Nonfunctioning Incidental Pancreatic Neuroendocrine Tumors: Who, When, and How to Treat?

Marina Gorelik, DO*, Mahmoud Ahmad, MD, MBA, David Grossman, MD, Martin Grossman, MD, Avram M. Cooperman, MD

KEYWORDS

- Pancreatic neuroendocrine tumor (PNET)
- Nonfunctioning pancreatic neuroendocrine tumor (NF-PNET)
- Surveillance

KEY POINTS

- More than 50% nonfunctioning (NF) pancreatic neuroendocrine tumors (PNETs) are incidental findings on cross-sectional imaging.
- Asymptomatic NF-PNETs are indolent, and surveillance is safe and reasonable.
- Size is a less important determinant of therapy than grade, Ki-67, symptoms, and imaging.
- Surgical options include enucleation, distal and central pancreatectomy, and pancreaticoduodenectomy resection.
- A multidisciplinary approach with colleagues and informed consent with patients and families are essential.

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are an interesting, diverse, rare group of neoplasms with a varied course and prognosis. They account for 1% to 2% of all pancreatic neoplasms and have a low incidence of 0.43 per 100,000.1 With a prognosis far better than pancreatic adenocarcinoma, they range from benign to low-grade malignant lesions and much less often as high-grade or metastatic lesions.2–4 More than 50% of NF-PNETs are incidental findings2–5 on cross-sectional imaging and most of these lesions are asymptomatic and indolent and found in elderly patients with comorbidities.3,5 Despite consensus management recommendations, which not surprisingly are surgery based or biased, legitimate doubts persist regarding the need to treat and which NF-PNETs may be observed. This article reviews the natural history,
presentation, and guidelines for therapy for NF-PNET, reflective of the authors’ understanding and unintended biases.

CLASSIFICATION

The PNET cell of origin was believed to originate from islet cells, but recent studies suggest that a pluripotent stem cell of the ductal-acinar system may be the precursor cell.6,7 PNETs demonstrate important genetic differences from pancreatic adenocarcinoma that involve distinct mutations from adenocarcinoma.6–8

PNETs are classified as functional (F) or Non functioning (NF). F-PNETs hypersecrete single or multiple hormones, causing a constellation of symptoms and often a dramatic presentation4; 60%-90% of all PNETs are NF and do not produce clinical syndromes9; 90% of PNETs are sporadic and 10% are associated with genetic syndromes, such as multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau disease, neurofibromatosis type 1, and tuberous sclerosis.4,6 The most common pancreatic neoplasms in MEN1 are gastrinomas and insulinomas.4,6

CLINICAL PRESENTATION

NF-PNETs are diagnosed most often by imaging or endoscopic studies as incidental findings. Less often patients present with nonspecific symptoms9 abdominal pain, weight loss, and/or jaundice.5,9 Symptoms are caused by tumor invasion or encroachment or displacement of contiguous structures, and symptomatic lesions are larger than non-symptomatic lesions.5 NF-PNETs may not produce hormones or peptides, produce them at low levels and without symptoms, or secrete peptides that cause no symptoms4,5; 60% to 100% of NF-PNETs secrete 1 or more peptides, such as chromogranin A (CgA), neuron-specific enolase, pancreatic polypeptide, ghrelin, neurotensin, motilin, or subunits of human chorionic gonadotrophin, which do not cause symptoms.10

F-PNETs have a wide range of clinical presentations, depending on which hormone(s) is/are hypersecreted. The most common F-PNETs include insulinomas, gastrinomas, glucagonomas, VIPomas, and somatostatinomas. Other unusual F-PNETs have been reported. F-PNETs are summarized in Table 1.5,11–15

DIAGNOSIS

Symptomatic patients require laboratory and imaging studies to identify and localize the hypersecreted hormones. With NF neoplasms, measurement of nonspecific circulating markers, such as CgA, pancreatic polypeptide, neuron-specific enolase, and pancreastatin, help establish a diagnosis.10,16–18 CgA is the most sensitive marker, with a sensitivity of 60% and specificity of 80%.17–19 Higher CgA levels correlate with greater tumor burden, metastatic disease and may be used to assess response to therapy.17,18 Neuron-specific enolase is an insensitive tumor marker (30%–40%), but its specificity is almost 100%.18,19

