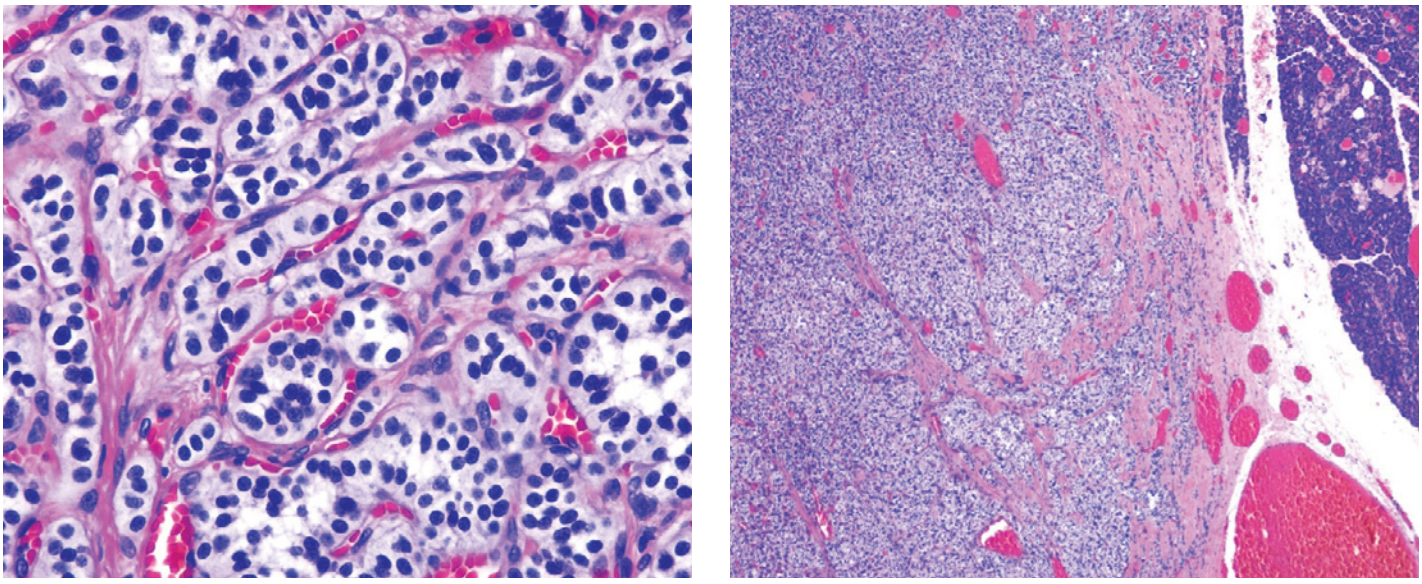


FIGURE 1. Pancreatic neuroendocrine tumor after endoscopic ultrasound fine-needle biopsy. Images on the left (40x) and right (4x) show immunohistochemical stains of the biopsies. The cells are strongly cytokeratinAE1/AE3-positive, with a granular cytoplasmic pattern of staining and paranuclear accentuation in many cells. Findings indicate a well-differentiated neuroendocrine tumor.

rate of less than 50%.[11,15,16] Common molecular alterations in well-differentiated NETs are in the *MEN1*, *DAXX*, *ATRX*, *mTOR*, *CDKN2A*, and *SET2* genes.[17] All pancreatic NETs are considered malignant; however, small, well-differentiated T1 tumors have an excellent prognosis.[11]

Neuroendocrine carcinomas are distinct malignancies from the well-differentiated NETs **[Table]**. They can be divided into small-cell and large-cell carcinomas. Small-cell carcinomas are characterized by closely packed cells with a high nuclear-to-cytoplasmic ratio, hyperchromasia, nuclear molding, high mitotic rate, and abundant apoptosis. Large-cell neuroendocrine carcinomas show large, closely packed cells with vesicular chromatin and a prominent nucleolus. The threshold between high-grade (grade 3) well-differentiated NETs and large-cell neuroendocrine carcinomas can be difficult. Rarely, some well-differentiated NETs transform into neuroendocrine carcinomas.[16-18] Neuroendocrine carcinomas frequently show mutations in both the *p53* and *Rb1* genes. They may also demonstrate gene mutations seen in pancreatic adenocarcinoma, such as *KRAS*, *CDKN2A*, and *SMAD4* mutations.[17]

