Recent Updates on Neuroendocrine Tumors From the Gastrointestinal and Pancreatobiliary Tracts

Joo Young Kim, MD, PhD; Seung-Mo Hong, MD, PhD

● *Context.*—Gastrointestinal (GI) and pancreatobiliary tracts contain a variety of neuroendocrine cells that constitute a diffuse endocrine system. Neuroendocrine tumors (NETs) from these organs are heterogeneous tumors with diverse clinical behaviors. Recent improvements in the understanding of NETs from the GI and pancreatobiliary tracts have led to more-refined definitions of the clinicopathologic characteristics of these tumors. Under the 2010 World Health Organization classification scheme, NETs are classified as grade (G) 1 NETs, G2 NETs, neuroendocrine carcinomas, and mixed adenoneuroendocrine carcinomas. Histologic grades are dependent on mitotic counts and the Ki-67 labeling index. Several new issues arose after implementation of the 2010 World Health Organization classification scheme, such as issues with well-differentiated NETs with G3 Ki-67 labeling index and the evaluation of mitotic counts and Ki-67 labeling.

Hereditary syndromes, including multiple endocrine neoplasia type 1 syndrome, von Hippel-Lindau syndrome, neurofibromatosis 1, and tuberous sclerosis, are related to NETs of the GI and pancreatobiliary tracts. Several prognostic markers of GI and pancreatobiliary tract NETs have been introduced, but many of them require further validation.

Objective.—To understand clinicopathologic characteristics of NETs from the GI and pancreatobiliary tracts.

Data Sources.—PubMed (US National Library of Medicine) reports were reviewed.

Conclusions.—In this review, we briefly summarize recent developments and issues related to NETs of the GI and pancreatobiliary tracts.

(*Arch Pathol Lab Med.* 2016;140:437–448; doi: 10.5858/arpa.2015-0314-RA)

N euroendocrine tumors (NETs) from the gastrointestinal (GI) and pancreatobiliary tracts are heterogeneous tumors with diverse biologic and clinical behaviors that vary according to the primary tumor origin, type of neuroendocrine cell, and pathologic features.[1–4] The distribution patterns of NETs in the GI tract seem to be different between Eastern and Western populations.[1,5] The most common location of NETs in the GI tract among patients in the United States is the small intestine (38%), followed by the rectum (34%), colon (16%), stomach (11%), and unknown sites (1%), according to analysis of the Surveillance Epidemiology End Results database.[5] The average incidence of GI NETs is 2.5 cases per 100 000 per year, and the recently increased incidence of GI NETs in the United States is due to increased detection of gastric and rectal NETs.[5] In contrast, the rectum (48%) is the most frequent location of NETs in the GI tract of patients in Korea, followed by the stomach (15%), pancreas (9%), colon (8%), small intestine (8%), liver (7%), appendix (3%), and biliary tract (2%).[1] The incidence of NETs in the GI tract and pancreas has increased in recent years, mainly because of a marked increased detection of rectal NETs, whereas the incidences of NETs in other parts of the GI tract are unchanged in the Korean population.[1]

DISTRIBUTIONS OF NORMAL ENDOCRINE CELLS AND THEIR PRODUCTION

The GI and pancreatobiliary tracts contain a variety of neuroendocrine cells that constitute a diffuse endocrine system. Endocrine cells in the GI tract consist of less than 1% of the mucosa; are normally distributed at the surface or base of glandular epithelial cells, such as in the gastric pits of the stomach and the crypts of the small intestine and colorectum; and contain secretory granules that release various peptide hormones.[6,7] Endocrine cells comprise 1% to 2% of the volume of the adult pancreas and most form well-circumscribed nests called *islets of Langerhans*; a few scattered endocrine cells are also present in the main pancreatic and larger interlobular ducts but are not observed in the smaller ducts.[8] Endocrine cells in the pancreas produce several peptide hormones, including insulin, glucagon, somatostatin, pancreatic polypeptide (PP), and vasoactive intestinal peptide. The most common cells are insulin-producing β cells, which account for 60% to 80% of all islet cells and are centrally located in the islets,[8] whereas glucagon-producing α cells are located at the periphery of

