Pancreatic Neuroendocrine Neoplasms

Landscape and Horizon

Laura H. Tang, MD, PhD

• Context.—Since the initial description of pancreatic endocrine pathology and the recognition of islet cell tumors in the 1800s, there have been noteworthy advances in the pathobiology of pancreatic neuroendocrine neoplasms (PanNENs), and definition of the important distinction between well-differentiated neuroendocrine tumor (PanNET) and poorly differentiated neuroendocrine carcinoma (PanNEC). The evolving knowledge has resulted in a continuous update in terminology, classification, and grading system for this group of neoplasms. Pancreatic neuroendocrine tumors associated with hereditary conditions have been linked to unique molecular and genetic events, and sporadic PanNETs have specific gene signatures. Based on accumulative experience and knowledge, therapeutic strategies have been defined for this group of neoplasms.

Objective.—To review the evolution and description of the pathologic-genomic evolution of PanNENs, and to facilitate accurate pathologic interpretation for the corresponding clinical management.

Data Sources.—Literature review of published studies and author’s own work.

Conclusions.—Evolving experience and knowledge have established subtypes of pancreatic neuroendocrine neoplasms, based on their genotype and phenotype. Accurate pathologic interpretation of the specific neoplasm has significant implications for therapy and prognosis.


The digestive function of the pancreas was recognized as the “abdominal salivary gland” by French physiologist Claude Bernard (1813–1878). The complex physiologic role was considered as “pancreas has a secretion outwards, but also inwards into the blood” by Rudolf Virchow (1821–1902). As a medical student of Rudolf Virchow, Paul Langerhans Jr (1847–1888) depicted 9 types of cells in the pancreas and described islet for the first time as “small heaps of cells with shiny cytoplasm” in his doctoral thesis in 1869. The study of Édouard Lagasse identified the site of “internal secretion” of the pancreas and he postulated that the small cellular clusters in the pancreas produced secretions that played a regulatory role in digestion. In 1893 he honored Langerhans’ initial work and named the smaller cluster of cells in the pancreas the “islet of Langerhans” (Figure 1).

Islet cell tumor was first recognized in an autopsy specimen by Nicholls in 1902. Following the discovery of the glucose regulatory function of insulin by Banting and Best et al in 1921, insulinoma derived from β-cell of the islet was reported in 1924. A prominent pathologist, Virginia K. Franzt at Columbia University in New York, described a case of glucagonoma in great detail in the first one-stage pancreatectoduodenectomy performed by Allan Whipple in 1940 (Figure 2). However, the production of glucagon by the tumor could not be confirmed until radioimmunoassay became available in 1966. Subsequently, other functional islet tumors of the pancreas were documented including gastrinoma associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome and VIPoma associated with Verner-Morrison syndrome. In addition, nonfunctional pancreatic neuroendocrine tumors (PanNETs) were initially designated as “endocrine-inactive islet cell tumor.” With the recognition of the amine precursor uptake and decarboxylation (APUD) nature of neuroendocrine cells in the gastrointestinal tract and the pancreas, tumors derived from these cells were generically termed APUDomas in 1969 by Anthony Pearse, but this generic term is no longer used in the current classification system of neuroendocrine tumors.

Before 2010 pancreatic tumors with neuroendocrine lineage were classified by the World Health Organization (WHO) as either “well-differentiated endocrine tumor” when the disease was localized or “well-differentiated endocrine carcinoma” when metastasis occurred. Since 2010, the preferred terminology is pancreatic neuroendocrine neoplasm (PanNEN) including both well-differentiated neuroendocrine tumor (PanNET) and poorly differentiated neuroendocrine carcinoma (PanNEC) regardless of clinical stage. Despite evolving concepts and ongoing efforts to
update classifications, misperceptions still exist regarding terminology, tumor grade, and differentiation of PanNENs.

TERMINOLOGY, CLASSIFICATION, AND GRADING SYSTEMS

The current WHO (2019) classifies PanNEN as follows:

1. pancreatic neuroendocrine microadenoma (<5 mm);
2. well-differentiated neuroendocrine tumor including non-functional NET and functional NET (with clinical evidence of hormone release, such as insulinoma, glucagonoma, gastrinoma, VIPoma); and
3. poorly differentiated PanNEC including small cell carcinoma or large cell carcinoma.