Incidental NF-PNETs, are localized on discovery but further evaluation may include a pancreatic protocol CT scan, MRI, endoscopic ultrasound (EUS), and/or somatostatin receptor studies. PNETs usually hyperenhance with intravenous contrast in the arterial phase of a triple-phase CT scan.20,21 The benefits of MRI include less radiation and better detection of liver metastasis.21 PNETs have low signal intensity on T1-weighted images and high signal intensity on T2 images.21 Although most PNETs are solid, approximately 10% are cystic with smooth margins and enhance peripherally on arterial and portal phases.21 EUS is quite sensitive for diagnosing and staging most NF-PNETs, by fine-needle aspiration of the lesion and suspicious lymph nodes.22,23
<table>
<thead>
<tr>
<th>Name</th>
<th>Hormone</th>
<th>Tumor Location</th>
<th>Functional Pancreatic Neuroendocrine Tumor (%)</th>
<th>Malignant (%)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>Insulin</td>
<td>Pancreas</td>
<td>35–40</td>
<td>&lt;10</td>
<td>Hypoglycemia, Anxiety, tremors, palpitations, Weight loss</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Gastrin</td>
<td>75% gastrinoma triangle, 25% duodenum</td>
<td>16–30</td>
<td>60–90</td>
<td>Epigastric pain, Diarrhea, Refractory or complicated ulcer disease</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Vasoactive intestinal peptide</td>
<td>75% pancreas, 20% neurogenic, 5% duodenum</td>
<td>&lt;10</td>
<td>50–70</td>
<td>Secretory diarrhea, Achlorhydia, Hypokalemia, Dehydration</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>Pancreas</td>
<td>&lt;10</td>
<td>60–80</td>
<td>Necrolytic migratory erythema, Glucose intolerance, Stomatitis</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Somatostatin</td>
<td>66% pancreas, 33% duodenal</td>
<td>&lt;5</td>
<td>&gt;70</td>
<td>Diabetes, Cholelithiasis, Steatorrhea</td>
</tr>
<tr>
<td>GRFoma</td>
<td>Growth hormone–releasing hormone</td>
<td>Pancreas 30%, Lung 54%, Jejunum 7%, Other 13%</td>
<td>Unknown</td>
<td>&gt;60</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>ACTHoma</td>
<td>ACTH (corticotropin)</td>
<td>Pancreas</td>
<td>Unknown</td>
<td>&gt;95</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Others</td>
<td>Carcinoid, Parathyroid hormone–related protein, Renin, Luteinizing hormone, Erythropoietin, Cholecystokinin, Glucagon-like peptide 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Somatostatin scintigraphy uses the overexpression of somatostatin receptors present on many NF-PNETS to allow identification and to predict therapeutic response to labeled somatostatin analogs.24–26 There are 2 primary types of somatostatin receptor–based images available. The octreoscan, which uses the ligand indium In 111-DPTA-D-Phe-1-octreotide, and the newest somatostatin receptor–based imaging modality, which uses the positron emitter gallium Ga 68 to label somatostatin analogs.24–29 The most common of these analogs are 68Ga-DOTATATE, 68Ga-DOTATOC, and 68Ga-DOTANOC.25–30 The PET images are fused with CT to enhance resolution. 68Ga-DOTATATE PET/CT detects 95.1% of lesions, significantly higher than the 45.3% with CT or MRI and the 30.9% with 111In-pentetreotide SPECT/CT, and has the additional benefits29 of staging and detecting recurrence after treatment.27–29

Fludeoxyglucose F 18 (FDG) PET is used to detect many malignancies, but most neuroendocrine tumors (NETs) are metabolically inactive and do not take up the tracer.30 Higher-grade NETs are more apt to uptake FDG, suggesting a more aggressive lesion.30 FDG avidity correlates with early tumor progression and increased mortality.30

STAGING

Over the past decade, there has been a shift from “benign” or “malignant” to “170 stratification,” which identifies factors that predict behavior. The current classification and staging systems were proposed by the World Health Organization (WHO), the European Neuroendocrine Tumor Society (ENETS), and the American Joint Committee on Cancer (AJCC).5 The WHO system is based on tumor proliferation rates and in 2010 classified PNETs into 3 main groups: NETs (NET-G1 and NET-G2) and neuroendocrine carcinoma G3.5,31 Ki-67 is a nuclear protein that is expressed only during active but not resting phases of cell cycles.31 NET-G1 and NET-G2 tumors are considered well-differentiated neoplasms.31 NET-G1 neoplasms have a mitotic count of less than 2 per 10 high-power fields (HPFs) and a Ki-67% less than or equal to 2%.31 NET-G2s have mitotic counts of 2 to 20 per 10 HPFs and a Ki-67% of 3% to 20%,31 while NET-G3 is characterized by mitotic counts greater than 20 per 10 HPFs and a Ki-67 greater than 20.31

ENETS and AJCC staging is based on the tumor-nodes-metastasis (TNM) classification. In 2010, the AJCC proposed a specific TNM staging system for PNETs, which includes local disease (stage I), locally advanced/resectable tumors (stage II), locally advanced/unresectable tumors (stage III), and distant metastatic tumors (stage IV).5