Cell Type	Hormone Produced	Distribution
α	Glucagon	Pancreas
β	Insulin	Pancreas
δ (D)	Somatostatin	Stomach, small intestine, pancreas, appendix, colorectum
EC	Serotonin	Stomach, small intestine, pancreas, appendix, colorectum
ECL	Histamine	Stomach
G	Gastrin	Stomach, duodenum
I	Cholecystokinin	Small intestine
K	Gastric inhibitory peptide	Small intestine
L	Glucagon-like peptide 1, peptide YY	Rectum, small intestine
M	Motilin	Small intestine
N	Neurotensin	Small intestine
P/D1	Ghrelin	Stomach, small intestine, appendix, colon
PP	Pancreatic polypeptide	Pancreas
S	Secretin	Small intestine, pancreas
VIP	Vasoactive intestinal peptide	Pancreas, stomach, small intestine, appendix, colorectum

Abbreviations: EC, enterochromaffin; ECL, enterochromaffin-like.

[a] Modified by permission from Macmillan Publishers Ltd: [109]Furness JB, Rivera LR, Cho HJ, Bravo DM, Callaghan B. *Nat Rev Gastroenterol Hepatol*. 2013;10(12):729–740.

islets and constitute 15% to 20% of the islet volume. Somatostatin-producing δ cells and PP-producing cells constitute the remaining portions.[8] Extrahepatic biliary epithelia also contain scattered endocrine cells in the intrapancreatic portion of the common bile duct.[9]

Understanding the normal distribution of endocrine cells in the GI and pancreatobiliary tracts is important because there is a correlation between the distributions of specific types of endocrine cells and the preferential primary sites of specific hormone-producing NETs in the GI and pancreatobiliary tracts. However, there are some exceptions, such as no occurrence of cholecystokinin-, gastric inhibitory polypeptide-, motilin-, or secretin-producing tumors in the small intestine.[10] Similarly, the predominance of enterochromaffin (EC) cell serotonin-producing NETs in the ileum and appendix and δ cell somatostatin-producing NETs in the duodenum and ampulla is abnormal despite the even distribution of EC and δ cells throughout the GI and pancreatobiliary tracts.[10] Aberrant gastrin-producing tumors (gastrinomas) in the pancreas also cannot be explained by the normal distribution of endocrine cells in the GI and pancreatobiliary tracts. We summarize the normal distributions of various types of endocrine cells in the GI and pancreatobiliary tracts in Table 1.

NEUROENDOCRINE MARKERS

Endocrine cells in the GI and pancreatobiliary tracts and NETs are labeled by neuroendocrine markers, including synaptophysin, chromogranin A, CD56/NCAM1, Leu7/B3GAT1, protein gene product 9.5 (PGP9.5), and neuron-specific enolase. Synaptophysin is considered the most sensitive neuroendocrine marker, whereas chromogranin A is the most specific. Therefore, only synaptophysin and chromogranin A are recommended for use in routine practice, and other neuroendocrine markers, such as CD56/NCAM1, Leu7, and neuron-specific enolase, are not recommended because of their low specificity.[11]

Most GI NETs express CDX2, whereas some pancreatic NETs also express CDX2.[12] Several transcription factor proteins, such as pancreatic and duodenal homeobox 1 (PDX1), islet 1 (ISL-1), and PAX8, have been reported to be pancreas specific.[13] In the setting of metastatic NETs with an unknown primary site, use of a panel of immunohistochemical staining with CDX2, ISL-1 (or PDX1), and thyroid transcription factor 1 (TTF-1) can help to identify the primary origin of the metastatic NETs,[13] although some studies reported that these markers can also be expressed in NETs from other locations.[14–18]

BCL2 overexpression, loss of RB expression, and abnormal p53 expression (either total loss or overexpression) were more commonly seen in poorly differentiated neuroendocrine carcinomas (NECs), whereas expression of those proteins was reported in a few well-differentiated NETs.[19] Therefore, BCL2, RB, and p53 immunohistochemical staining can be useful in some settings for discriminating well-differentiated NETs from poorly differentiated NECs.[19]

WORLD HEALTH ORGANIZATION CLASSIFICATIONS OF NEUROENDOCRINE TUMORS

The term *carcinoid* has been used for several decades to describe most GI NETs after it was proposed by the World Health Organization (WHO) in 1980. The term is not used for several other tumors, such as pancreatic islet cell tumors and small cell carcinomas.