Pancreatic neuroendocrine microadenoma, while arbitrarily designated by its size (smaller than 5 mm), is considered a precursor neoplasm of well-differentiated PanNET, particularly in the setting of hereditary conditions and functional PanNETs, in which numerous microadenomas of varying sizes can be seen in the background before they are large enough (>5 mm) to be designated as NETs. One common issue is how to distinguish an enlarged islet or an aggregate of islets from a microadenoma. Normal pancreatic islets comprise 2 predominant endocrine cell populations: glucagon-producing α-cells located in the periphery and insulin-producing β-cells located in the center of the islet. The α-cell and β-cell distribution can be delineated by immunohistochemistry of glucagon and insulin. Regardless of the size of the islet, if the glucagon and insulin distributions reveal a normal pattern, it is not a neoplasm. Since a microadenoma represents a neoplastic process, hormone production either is clonal, with abnormal distribution, or derives from the random expression of multiple pancreatic or nonpancreatic peptide hormones.

Aggregation of islets is a phenomenon commonly seen in the atrophic pancreas, secondary either to duct obstruction by tumor or diffuse chronic pancreatitis. In fact, the discovery of insulin by Banting and Best et al. in 1921 occurred by injecting an extract of atrophic pancreas (with islet aggregates) induced by duct ligation to reverse diabetes in dogs. Islet aggregates are sometimes considered synonymous to “nesidioblastosis,” but this is a misconception. As a historical perspective, George F. Laidlaw coined the term nesidioblastosis in 1938, combining the Greek words for islet (nesidion) and builder (blastos) to emphasize that cells differentiate and bud from the pancreatic ductal epithelium to form new islet tissue; this was believed to be the pathogenic mechanism of congenital hyperinsulinemia. Thus, in the 1970s and 1980s nesidioblastosis was synonymous with congenital hyperinsulinemia. In 1995 the genetic basis for congenital hyperinsulinemia was identified as an inactivating mutation in the subunits that form the β-cell plasma membrane ATP-dependent potassium channel. Therefore, it is the malfunction, and not the proliferation, of β-cells that is accountable for the condition of hyperinsulinemia. The preferred terminology now is idiopathic hyperinsulinism of infant or adult. To avoid confusion, the term nesidioblastosis is not recommended for hyperinsulinism or islet aggregates in atrophic pancreas.

Pancreatic neuroendocrine tumors are historically classified as functional NETs with clinical evidence of hormone release and associated symptoms, and nonfunctional NETs. They are further stratified by tumor differentiation and...
tumor grade, and the 2 categories have sometimes been used interchangeably or mixed, which has generated considerable confusion. In view of the pathogenesis of PanNENs and the impact on clinical management, PanNENs are best classified as well-differentiated PanNET and poorly differentiated PanNEC. 12,15,16

Well-differentiated PanNETs exhibit characteristic pathologic features of neuroendocrine lineage and resemble nonneoplastic islet aggregate (A) with a normal central insulin (B) and peripheral glucagon (C) distribution on immunostaining. A pancreatic neuroendocrine microadenoma (D) lacks insulin expression (E) and has clonal production of glucagon (F) on immunostaining (hematoxylin-eosin, original magnification ×100 [A and D]; original magnification ×100 B, C, E, and F).
their nonneoplastic counterpart, that is, cells of islet in most situations.\textsuperscript{17,18} The tumor cells contain neuroendocrine secretory granules in the cytoplasm, which is reflected in the diffuse and strong immunoreactivity to neuroendocrine markers such as chromogranin-A and synaptophysin. Most PanNETs are low to intermediate grade (WHO G1 and G2) with clinically stable disease, but they can, albeit rarely, progress to high grade (WHO G3) with mitotic activity greater than 20 per 10 high-power fields and Ki-67 proliferative index above 20\% (Figure 5, A through C). The high-grade component in a PanNET is usually not homogenous, and a lower-grade counterpart can be observed in resection specimens or in specimens from different sites, namely, primary versus metastasis.\textsuperscript{16} However, G3 NET can be rarely seen at initial presentation without obvious progression. The distinction between a high-grade PanNET (WHO G3) and NEC in small biopsy specimens can be challenging (see below). Poorly differentiated PanNECs do not resemble neuroendocrine cells of the islet; they rarely resemble any nonneoplastic epithelial cell counterparts and have high-grade cytologic features with only partial expression of neuroendocrine markers on immunohistochemistry.\textsuperscript{15} Although they exhibit a neuroendocrine phenotype, some PanNECs are associated with a conventional ductal adenocarcinoma or other nonneuroendocrine carcinoma (18\%)\textsuperscript{12}; these combinations are not observed in PanNETs. This phenomenon suggests that PanNECs represent a neoplastic transformation from a conventional adenocarcinoma counterpart or its neoplastic precursor in the pancreas. Poorly differentiated PanNECs are inevitably and uniformly high grade, thus a designation of tumor grade is not necessary and may generate confusion with the distinct entity of WHO G3 PanNETs. Similar to PD-NEC from other anatomic sites, that is, lung and gastrointestinal tract, PanNECs exhibit small cell and large cell/non–small cell phenotypes with characteristic morphologic features (Figure 6, A and B).

