Islet Cell Tumors of the Pancreas

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KEYWORDS

• Islet cell tumor • Pancreatic neuroendocrine tumors (PNET) • Pancreas
• Pancreas cancer • Targeted molecular therapy

KEY POINTS

- Islet cell tumors of the pancreas, also known as pancreatic neuroendocrine tumors (PNETs), are rare neoplasms that constitute fewer than 5% of pancreatic tumors.
- Although PNETs may present with distinct clinical syndromes, most of these tumors are nonfunctional.
- In a minority of cases, PNETs arise in the background of known genetic syndromes such as multiple endocrine neoplasia type I or von Hippel-Lindau syndrome.
- Surgery remains the cornerstone of treatment, provided that 90% of the tumor burden can be resected.
- For nonresectable well-differentiated lesions, somatostatin analogues, chemotherapy, targeted molecular therapy, and peptide receptor radiotherapy are appropriate options that lead to increased survival.

INTRODUCTION

Islet cell tumors of the pancreas, also known as pancreatic neuroendocrine tumors (PNETs), are a group of tumors that arise from the endocrine pancreas. Although PNETs may produce distinct clinical syndromes, most of these neoplasms are asymptomatic and present as an incidental finding. PNETs are a distinct group of neuroendocrine tumor (NET), with important biological differences from luminal (carcinoid) neoplasms. This article summarizes the important characteristics of PNETs with regard to epidemiology, pathology, diagnosis, and treatment, with a focus on new developments and their potential roles in the evolving management of this disease.

EPIDEMIOLOGY

PNETs are rare neoplasms that constitute fewer than 5% of pancreatic tumors, and only 7% of all NETs.[1,2] Nevertheless, in both Europe and North America, the incidence

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of PNETs is rising.[3] Data from the Surveillance, Epidemiology, and End-Results Program suggest an incidence of 0.43/100,000 person-years today, compared with 0.17 in the 1970s.[2,3] This increase may be due to advances in diagnostic imaging and increased utilization of these technologies. Interestingly, autopsy studies have reported a widely varied incidence from 0.07% to as high as 10%, suggesting that many of these tumors are clinically silent and often go undiagnosed.[3–5] Approximately 90% of PNETs diagnosed in the United States are nonfunctioning.[6] PNETs can present at any age; however, the incidence peaks in the sixth and seventh decades.[6] Not surprisingly, functional tumors present earlier than nonfunctional tumors (mean age 55 vs 59 years).[6]

SYNDROMIC ASSOCIATION

Although 90% of PNETs occur sporadically, these tumors are also well-recognized features of 4 familial syndromes: multiple endocrine neoplasia type I (MEN1), von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC).[7,8] Each of these syndromes is inherited in an autosomal dominant pattern, and the causative genes are *MEN1*, *VHL*, *NF1*, and *TSC1/2*, respectively. Whereas most patients (80%–100%) with *MEN1* develop PNET, the frequency is much lower among the 3 other syndromes. Among patients with VHL, NF1, and TSC, 10% to 17%, 0% to 10% (almost all duodenal somatostatinomas), and fewer than 1%, respectively, develop PNETs.[9] In general, PNETs that arise in the background of a familial syndrome tend to follow a more indolent course than sporadic tumors.

Multiple Endocrine Neoplasia Type I

MEN1 is characterized by PNETs in association with pituitary and parathyroid tumors. Almost all patients with MEN1 (>95%) will develop a PNET during their lifetime, although most of these will be nonfunctioning "micro-adenomas" (smaller than 0.5 cm) that are typically multifocal.[7,10,11] Fewer than 15% of these nonfunctioning tumors will be large enough to be symptomatic.[10] Functioning PNETs that are symptomatic occur in between 20% and 70% of patients with MEN1, with approximately 55% of these patients presenting with Zollinger-Ellison (ZE) syndrome due to an underlying gastrinoma, and 20% presenting with symptoms from an insulinoma.[7,8,10] Other functioning PNETs, such as VIPoma, glucagonoma, and somatostatinoma occur in fewer than 3% of patients with MEN1.[12] The management of patients with MEN1 with PNETs is of particular significance, as PNETs are the leading cause (40%) of disease-specific mortality among patients with MEN1.[13,14] Furthermore, the mean age of death among patients with MEN1 with PNETS is 55 years, which is lower than that of both the general population and patients with non-MEN1 PNETs.[14]

Von Hippel-Lindau Syndrome

Although pancreatic lesions are common in VHL, only 10% to 17% of patients with VHL develop PNETs.[7,8] Furthermore, almost all VHL-associated PNETs are nonfunctioning. The mean age of diagnosis of PNETs is 29 to 38 years, and unlike MEN1, most of these lesions are solitary as opposed to multifocal.[8]

CLASSIFICATION AND STAGING

Originally referred to as islet cell tumors, PNETs were renamed as such in 2010 by the World Health Organization (WHO). Over the past 10 years, groups such as WHO, American Joint Committee on Cancer (AJCC), and the European Neuroendocrine