The WHO 2000 classification divided NETs from the GI and pancreatobiliary tracts into well-differentiated endocrine tumors, well-differentiated endocrine carcinomas, and poorly differentiated endocrine carcinomas, based on the degree of differentiation.[4] Well-differentiated endocrine tumors were further classified into benign tumors and low-grade malignant tumors, based on the tumor size, mitotic rate, Ki-67 labeling index, lymphovascular invasion, and symptoms, in association with hormonal oversecretion,[4] whereas *poorly differentiated endocrine carcinomas* usually indicate small cell and large cell carcinomas. Well-differentiated NECs have been regarded as low-grade malignancies, and poorly differentiated NECs were considered high-grade malignant tumors.[4] Both well-differentiated and poorly differentiated endocrine carcinomas are invasive cancers with the ability to metastasize to distant organs.[4] The term *neuroendocrine neoplasm* has been accepted as general nomenclature instead of *carcinoid* because *carcinoid* does not convey the malignant nature of the tumors and can be confused with *carcinoid syndrome*.[2,20]

The recent WHO 2010 classification categorized all NETs from the GI and pancreatobiliary tracts as malignant tumors, except for gangliocytic paraganglioma and pancreatic neuroendocrine microadenomas, which are classified as

Table 2. Distribution and International Classification of Diseases for Oncology, 3rd Ed. (ICD-O-3) Codes of Neuroendocrine Tumors (NETs) in the Gastrointestinal and Pancreatobiliary Tracts in the 2010 World Health Organization Classification

NET Classification	Location	ICD-O-3 Code
NET G1	All organs	8240/3
NET G2	All organs	8249/3
Neuroendocrine carcinoma	All organs	8246/3
Large cell NEC	All organs	8013/3
Small cell NEC	All organs	8041/3
EC cell serotonin-producing NET	All organs	8241/3
Gastrin-producing NET (gastrinoma)	Stomach, ampulla, small intestine, pancreas	8153/3
Glucagon-producing NET (glucagonoma)	Pancreas	8152/3
Gangliocytic paraganglioma	Ampulla, small intestine	8683/0
Somatostatin-producing NET (somatostatinoma)	Ampulla, small intestine, pancreas	8156/3
Insulin-producing NET (insulinoma)	Pancreas	8151/3
VIPoma	Pancreas	8155/3
L cell, Glucagon-like peptide and PP/PYY-producing NETs	Small intestine, appendix, colorectum	8152/1
Goblet cell carcinoid	Appendix, extrahepatic bile duct	8241/3
Tubular carcinoid	Appendix, extrahepatic bile duct	8245/1
Mixed adenoneuroendocrine carcinoma (MANEC)	All organs	8244/3
Neuroendocrine microadenoma	Pancreas	8150/0

Abbreviations: EC, enterochromaffin; G, grade; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; PP, pancreatic polypeptide; PYY, peptide YY; VIP, vasoactive intestinal peptide.

benign tumors, and L-cell–type (glucagon-like peptide [GLP] and peptide YY [PYY]-producing) NETs and tubular carcinoids, which are classified as uncertain malignancies.[20] We summarize the NETs from the GI and pancreatobiliary tracts under the current WHO 2010 scheme in Table 2. In general, well-differentiated NETs are well-circumscribed, cellular tumors with sheets of uniform tumor cells. Variable growth patterns, including nests, trabecular, glandular, gyriform, acinar, and solid patterns, have been observed for NETs from the GI and pancreatobiliary tracts. The nuclei are round to oval and stippled, and the chromatin shows the typical "salt-and-pepper" pattern. The 2010 WHO classification divides NETs of the digestive tracts into NET grade (G) 1, NET G2, and NECs, based on mitotic counts and the Ki-67 proliferation index, regardless of tumor size, extent, or location (Table 3).[20] In contrast, mixed adenoneuroendocrine carcinomas contain both malignant glandular and NEC components, and each component should be more than one-third of the tumor volume (Figure 1, A).

