Surgical Management of Pancreatic Neuroendocrine Tumors

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KEYWORDS

• Pancreatic neuroendocrine tumor • PNET • Management • Surgery • Review

KEY POINTS

- Management of pancreatic neuroendocrine tumors (PNETs) is challenging because of their heterogeneous pathologic features and unpredictable clinical behaviors.
- Although most PNETs are nonfunctional, certain PNETs are functional and can present with classic endocrinopathies related to hormone excess.
- Surgery remains the cornerstone of management for localized disease, and operative approaches are customized to the clinical behavior of the particular PNET.
- Frequent evaluation of vague abdominal symptoms using axial imaging has led to an upsurge of incidentally detected, small, asymptomatic PNETs resulting in management controversies.

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are the second most common pancreatic neoplasm behind adenocarcinoma, with an overall incidence of approximately 5:1,000,000 and an estimated prevalence of 1:100,000.[1,2] PNETs are most frequently detected between the fourth and sixth decades of life. Approximately 10% to 30% of PNETs are associated with familial syndromes including multiple endocrine neoplasia type I (MEN I) and von Hippel-Lindau syndrome.[1–3] PNETs may overproduce certain hormones and present with classic endocrinopathies. Most, however, are nonfunctional incidentalomas detected on imaging obtained for unrelated reasons. With the increased use of axial imaging to evaluate vague abdominal symptoms, the rate of detection has increased fourfold to sevenfold since the year 2000, and the size of the tumors at time of diagnosis has markedly decreased.[4] PNETs have traditionally

Financial Disclosures: The authors have no financial disclosures to report or conflicts of interest related to this work.

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Surg Clin N Am 96 (2016) 1447–1468
http://dx.doi.org/10.1016/j.suc.2016.07.002 **surgical.theclinics.com**

been thought to be biologically less aggressive than pancreatic adenocarcinomas but there has been increased recognition that the pathologic potential of PNETs is highly variable.[5,6] Many PNETs are indolent with a small proclivity to metastasize and with very favorable long-term prognoses, while others are high-grade tumors that demonstrate a relentless progression to early metastases that makes their biology seem more aggressive than typical for ductal adenocarcinomas.

Surgical resection remains the primary curative modality in the management of PNETs.[7] The current trend toward early incidental detection of the tumors combined with their heterogeneous and unpredictable pathology challenge optimal treatment decision making. In the current review, we discuss the surgical management of functional and nonfunctional PNETs with particular attention to the surgical management of small ($\leq$2 cm) asymptomatic, nonfunctional PNETs (NF-PNETs).

PATHOPHYSIOLOGY

PNETs are neuroendocrine tumors arising from the cells that make up the pancreatic islets. The underlying etiology of PNETs is believed to be acquired and/or from congenital genetic alterations in the cell of origin, but there is no genetic mutation that has been consistently and definitively associated with the development of these tumors. The most frequently mutated genes found in PNETs involve chromatin-remodeling genes, such as *MEN I* (44%) and *DAXX/ATRX* (43%), and genes of the mammalian target of Rapamycin pathway (15%).[5,8] Well-differentiated PNETs lack the alterations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* genes frequently encountered in pancreatic ductal adenocarcinomas, whereas poorly differentiated PNETs do exhibit genetic alterations found in pancreatic ductal adenocarcinomas.[9]

Functional PNETs by definition produce and secrete 1 or more active hormones. They must manifest the characteristic endocrinopathy to be considered functional. Hormones produced by PNETs include insulin, gastrin, glucagon, somatostatin, vasoactive intestinal peptide (VIP), pancreatic polypeptide, and cholecystokinin.[2,10,11] Additionally, both functional and NF-PNETs can express peptides characteristic of NETs in general, such as chromogranin A and synaptophysin. These are commonly used for purposes of diagnosis and surveillance as serologic and/or histologic markers of PNETs. Overproduction of chromogranin A and synaptophysin are not typically associated with characteristic endocrinopathies.

PNETs frequently express somatostatin receptors (SSTR1-5), which are normally present throughout the central nervous system, the gastrointestinal tract, and the endocrine and exocrine glands.[5,12] PNETs express a range of SSTRs, and synthetic somatostatin analogs, such as octreotide or lanreotide, have varying activity profiles against the range of SSTRs expressed by PNETs.

CLASSIFICATION AND STAGING

Tumors are first categorized as either functional or nonfunctional, as symptoms related to the tumor may be the primary driver for therapeutic intervention, particularly in small lesions. The vast majority of PNETs, as many as 90% in select series, are nonfunctional. Functional PNETs occur in approximately 10% of cases and are named based on their clinical endocrinopathy. They include insulinomas, gastrinomas, VIPomas, glucagonomas, and somatostatinomas (**Table 1**).[1,13] Functionality of PNETs appears to be independent of both grade and stage.

Among the various subtypes of functional tumors, insulinomas are generally less aggressive and rarely present with metastatic disease, whereas gastrinomas tend to have a higher proclivity for metastasis. In general, a loss in differentiation tends to