Clinically, PanNET and PanNEC are also distinct, as based on their presenting symptoms, radiographic characteristics, biomarkers, treatment, and prognosis (Table 1). Many nonfunctional PanNETs are identified incidentally and patients do not have symptoms associated with high-grade malignancy. Most PanNETs (>85\%) show avidity on somatostatin receptor scintigraphy (SSRS) imaging (Octrascan and Gallium-68 Dotatate PET/CT [positron emission tomography/computed tomography]). In contrast, given their low proliferative activity, lower-grade PanNETs are usually negative on FDG-PET (fluorodeoxyglucose-PET) scans.\textsuperscript{19} Patients with PanNEC may present with neoplastic syndromes secondary to ectopic hormone production, such as ACTH, but they uncommonly exhibit conditions associated with functional pancreatic peptide hormone hypersecretion; they may have elevated serum carcinoembryonic antigen (e.g., CEA, CA 19.9, CA 125) but uncommonly have measurable chromogranin-A.\textsuperscript{20} PanNECs are detectable on FDG-PET scans, with a high standardized uptake value, and are usually negative or have focal avidity on SSRS.\textsuperscript{19} Patients with PanNEC have rapid clinical progression and require prompt cytotoxic chemotherapy, usually with platinum-based regimens, and they are likely to have a transient but refractory response, particularly those with small cell carcinomas.\textsuperscript{21}

Genomic investigation has established that more than 40\% of PanNETs have \textit{DAXX}/\textit{ATRX} and \textit{MEN1} gene mutations\textsuperscript{22,23}; but these mutations are not identified in pancreatic NECs. In contrast, commonly mutated genes in pancreatic ductal adenocarcinomas (\textit{TP53}, \textit{SMAD4}, \textit{KRAS}) are frequently seen in PanNECs with additional \textit{RB} gene mutations, which are extremely rare in PanNETs.\textsuperscript{24} Thus PanNEC represents a neoplastic entity that is genetically more closely related to a ductal adenocarcinoma than a PanNET. Therefore, from a histogenetic point of view, it appears that PanNETs have a neuroendocrine/endocrine cell lineage; in contrast, PanNECs are likely of glandular epithelium origin. Thus, PanNEC does not represent genetic progression from a lower-grade PanNET\textsuperscript{19} (Figure 7).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Grade heterogeneity of well-differentiated pancreatic neuroendocrine tumor assessed by proliferative index (Ki-67 immunohistochemistry). A, World Health Organization G1 (≤ 3\%). B, World Health Organization G2 (≤20\%). C, A lower-grade G1 tumor (upper) with high-grade (G3) transformation with a proliferative index above 20\% (lower) (original magnifications ×100 [A and B] and ×50 [C]).}
\end{figure}
There is considerable clinical significance to emphasize that high-grade PanNENs include both G3 PanNET and PanNEC. Both neoplasms are relatively rare, and mitotic activity and Ki-67 proliferative index are for grading but not for classification between PanNET and PanNEC in isolation. The distinction between these 2 high-grade neuroendocrine neoplasms can be challenging in small biopsy specimens particularly when the NEC is non–small cell type and requires clinicopathologic correlation and additional ancillary immunohistochemistry and molecular tests (Table 1).