Diagnostic evaluation

The clinical presentation of pancreatic NETs can be diverse. Insulinomas can cause intermittent hypoglycemia. Abdominal pain, heartburn, peptic ulcers, or diarrhea can direct clinicians to look for a gastrinoma in Zollinger-Ellison syndrome. VIPomas can cause a rare syndrome of hypokalemia, hypochlorhydria, and watery diarrhea. Nonfunctioning pancreatic NETs can cause complications such as weight loss, abdominal pain, and jaundice from mass effect. Nonfunctioning pancreatic NETs are often found when imaging is being done for another indication.

A thorough elevation of pancreatic NETs starts with imaging, includes a functional assessment, and is confirmed by cytology or histology. Routine CT with portal venous phase may miss a pancreatic NET, because the lesion can appear isodense or only mildly hyperdense to the background parenchyma.[19] On arterial phase CT, these lesions demonstrate arterial phase hyperenhancement.[14] Therefore, multiphase cross-sectional imaging is essential to define these lesions **[Figure 2]**. On MRI, the lesions are hypointense on intrinsic T1 phases and high signal on T2-weighted sequences and demonstrate avid arterial phase enhancement on postcontrast T1 sequences.[20,21] Other arterial enhancing lesions can mimic pancreatic NETs on CT, including solid pseudopapillary neoplasms, pancreatic metastases (e.g., renal cell carcinoma), acinar cell carcinomas, pancreatic hamartomas, pseudoaneurysms, intrapancreatic splenules, and exophytic gastrointestinal stromal tumors.[22,23] The most appropriate way to initiate investigation of a pancreatic lesion is a pancreatic-protocol CT scan.

Depending on the diagnostic evaluation, further noninvasive imaging may be indicated, including an octreotide scan or PET. Three PET radiopharmaceuticals are available for suspected pancreatic NETs: gallium-68 DOTA-Tyr(3)-octreotate (Ga-68 DOTATATE), gallium-68 DOTA-D-Phe1-Tyr(3)-octreotide (Ga-68 DOTATOC), and copper-64 DOTA-Tyr(3)-octreotate (Cu-64 DOTATATE).[24]

Functional testing with biomarkers is usually performed by a local specialist in endocrinology, gastroenterology, hepatopancreaticobiliary surgery, or oncology. The specialist interrogates symptoms, elicits a family history, and examines the patient for signs of multiple endocrine neoplasia type 1, von Hippel-Lindau disease,