Grade 1 is a NET with a mitotic count of less than 2 per 10 high-power fields (HPFs) and/or less than 3% Ki-67 labeling index; G2 is a NET with a mitotic count of 2 to 20 per 10 HPFs and/or a 3% to 20% Ki-67 labeling index; and NEC is a small cell carcinoma or large cell carcinoma with a mitotic rate of more than 20 per 10 HPFs and/or greater than a 20% Ki-67 labeling index. For precise evaluation of the grading, a minimum of 50 HPFs for the mitotic count and at least 500 cells for the Ki-67 labeling index should be counted from hot spots.[21] In about one-third of the NET cases, a discrepancy between the grades of the mitotic count

and Ki-67 labeling index are observed and, on these occasions, the higher grade, either that of the mitotic count or the Ki-67 labeling index, should be used.[22] An increased mitotic activity and proliferation index have been associated with an aggressive clinical behavior and poor prognosis.[23,24]

ISSUES WITH GRADING

Issues With the Mitotic Count

The mitotic count should be calculated from the most active areas (or *hot spots*), which are recognized by scanning the sample under intermediate magnification.[11] As described above, a minimum of 50 HPFs should be carefully evaluated to precisely determine the mitotic count, a task that requires a minimum of about 3 minutes.[25] In general, 10 HPFs with a ×40 objective lens on a light microscope are equivalent to an area of 2 mm^2. However, the exact area depends on the eyepiece field, which varies among light microscope manufacturers and models.[25] It is extremely difficult to discriminate true mitosis from mitosis mimics, including pyknosis, apoptotic bodies, or shrunken nuclei, but such discrimination is important because, otherwise, the area is not counted as mitosis.[25,26] These issues lead to poor reproducibility of mitotic counts between observers.[11] Recently, a mitosis-specific marker, phosphohistone H3 (PHH3), was introduced for the assessment of mitotic counts in NETs.[25] Mitotic counts determined by PHH3 staining and hematoxylin-eosin staining showed a high concordance rate, but their results need to be validated using many cases.[25]

Issues With Ki-67 Quantification

Ki-67 is expressed in cells during all active phases of the cell cycle, except for the resting (G0) phase. As the time from clamping of vessels and surgical resection of NET to tissue fixation increases, the mitotic counts in surgically resected specimens tend to decrease abruptly.[27] Therefore, grading by the Ki-67 labeling index is always higher than grading by mitosis. Evaluation of the Ki-67 labeling index may be influenced by several factors, such as the use of different clones of the Ki-67 antibody, use of different Ki-67 staining protocols among laboratories, different thicknesses of the section used for Ki-67 staining, and the density of the

Table 3. World Health Organization 2010 Classification of Neuroendocrine Tumors (NETs) in the Gastrointestinal and Pancreatobiliary Tracts

Grade	Mitotic Count/ 10 HPFs	Ki-67 Labeling Index, %
NET, grade 1	<2	<3
NET, grade 2	2–20	3–20
NEC, grade 3	>20	>20

Abbreviations: HPF, high-power field; NEC, neuroendocrine carcinoma.