**PATHOLOGIC FEATURES AND MORPHOLOGIC VARIANTS**

Most PanNETs are sharply demarcated from the adjacent pancreatic parenchyma, or encapsulated. Small tumors are

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**Table 1. Distinction Between Well-Differentiated Pancreatic Neuroendocrine Tumor (WD-PanNET) (G3) and Poorly Differentiated Pancreatic Neuroendocrine Carcinoma (PD-PanNEC) by Clinicopathologic and Molecular Characteristics**

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>WD-PanNET (G3)</th>
<th>PD-PanNEC</th>
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<tbody>
<tr>
<td>Presentation</td>
<td>Either incidental findings or mildly symptomatic</td>
<td>High-grade malignancy–associated symptoms with rapid disease progression</td>
</tr>
<tr>
<td>Radiology</td>
<td>Diffuse avidity on SSRS</td>
<td>Negative or weak/local activity on SSRS</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Elevated neuroendocrine markers (chromogranin-A)</td>
<td>PET finding positive with high SUV</td>
</tr>
<tr>
<td>Pathologic assessment</td>
<td>A spectrum of tumor grades: a component lower-grade tumor; or prior lower-grade tumor in another specimen</td>
<td>Homogenously high grade: no low-grade component; a component of ductal adenocarcinoma</td>
</tr>
<tr>
<td>Ancillary tests</td>
<td>Loss of Daxx or Atrx expression</td>
<td>Loss to Rb, SMAD4, and/or abnormal p53 expression</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>Expression of SSR2</td>
<td>Uncommon SSR2 expression</td>
</tr>
<tr>
<td>Gene mutations</td>
<td>$DAXX/ATRX$ and/or $MEN1$, $PI3K/mTOR$ (TSC1/2, $PTEN$) &gt;40%</td>
<td>$TP53$, $SMAD4$, $KRAS$, $RB1$ in most</td>
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Abbreviations: PET, positron emission tomography; SSRS, somatostatin receptor scintigraphy; SUV, standardized uptake value; SSR2, type 2 somatostatin receptor.
usually homogeneous and fleshy in consistency (Figure 8, A). Partially cystic tumors are not uncommon and are secondary to degenerative changes (Figure 8, B). Large PanNETs are often bosselated or multinodular lesions (Figure 8, C), which can exhibit gross invasion into peripancreatic tissues, mesentery, or adjacent organs (stomach, duodenum, colon, and spleen). Vascular invasion may be grossly evident, particularly into the splenic vein. Most PanNETs do not involve the pancreatic duct. However, a variant of serotonin-producing PanNET has been described that arises from the pancreatic duct with associated fibrosis similar to the mesenteric fibrosis seen in NETs of the small intestine; these tumors may generate

Figure 7. Pathogenic pathways of well-differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC). WD-NETs are believed to arise from either diffuse neuroendocrine cell system (A) or islet of the pancreas (B). Most NETs are lower grade (WHO G1/G2) with clinical stable disease but can rarely transform to higher-grade tumors (WHO G3) with associated clinical disease progression (left). Poorly differentiated NECs likely represent a variant of conventional carcinoma derived from glandular (C) or squamous epithelium (D). Thus, sometimes they can be seen in combination with a conventional carcinoma. NECs are usually homogenously high grade and they are refractory to platinum-based chemotherapy. Patients with PD-NEC have rapid disease progression even at the initial presentation and poor clinical outcome (chromogranin-A, original magnification ×200 [A]; hematoxylin-eosin, original magnification ×100 [B through D]).

Figure 8. Gross appearance of well-differentiated pancreatic neuroendocrine tumor. A, Small tumors are usually well demarcated with fleshy but soft consistency. B and C, Large tumors have a multinodular appearance and may reveal cystic/degenerative change or be locally invasive into the adjacent organs.
a clinical impression of ductal adenocarcinoma because of the presentation of duct obstruction and jaundice. Pancreatic resection specimens of PanNEC are uncommon both because of its rarity and early presentation of metastasis.

Microscopically, most PanNETs are easily recognized by a few characteristic histologic patterns, that is, loosely cohesive, nested, trabecular/gyriform, hyaline vascular architecture, clear cell change, or pleomorphic type (Figure 9, A through F). Groups of neoplastic cells are separated by enriched and delicate vessels. Most PanNETs are hypercellular and stroma poor; however, in some cases, collagen expansion of the vascular wall can produce densely

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hereditary PanNET has been described in a few isolated undifferentiated ductal adenocarcinomas. In contradistinc-
features can be confused with poorly differentiated or pleomorphic PanNETs (Figure 9, F). Tumors with such PanNETs with marked nuclear atypia have been designated the most common metastatic malignancy in the pancreas. should be distinguished from renal cell carcinoma, which is -sion reminiscent of a benign vascular lesion particularly in liver biopsies (Figure 9, D). The tumor cells have copious and granular eosinophilic or amphophilic cytoplasm and are usually polygonal and without distinct cell borders. The nucleus is centrally or peripherally located and the latter results in a plasmacytoid appearance (Figure 9, A). The nuclei are usually uniform in size and shape and characteristically have a finely stippled appearance and are better appreciated in well-fixed tissue. In poorly preserved tissue, nuclei may have coarsely clumped chromatin, open chromatin, or hyperchromasia.