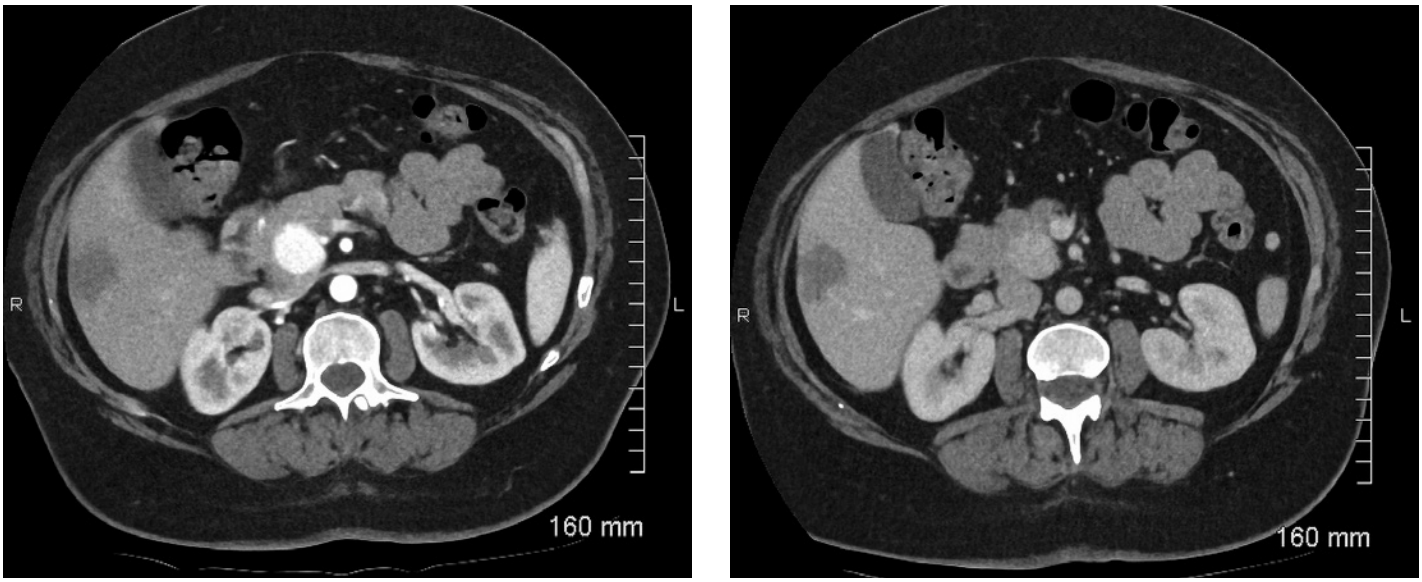


FIGURE 2. Multiphase CT imaging of the pancreas with arterial phase (left) and portal venous phase (right). There is a 2.6 × 2.7 × 2.4 cm circumscribed hypervascular mass in the medial head of the pancreas. Enhancement of these masses is most avid on the arterial phase, where it is similar in attenuation to arterial blood pool.

neurofibromatosis type 1, or tuberous sclerosis complex.[13] North American guidelines recommend against routine use of nonspecific tumor markers such as chromogranin A.[13]

Endoscopic ultrasound

In British Columbia, endoscopic ultrasound and fine-needle biopsy are available at Victoria General Hospital, Vancouver General Hospital, St. Paul's Hospital, Royal Columbian Hospital, Surrey Memorial Hospital, Royal Inland Hospital, and Kelowna General Hospital. Endoscopic ultrasound has good accuracy for pancreatic NETs[26,27] and facilitates tissue acquisition for most patients.[28] Endoscopic ultrasound is more sensitive than CT[29] and is superior to MRI and somatostatin receptor scintigraphy for pancreatic NET localization; it has reported sensitivities of 82% to 93% and is recommended in guidelines for pancreatic NET diagnosis.[30] Even small pancreatic NETs should be confirmed on biopsy if possible.[31] Endoscopic ultrasound prior to surgery is beneficial. A meta-analysis of 612 patients showed a preoperative sensitivity for pancreatic NET detection of 97%.[32]

For small nonfunctioning pancreatic NETs with low proliferative activity, surveillance with endoscopic ultrasound or cross-sectional imaging is often appropriate. Novel technologies in endoscopic ultrasound that use IV contrast, tissue harmonics, and elastography may be useful in differentiating pancreatic NETs from benign pancreatic lesions in the future. Endoscopic ultrasound can also play a role in the treatment of pancreatic NETs using endoscopic ultrasound–guided tattooing or fiducial insertion to target radiotherapy and surgical treatment. For nonsurgical candidates, endoscopic ultrasound–guided ablation therapy with ethanol and radiofrequency ablation have been studied for local tumor control.[33]

Prognosis

Pancreatic NETs encompass a spectrum of disease, ranging from low-grade indolent tumors to rapidly progressive disease. Tumor histology, grade, Ki-67 score, and clinical stage are important features for estimating prognosis and response to treatment. For localized, resectable disease, 5-year overall survival rates are 97%, 87%, and 73% for stages I, II, and III, respectively, by European Society of Neuroendocrine Tumors staging.[34] Ki-67 is a protein found in dividing cells and is useful for quantifying the risk of tumor growth and spread. Tumor grade, Ki-67 score, and differentiation are strong predictors of prognosis.[35] Based on surveillance, epidemiology, and end results data for patients with stage IV or metastatic disease, 5-year overall survival rates are 51%, 45%, and 12% for tumor grades 1, 2, and 3, respectively.[6] In contrast, pancreatic neuroendocrine carcinomas have a poor prognosis, with a median overall survival of 8 to 17 months.[36] Therefore, when counseling a patient regarding a diagnosis of pancreatic NET, it is important to incorporate both clinical and pathologic features.