Gastrointestinal and Pancreatobiliary Neuroendocrine Tumors—Kim & Hong **439**
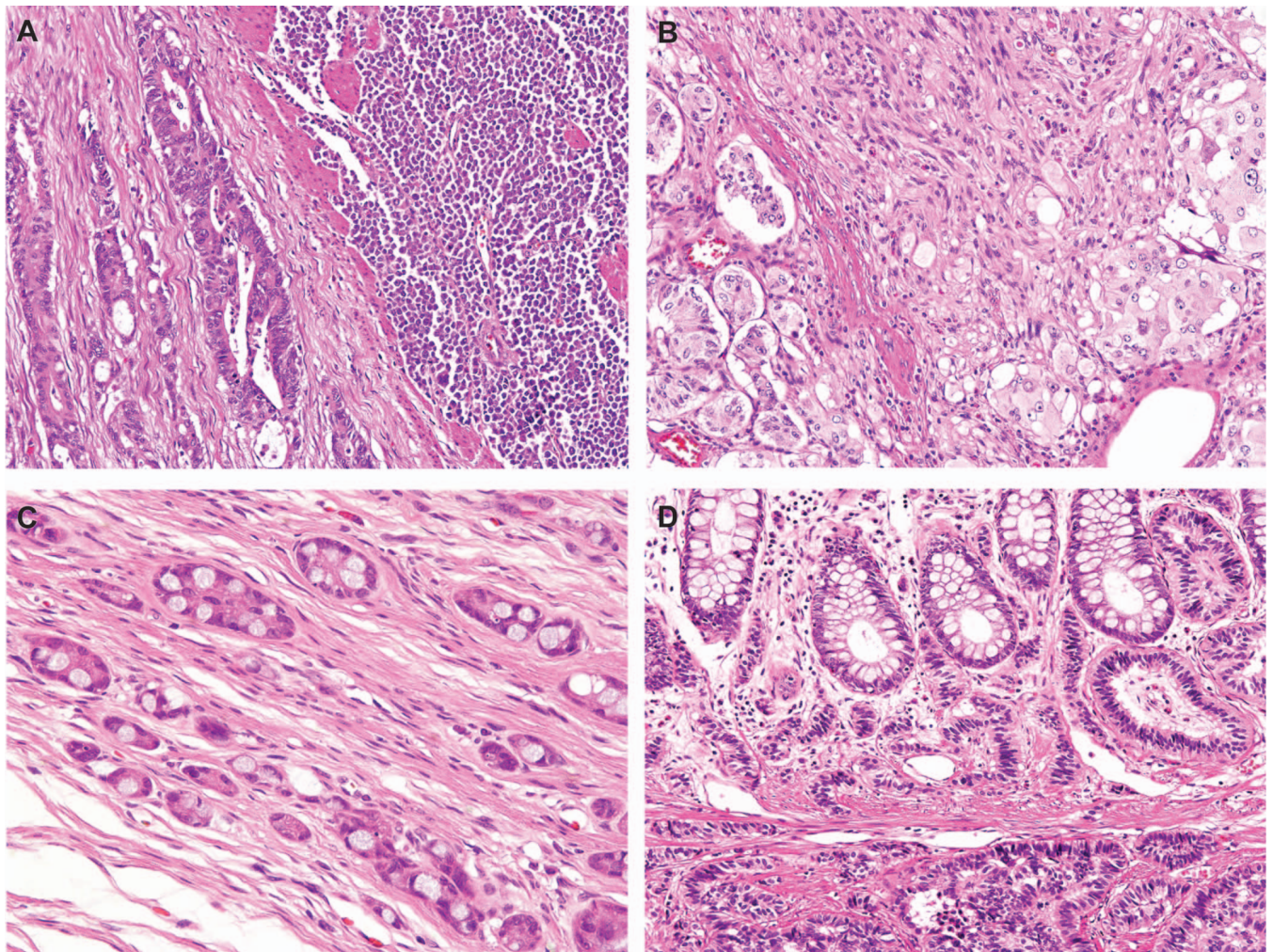
Figure 1. *Representative microscopic images of gastrointestinal neuroendocrine tumors. A, Mixed adenoendocrine carcinomas show mixed carcinomas containing both malignant glandular (left half) and small cell carcinoma (right half) components. B, Gangliocytic paraganglioma of the duodenum showing epithelioid neuroendocrine cells (left), schwannian cells (center), and ganglion cell (right) components. C, Goblet cell carcinoids of the appendix showing nests of signet ringlike cells with mild-to-moderate dysplasia. D, L-cell–type rectal neuroendocrine tumor showing a predominantly trabecular pattern (hematoxylin-eosin, original magnifications ×200 [A and B] and ×400 [C and D]).*

tumor cells. For Ki-67 counting, strong, dark-brown nuclear staining is recommended for counting, whereas cytoplasmic staining or weak nuclear labeling should not be counted.[26] In routine pathology practice, the most commonly used method for the evaluation of Ki-67 labeling is a quick count under microscopic examination, the so-called eyeball estimation. In addition, several other methods are used to assess Ki-67 labeling, including manual counting and automated digital image analysis.[28–30] Although there are still controversies about the agreement of Ki-67 labeling with the eyeball estimation (good[28] versus poor[29,30] inter-observer agreement rate), use of the eyeball estimation is discouraged in routine practice because of its inaccuracy, especially at the G1 to G2 boundary.[30] On the other hand, manual counting of camera-captured or printed images is considered to be the most practical, reproducible, and cost-effective method of calculating the Ki-67 labeling index.[26,30]

ISSUES WITH G3 WELL-DIFFERENTIATED NEUROENDOCRINE TUMORS

In the 2010 WHO classification scheme, NECs are defined as poorly differentiated tumors with a mitotic rate of more than 20 per 10 HPFs and/or a greater than 20% Ki-67 labeling index.[20] The NECs are subclassified as small cell carcinomas or large cell carcinomas. However, a recent study of pancreatic NETs showed that the survival time of patients with well-differentiated G2 discordant (mitotic count G2 and Ki-67 index G3) NETs was better than that of patients with poorly differentiated NECs and worse than that of patients with well-differentiated G2 concordant (both mitotic count and Ki-67 index G2) NETs.[31] Well-differentiated tumors with a Ki-67 index less than 55% do not respond as well to a platinum-based chemotherapy regimen as do poorly differentiated tumors with a higher Ki-67 index.[32] Based on these results, G3 tumors, according to the 2010 WHO classification scheme, can be further classified by tumor differentiation as well as proliferation status.[26,33]