Uncommon morphologic variants of PanNET include oncocytic phenotype, clear cell change (Figure 9, E) and should be distinguished from renal cell carcinoma, which is the most common metastatic malignancy in the pancreas. PanNETs with marked nuclear atypia have been designated pleomorphic PanNETs (Figure 9, F). Tumors with such features can be confused with poorly differentiated or undifferentiated ductal adenocarcinomas. In contradistinction to their bizarre cytologic features, most pleomorphic PanNETs do not demonstrate an increased proliferative activity or unfavorable outcome.

HEREDITARY PANCREATIC NEUROENDOCRINE TUMOR SYNDROMES

Four hereditary associations with PanNET have been previously established and include (1) multiple endocrine neoplasia type 1 and type 4 (MEN-1/4), (2) Von Hippel–Lindau disease (VHL), (3) neurofibromatosis type 1 (NF1), and (4) tuberous sclerosis (TSC) (Table 2). All of the 4 conditions are inherited as autosomal dominant disorders. The frequencies of PanNET are higher in MEN1 (30%–80%) and VHL (17%)22,26; they are extremely rare in NF1 and TSC.29 However, NF1-associated duodenal and ampullary somatostatinoma is more common.20 Recently, a fifth hereditary PanNET has been described in a few isolated cases and is currently given the name of Mahvash disease, which is an autosomal recessive hereditary condition with homozygous or biallelic heterozygous mutation of glucagon receptor.31 The patients present with asymptomatic hyperglucagonemia and develop multiple glucagonomas. Based on limited case reports, the penetrance is 100% by age 60 years.32 In addition, insulinomatosis, which is not associated with MEN-1/4, has been described and its molecular and genetic mechanisms remain to be further delineated.33,34

The pathologic relevance in examining pancreatic specimens with these hereditary conditions is the fact that precursor microadenomas are present in MEN1 (predominantly insulin and glucagon producing in the pancreas and gastrin producing in the duodenum) and in Mahvash disease (glucagon producing). The microscopic finding of a spectrum of abnormal islets with varying sizes in the background should raise the concern for these 2 hereditary conditions (Figure 10, A and B). Multiple PanNETs are often observed in MEN1, VHL, and Mahvash disease. This can be a challenge in management when the patient is symptomatic, and the source of hormone production can be from one of several tumors. In addition to NETs in the pancreas, patients with VHL also develop serous cystadenomas that can coexist with PanNETs.18

DIFFERENTIAL DIAGNOSIS

Diagnosis of a PanNET in a surgically resected specimen is not particularly difficult since both architectural and cytologic features are well defined. PanNET in a pancreatic biopsy specimen or fine-needle aspiration with limited and suboptimal material can be challenging. Thorough evaluation of available clinical and radiographic information, if provided, would facilitate the pathologic evaluation and support final pathologic interpretation. Varying degrees of immunoreactivity to neuroendocrine markers is seen in both primary and metastatic tumors in and to the pancreas. These include (1) acinar cell carcinoma/pancreatoblastoma, mixed acinar and NEC, which can be encountered more often than expected if differential diagnosis is not considered; (2) true NEC, adenocarcinoma with neuroendocrine differentiation; (3) solid and pseudopapillary neoplasm; (4) peripancreatic pheochromocytoma; (5) unusual histologic pattern of a ductal adenocarcinoma; (6) primitive neuroectodermal tumor; and (7) metastasis (renal cell carcinoma, melanoma) (Figure 11, A through F; Table 3).