Tables 2 and 3 present the current WHO, AJCC, and ENETS classification systems.31 Both the ENETS and the AJCC system have been validated and provide important prognostic information for PNETs.2,5

MOLECULAR BIOLOGY

The most frequent genetic alterations in PNETs occur in the MEN1 gene, death-domain–associated protein (DAXX)/mental retardation syndrome X-linked gene (alpha

| Table 2 |
| 2010 World Health Organization classification of neuroendocrine tumor |

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic Count (Mitoses per 10% High-power Fields)</th>
<th>Ki-67 Index</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (low)</td>
<td>&lt;2</td>
<td>≤2</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2 (intermediate)</td>
<td>2–20</td>
<td>3–20</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G3 (high)</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>
thalassemia/mental retardation syndrome X-linked (ATRX)), and the mammalian target of rapamycin pathway (mTOR). WHO grade 3 neoplasms, or neuroendocrine carcinomas, are genetically distinct, with TP53 and RB mutations found frequently. 

The protein menin, encoded by the MEN1 gene, regulates gene transcription by coordinating chromatin remodeling. This mutation is observed in sporadic and hereditary lesions, and inactivating mutations in MEN1 are detected in 25% to 30% of sporadic PNET cases. There is no current way to clinically target MEN1 mutations.

The mTOR pathway is a key driver of pancreatic NETs. Exome sequencing has shown that a large number of well-differentiated PNETs have somatic genetic mutations that encode proteins in the mTOR pathway. Several therapeutic agents that target elements of the mTOR pathway have been developed. The mTOR inhibitor, everolimus, markedly extended the progression-free survival in unresectable PNETs in the phase III RADIANT-3 and 4 trials.

The proteins encoded by ATRX and DAXX are related to chromatin remodeling at telomeres. Loss of ATRX/DAXX function is associated with the alternative lengthening of telomeres, a telomerase-independent mechanism, important for survival of telomerase-negative cancer cells. Somatic inactivating mutations in ATRX and DAXX were detected in 18% and 25% of PNET’s, but as yet there is no way to target and treat DAXX/ATRX mutations.

PNETs highly express many proangiogenic molecules, such as hypoxia-inducible factor 1α and vascular endothelial growth factor (VEGF). Antiangiogenic strategies, including the VEGF inhibitor bevacizumab and the VEGF receptor–targeted tyrosine kinase inhibitor sunitinib, are currently used.

**MANAGEMENT**

Significant refinements in resolution of CT and MRI have resulted in display of smaller incidental prostate, breast, and pancreatic neuroendocrine lesions (incidentalomas).
Most never become symptomatic, alter lifespan, or require therapy and are overdiagnosed. Overdiagnoses have resulted in costly and unnecessary intervention for lesions that might never manifest clinically. This is the genesis of the “Who, When and How to Treat” controversy of NF-PNETs. Unlike incidental prostate and breast lesions in which overdiagnosis is well documented, it is suggested in NF-PNETs because experience and studies are fewer.

Stanley Hoerr’s adage, “It is hard to make asymptomatic patients better,”35 is appropriate when deciding treatment of indolent asymptomatic NF-PNETs. Absent controlled trials, logic, tumor characteristics, markers, and individual experience are invoked to predict course and outcomes. Some investigators favor resecting all NF-PNETs to avoid growth and progression36–40; others are more selective, using size and growth on serial scans to determine therapy41–54; whereas others favor biopsy to evaluate the molecular markers that correlate with behavior.49,51–53

The concern that all NF-PNET will grow, metastasize, and become fatal has led some to advise resection for all PNETs. Gratian and colleagues reviewed the National Cancer Database of 1854 NF-PNETs less than or equal to 2 cm, identified by *International Classification of Disease for Oncology* (3rd edition) codes; 39% presented with regional lymph node metastases and 10% with distant metastases. The 5-year overall survival for nonoperated patients was 27.6% compared with 83.0% for partial pancreatectomy and 72.3% for pancreaticoduodenectomy. The investigators favor resection because all NF-PNETs are potentially malignant. These outcomes are at marked variance with all current studies. Patients were not separated into F or NF, symptomatic or indolent, or incidentally diagnosed PNETs. Also, preoperative biopsy, grading, and nuclear studies were not mentioned.