STAGING OF GI AND PANCREATOBILIARY TRACT NEUROENDOCRINE TUMORS

The American Joint Committee on Cancer (AJCC)[34] and the European Neuroendocrine Tumor Society (ENETS)[21,35–37] proposed special staging systems for GI tract and pancreas

Table 4. Classification of Gastric Enterochromaffin-Like Cell Histamine-Producing Neuroendocrine Tumors[a]			
Classification	I	II	III
Incidence, %	55–88	8–13	12–23
Multifocality	Multiple	Multiple	Single
Peritumoral oxyntic mucosa	Atrophic	Hypertrophic	Normal
Size, cm	0.5–1	<2	>2
Location	Corpus	Corpus	Any
Sex	M < F	M = F	M > F
Hypergastrinemia	Yes	Yes	No
Antral G-cell hyperplasia	Yes	No	No
Associated disease	Chronic atrophic gastritis	Multiple endocrine neoplasia 1, Zollinger–Ellison syndrome	No
Precursor lesion	Yes	Yes	No
WHO 2010 classification	Grade 1	Grades 1 or 2	Grades 1–3
Lymph node metastasis, %	5	30	70

Abbreviation: WHO, World Health Organization.

[a] Data derived from La Rosa and Vanoli,[33] 2014.

NETs according to the tumor size and extension in each organ. In the staging system of the AJCC, NETs of the stomach, small intestine, colorectum, and appendix have specially designated staging systems for NETs distinct from their cancer staging, whereas pancreatic NETs share a single staging system with exocrine pancreatic carcinomas.[38] The AJCC and ENETS staging for almost all GI tract NETs, including NETs of the stomach, duodenum, ampulla, jejunum, ileum, and colorectum, are identical, whereas some differences exist in T classification of the pancreatic and appendiceal NETs between AJCC and ENETS staging.[3,21,35,38] There is no suggested staging system for biliary tract NETs in either the AJCC or the ENETS staging system. Several studies compared T-classification schemes of the AJCC and NETS staging systems of pancreas NETs and reported different results.[39–41] One study[40] demonstrated the superiority of the ENETS staging system, whereas another study[39] reported superiority of the AJCC staging system for pancreas NETs.

GI AND PANCREATOBILIARY TRACT NEUROENDOCRINE TUMORS FROM EACH SITE

Gastric NETs

Most of the GI tract NETs are solid masses, whereas multiple NETs are usually associated with multiple endocrine neoplasia type 1 (MEN1) or Zollinger-Ellison syndrome, especially in the stomach or duodenum. These NETs are well-circumscribed masses located in the mucosal or submucosal layer of the GI tract. The most common gastric NETs are enterochromaffin-like (ECL)-cell (histamine-producing) tumors. Interestingly, the International Classification of Diseases for Oncology (ICD-O) code for ECL-cell–type NETs was not present in the gastric NET section in the 2010 WHO "Blue Book."[20] Other hormone-producing NETs, including EC-cell (serotonin-producing) NETs or G-cell gastrin-producing tumors (also known as gastrinomas), are very rare.[4] Immunohistochemical detection of ECL cells is specifically performed not by histamine but by vesicular monoamine transporter 2 because of the difficulty in detecting histamine immunohistochemical staining.[42,43] The ECL-cell NETs are categorized into 3 subtypes, based on the histology of the adjacent mucosa, antral G-cell hyperplasia, hypergastrinemia, and accompanying clinical condition.[33] The subtypes of gastric ECL-cell NETs are summarized in Table 4. Briefly, type I ECL-cell NETs are the most common subtypes and are associated with autoimmune chronic atrophic gastritis. Usually, multiple small-sized tumors (0.5–1 cm) are observed in the body or fundus. Hypergastrinemia and antral G-cell hyperplasia are commonly observed. Based on the 2010 WHO scheme, all type-I ECL-cell NETs are categorized as G1 NETs.[44]

Type-II ECL-cell NETs occur in patients with MEN1 or Zollinger-Ellison syndrome. MEN1 is a tumor suppressor gene on band 11q13 that encodes the menin protein.[45–49] Biallelic inactivation through a mutation in 1 allele of MEN1, coupled with the loss of the remaining wild-type allele, is identified in about 90% of gastric NETs. Multiple tumors of less than 2 cm are noted in the body or fundus, and the adjacent mucosa is hypertrophic.[44] Type-II ECL-cell NETs are categorized as G1 and, rarely, as G2 NETs.[44] Lymph node metastasis is more commonly observed in type-II tumors than it is in type-I tumors.