Management

Surgery is advised for functional pancreatic NETs.[25] Active surveillance with annual imaging has been advised for patients with nonfunctional pancreatic NETs that are less than 1 cm in size.[25,31] In a prospective study of patients with documented pancreatic NETs that were less than or equal to 2 cm, only 11% of patients showed an increase in pancreatic NET size of at least 0.5 cm/year, which was a study indication for surgical referral, over a median follow-up of 17 months.[37] The management of patients with nonfunctional pancreatic NETs 1 cm to 2 cm, without pancreatic duct obstruction,

can be tailored based on surgical risks and tumor biology. Referrals for surgery should be made when the nonfunctional pancreatic NET is 2 cm or larger or is associated with main pancreatic duct dilation.[25] Curative intent surgery for nonfunctional pancreatic NET has a 5-year survival rate of more than 70%.[38] Given the potential for late recurrences, the North American Neuroendocrine Tumor Society recommends surveillance imaging for at least 10 years after resection. Individual recommendations are based on tumor size, Ki-67 score, and the number of lymph nodes involved.[13]

Systemic therapy

Systemic therapy is reserved for patients with unresectable or metastatic disease. Currently, there is no evidence to support the use of systemic therapy in the adjuvant setting. The choice of systemic therapy depends on symptoms, somatostatin receptor status, tumor grade, and histology.

For patients with well-differentiated tumors, a Ki-67 score of less than 10%, and somatostatin receptor–positive disease, somatostatin analogues alone can be considered for first-line therapy with long-term responses reported.[39] However, for patients with well-differentiated pancreatic NETs and a high proliferation rate (Ki-67 > 10%), chemotherapy with capecitabine and temozolomide can be considered.[40,41] New data support the use of peptide receptor radionuclide therapy as first-line treatment in patients with a Ki-67 score of 20% or higher in combination with a somatostatin analogue or as second-line therapy for patients whose disease has progressed on somatostatin analogues.[42,43] Subsequent lines of therapy include tyrosine kinase inhibitors such as sunitinib, cabozantinib, or a mechanistic target of rapamycin inhibitors such as everolimus.[44-46]

In contrast, pancreatic neuroendocrine carcinomas are associated with aggressive behavior and poor prognosis. Neuroendocrine carcinomas are treated with cisplatin and etoposide or fluoropyrimidine-based doublet chemotherapy.

Summary

Pancreatic malignancy is a challenging topic to discuss with patients. This is particularly true if there is a delay in diagnosis. Most patients do not interact with an active group of advocates and survivors. Advocacy programs for other cancers have improved outcomes.[47] Finding the balance between informing a patient and not creating panic is a constant focus for physicians in this field.

Accurate prognostication and awareness of the stark contrast between the management of pancreatic NETs and that of pancreatic adenocarcinoma are critical. A pancreatic-protocol CT with arterial phase imaging is the first step in evaluating a patient with a suspected pancreatic NET. Subsequent referral for endoscopic ultrasound will enable tissue diagnosis and risk stratification. Endoscopic ultrasound providers will refer the patient to a pancreas surgeon or to BC Cancer based on staging data and functional testing. For oncologists and surgeons, deciding between active surveillance with yearly imaging and surgical resection often requires a multidisciplinary review. ■

Key points

1. A pancreatic-protocol CT is the starting imaging modality for a suspected pancreatic neuroendocrine tumor (NET).
2. Functional testing should be initiated by local specialists in endocrinology, gastroenterology, hepatopancreaticobiliary surgery, and oncology.
3. A referral for a local endoscopic ultrasound can facilitate detection, tissue diagnosis, and risk stratification.
4. The decision between surveillance and surgery is dictated by clinical factors, pancreatic NET size, functional status, stage, and patient goals.

Competing interests

Dr De Korompay has been a speaker and consultant for Penumbra, Inc. and Cook Medical. The remaining authors have no competing interests to declare.

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