Other groups favor surveillance for NF-PNETs. A Mayo Clinic study by Lee and colleagues41 reviewed patients with NF-PNETs from 2000 to 2011. There were 77 observed and 56 resected patients. The 77 patients had a median tumor size of 1.0 cm (0.3–3.2 cm) and a mean follow-up of 45 months. Tumor size did not change throughout follow-up and disease did not progress, and there was no disease-related mortality. Of the 56 operated patients, the median tumor size was 1.8 cm (0.5–3.6 cm) and the mean follow-up was 52 months. Operated patients also had no mortality or recurrence, but 46% had significant complications, half of which were pancreatic fistulas. This study confirmed that many PNETs are indolent and dormant and can be observed, and there is significant morbidity with pancreatic surgery regardless of surgeon experience and expertise.

Many favor 2 cm as the cutoff size to treat or follow. Bettini and colleagues49 correlated tumor size and malignant potential and noted higher grade and Ki-67 in larger lesions. In addition to a size greater than 2 cm, symptoms were an independent predictor of malignancy. Gaujoux and colleagues50 followed 41 patients with asymptomatic sporadic NF-PNETs less than 2 cm. After a median follow-up of 34 months, no patient had distant or nodal metastases on imaging. Other studies have found that larger NF-PNET size up to 3 cm did not correlate with behavior and factors other than size are more important.45 Jiang and colleagues found a correlation between radiologic tumor diameter of 2.5 cm, high tumor grade, symptoms, and lymph node metastases. Sallinen and colleagues52 stratified NF-PNETs into 3 groups: less than 2 cm, 2 cm to 4 cm and greater than 4 cm and noted size alone did not predict behavior. Aggressive behavior correlated with symptomatic disease and bile/pancreatic duct obstruction and dilatation even in tumors less than 2 cm. No small asymptomatic tumor developed distant disease or mortality. WHO 2010 grade was highly correlated with overall and disease-free survival. A WHO tumor grade 2 or 3 may be a better indicator of aggressive biology than size and
incidental tumors were 4 times less likely to progress than symptomatic patients. These findings suggest that incidental tumors remain indolent and tumor grade and degree of differentiation predict behavior, recurrence, and overall survival. The benefits of observation were reinforced in a matched case-control study by Sadot and colleagues, who demonstrated 5-year progression-free survival rates of 95% and 91% ($P = .3$) for observation and resection, respectively. At a median of 7 years, no patient developed cancer. The inclusion cutoff size was 3 cm, again suggesting that size is an inaccurate predictor of malignancy and progression.

A few small NF-PNETs are not dormant and display activity, usually by size increase and less often by symptoms; 19 patients in 3 crossover studies underwent surgery because of increase in tumor size, development of symptoms, or pancreatic duct dilatation. None with malignancy died or had recurrence. This suggests that observation does not compromise outcomes, even if surgery is indicated later, and most NF-PNETs are well behaved citizens.

Risk stratification involves determination of grade, which requires tissue samples acquired by fine-needle aspiration or core biopsy. Calcifications on preoperative CT scans may suggest aggressive behavior. Calcifications were present in 321% of PNET’s in one series and correlated this finding with higher tumor grade, lymph node, and liver metastasis. Worhunsky and colleagues studied tumor enhancement on CT and correlated it with clinicopathologic factors and overall survival in 118 patients with well-differentiated PNETs. Hypoenhancing PNETs were larger and more often intermediate grade, with higher rates of lymph node and synchronous liver metastases. Hypoenhancing lesions had a poorer prognosis than iso-enhancing and hyperenhancing tumors (5-year survival rates, 54% vs 89% vs 93%, respectively).

Surgical treatment, if needed for NF-PNET, depends on tumor size and location within the pancreas. When resection is necessary, 4 operations are favored: enucleation for lesions not contiguous to the pancreatic duct, distal resection of the tail and a segment of the body for distal lesions, central resection for lesions over the superior mesenteric vein not amenable to enucleation, and pancreaticoduodenal resection for some lesions in the head/uncinate of the pancreas.

Some technical tips that may be helpful are as follows. Enucleation is associated with a varying rate of pancreatic fistula. For lesions near the pancreatic duct, a preoperative stent placed by ERCP may help identify the duct tumor interface and serve as a stent if the duct is entered. If a stent is not used and intraoperative concern about a fistula is raised, an injection of secretin, which increases pancreatic secretion, resolves the issue. Finally, for central resection, the authors favor closing the distal duct rather than anastomosing it. This has limited fistula rates. The authors drain all resections and enucleations.

SUMMARY

Asymptomatic NF-PNETs are indolent, slow-growing tumors and surveillance is safe and reasonable. Despite consensus, size is less sensitive than grade and Ki-67. Decisions regarding therapy are multifactorial, and a multidisciplinary approach and decision making are a shared process with colleagues, patients, and families. Decisions are balanced by patient morbidities, preferences, and risks. As molecular diagnostics evolves, preoperative acquisition of tissue samples may become even more important in selecting surveillance or resection.
REFERENCES