PanNET has a relatively high incidence of metastasis (50%–80%), which is frequently seen in liver biopsies. The diagnostic approach to a metastatic PanNET should include neoplasm with morphologic features resembling PanNET: (1) exclusion of primary hepatic neoplasms with similar morphologic features, for example, hepatocellular carcinoma, peripheral cholangiocarcinoma, and angiolipoma; (2) consideration of a metastatic neuroendocrine neoplasm of nonpancreatic primaries, for example, gastrointestinal tract

<table>
<thead>
<tr>
<th>Table 2. Genetic and Clinicopathologic Characteristics of Hereditary Pancreatic Neuroendocrine Tumor Syndromes</th>
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<tr>
<td><strong>GENETICS</strong></td>
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<tr>
<td><strong>Genetics</strong></td>
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<tr>
<td><strong>Heterozygous mutations</strong></td>
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<tr>
<td><strong>AutoSomal dominant</strong></td>
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<tr>
<td><strong>Microadenomas</strong> (glucagon/insulin)</td>
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<tr>
<td><strong>Onset age</strong></td>
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<tr>
<td><strong>PanNET frequency</strong></td>
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Abbreviations: MEN, multiple endocrine neoplasia; NET, neuroendocrine tumor; NF1, neurofibromatosis type 1; PanNET, pancreatic neuroendocrine tumor; TSC, tuberous sclerosis complex; VHL, Von Hippel–Lindau syndrome.
(small bowel being most common), lung, and medullary thyroid carcinoma; and (3) elimination of other metastatic malignancies, which may imitate morphologic characteristics of a well-differentiated NET, for example, solid variant of breast ductal carcinoma, renal cell carcinoma, adrenal cortical carcinoma, urothelial carcinoma, and melanoma.

Representative microphotographs and morphologic characteristics of these neoplasms are provided and described in Figure 12, A through H.

In addition, tissue-processing artifacts in small biopsy specimens may complicate the interpretation of neuroendocrine neoplasms. Cellular crush artifact makes the distinction between a NET and NEC extremely challenging (Figure 13, A). Apart from documentation of neuroendocrine differentiation by positive immunoreactivity to chromogranin and synaptophysin, additional immunostaining with Ki-67 is useful to demonstrate the low-grade or high-grade nature of a PanNET and PanNEC (Figure 13, B).

**MOLECULAR AND GENOMICS**

In addition to the hereditary syndromes discussed earlier, which account for less than 10% of PanNETs, germline mutations in DNA damage repair genes, such as CHEK2 and MUTYH, have been identified in 17% of sporadic cases without apparent familial background.

In early investigations, cytogenetic and molecular genetic studies identified many chromosomal alterations in sporadic PanNETs, which appears to be an event of progressive accumulation associated with clinical tumor stage and disease progression. Deletions are more frequently detected in primary PanNET, while gains are seen in metastatic tumors. Activation of oncogenes does not appear to play a major role in PanNET development. Advances in next-generation sequencing technology have enabled genome-wide analyses of PanNETs, which have highlighted the molecular heterogeneity of the disease. Many of the genes targeted in the development of pancreatic ductal adenocarcinoma (including PanNEC and combined adeno- carcinoma and PanNEC) are not present in PanNETs. In particular, KRAS, TP53, p16/CDk4/2A, and SMAD4 are not mutated in most PanNETs. However, even in the absence of TP53 mutation, an impaired p53 pathway is evident by amplifications of the negative p53 regulators MDM2, MDM4, and WIP1 in PanNETs. In contrast, MEN1 (44%) and DAXX/ATRX (43%), genes involved in histone modification/remodelling and telomere maintenance, are frequently mutated in sporadic PanNETs. While DAXX and ATRX mutations are mutually exclusive more than 20% of tumors can harbor either DAXX or ATRX and MEN1 mutations. Thus, collectively about 60% of PanNETs carry MEN1/DAXX/ATRX mutations. Since these genes affect the epigenetic landscape, the epigenome including DNA methylation, histone modification, posttranscriptional regulation, and ultimately gene expression likely plays a critical role in the pathogenesis of PanNET.

**Table 3. Differential Diagnosis of Pancreatic Neuroendocrine Tumor With Other Pancreatic Solid Tumors**

<table>
<thead>
<tr>
<th>Primary Pancreatic Solid Tumors</th>
<th>Immunohistochemistry (in addition to NE markers)</th>
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<tbody>
<tr>
<td>Acinar cell carcinoma/pancreatoblastoma</td>
<td>Trypsin+/chymotrypsin+/β-catenin (nuclear)</td>
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<tr>
<td>Mixed acinar-NEC</td>
<td>p53+/Rb+/DAXX-ATRX-</td>
</tr>
<tr>
<td>PD-NEC</td>
<td>MUC1+/CA 125+/mCEA+/SMAD4-</td>
</tr>
<tr>
<td>Adenocarcinoma with NE differentiation</td>
<td>Cytokeratin+/vimentin+/CD56+/β-catenin (nuclear)/BCL10+</td>
</tr>
<tr>
<td>Solid and pseudopapillary neoplasm</td>
<td>Cytokeratin+/S100+ (in sustentacular cells)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Cytokeratin+/CD99-</td>
</tr>
<tr>
<td>Primitive neuroectodermal tumor</td>
<td>Pattern of insulin/glucagon distribution (normal in islet aggregations; abnormal in microadenoma)</td>
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</tbody>
</table>

Abbreviations: NE, neuroendocrine; NEC, neuroendocrine carcinoma; PD-NEC, poorly differentiated neuroendocrine carcinoma.
molecular mechanisms associated with these gene mutations remain to be further delineated, PanNETs with MEN1/DAXX/ATRX mutant genotype as a group correlate with a worse clinical prognosis than tumors carrying the wild-type alleles of MEN1/DAXX/ATRX. From their differential gene expression profiles, MEN1/DAXX/ATRX-mutant PanNETs exhibit gene signatures of islet α-cell lineage of the pancreas, while MEN1/DAXX/ATRX wild-type PanNETs...
is achievable. However, PanNETs encompass a heterogeneous spectrum of tumors with varying natural history, clinical symptoms, and unpredictable prognosis. This heterogeneity makes it challenging to standardize the surgical management of localized disease. The treatment by surgical resection versus active surveillance of small nonfunctional PanNETs remains a matter of debate, with several guidelines suggesting different approaches. A recent retrospective study, which used the National Cancer Database to identify 2004 patients with nonfunctional PanNETs, suggests that active surveillance is a safe approach for tumors smaller than 1 cm. Larger tumors likely need partial pancreatectomy with locoregional lymphadenectomy. Small PanNETs may be removed by enucleation if feasible. Other independent prognostic factors including age at diagnosis, Charlson-Deyo comorbidity score, tumor location within the pancreas, but not tumor grade (WHO G1 versus G2) should be taken into consideration when making clinical decisions of surgical intervention.

In contrast to conventional carcinomas, the condition of patients with locally advanced and metastatic PanNET can remain stable for many years. Asymptomatic patients with small tumor burden may be actively observed. Initial systemic therapy for patients with positive somatostatin receptor (SSTR) scintigraphy involves somatostatin analogs to slow disease progression. Patients who have high volume and symptomatic PanNETs with negative SSTR findings on scintigraphy may be treated with chemotherapy (capecitabine/temozolomide), liver-directed intervention (embolization, chemoembolization, radioembolization, cytodestruction/ablative), targeted agents, namely, everolimus and/or sunitinib, or peptide receptor radionucleotide therapy with 177Lu-DOTATATE.

Poorly differentiated PanNEC represents a biologically distinct entity from well-differentiated PanNET. Given the clinical presentation of advanced stage and rapid progression, most PanNECs are not amenable to surgical resection and require direct cytotoxic chemotherapy; platinum with etoposide is usually the first-line option.

**SUMMARY**

Accurate pathologic interpretation of the specific PanNEN has significant implications for therapy and prognosis. It is prudent for pathologists to integrate clinical information and to have the appropriate knowledge in tumor classification (NET versus NEC), differential diagnosis, molecular signatures and genotype of the tumor, and multidisciplinary management of the disease.

**REFERENCES**


**THERAPY**

Surgical resection remains the most effective modality for the treatment of locoregional PanNETs if complete resection is not feasible. However, PanNETs encompass a heterogeneous spectrum of tumors with varying natural history, clinical symptoms, and unpredictable prognosis. This heterogeneity makes it challenging to standardize the surgical management of localized disease. The treatment by surgical resection versus active surveillance of small nonfunctional PanNETs remains a matter of debate, with several guidelines suggesting different approaches. A recent retrospective study, which used the National Cancer Database to identify 2004 patients with nonfunctional PanNETs, suggests that active surveillance is a safe approach for tumors smaller than 1 cm. Larger tumors likely need partial pancreatectomy with locoregional lymphadenectomy. Small PanNETs may be removed by enucleation if feasible. Other independent prognostic factors including age at diagnosis, Charlson-Deyo comorbidity score, tumor location within the pancreas, but not tumor grade (WHO G1 versus G2) should be taken into consideration when making clinical decisions of surgical intervention.

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