Type-III tumors are sporadic tumors and usually present as a single mass. Type-III ECL-cell NETs occur sporadically in the absence of ECL-cell hyperplasia or dysplasia and are not associated with hypergastrinemia, chronic atrophic gastritis, MEN1, or Zollinger-Ellison syndrome.[44] Usually, single large tumor (>2 cm) can be observed in any part of the stomach. Type-III tumors occasionally display more aggressive behaviors than do type-I and type-II tumors, and type-III ECL-cell NETs are categorized as G1 to G3 NETs.[44]

Duodenal and Ampullary NETs

G-cell (gastrin-producing) NETs are the most common duodenal NETs, followed by somatostatin-producing NETs and gangliocytic paragangliomas. G-cell (gastrin-producing) NETs occur sporadically or in association with MEN1.[4] G-cell (gastrin-producing) NETs associated with Zollinger-Ellison syndrome are frequently metastatic and are usually deeply infiltrating tumors with unfavorable clinical outcomes.[20] Somatostatin-producing NETs are associated with neurofibromatosis type 1 and have a typical glandular pattern containing psammoma bodies.[50–52] Gangliocytic paragangliomas occur predominantly in the second portion of the duodenum and ampulla and show characteristically triphasic cellular components, including epithelioid neuroendocrine cells, schwannian cells, and ganglion cell components (Figure 1, B). The neuroendocrine cells have an eosinophilic cytoplasm with ovoid nuclei arranged in a pseudoglandular pattern or solid nests. Epithelioid cells are immunoreactive for progesterone receptor and PP, schwannian cells stain positive for S100 protein, and ganglion cells are immunopositive for synaptophysin.[51,53,54] Gangliocytic

paragangliomas usually have a benign clinical course, but larger tumors (>2 cm) can metastasize to the regional lymph node with mainly neuroendocrine components.[55,56]

Jejunal and Ileal NETs

Jejunal and ileal NETs comprise about half of small intestinal NETs and are predominantly located in the terminal ileum.[57,58] Jejunal and ileal NETs are multiple tumors in up to one-third of the cases.[59–61] Ileal NETs are composed of EC-cell serotonin-producing tumors with insular growth patterns. Many cases show invasion to the proper muscle layer or beyond and/or metastases at the time of diagnosis. One-third of patients with ileal NETs have metastasis, and patients with liver metastasis show signs of carcinoid syndrome, which manifests with symptoms of flushing and diarrhea from bypassing the hepatic clearance of serotonin from the portal circulation.[40]

Appendiceal NETs

Appendiceal NETs can be classified as classic NETs, including EC-cell (serotonin-producing) NETs, L-cell–type NETs, and tubular and goblet cell carcinoids, which are mixed adenoendocrine carcinomas with a more-aggressive clinical behavior.[62] Tubular carcinoids are arranged in small, discrete tubules, occasionally with inspissated mucin. Thus, this neoplasm can be misdiagnosed as a metastatic adenocarcinoma.

Goblet cell carcinoids are composed of tumor cells of partial neuroendocrine differentiation, mixed with nests of signet ringlike cells, with mild-to-moderate dysplasia (Figure 1, C).[63] Tumor cells are focally positive for staining with synaptophysin, chromogranin A, and CD56 and are diffusely positive for cytokeratin 20 and MUC2.[64–66] Goblet cell carcinoids are more aggressive than other appendiceal carcinoids, and 20% of cases have metastasis at the time of diagnosis.[67–69] Goblet cell carcinoids are subclassified according to histology and mucin immunophenotype as typical goblet cell carcinoids, signet ring cell type adenocarcinomas, and poorly differentiated adenocarcinomas, and patient survival depends upon the subtype.[67]

Colorectal NETs

Colorectal NETs are composed of colonic-predominant EC-cell (serotonin-producing) NETs and rectum-predominant L-cell–type (GLP- and PP/PYY-producing) NETs.[20] In 2010 WHO classification, L-cell–type NETs are classified as tumors with uncertain malignant potential (ICD-O code, M8152/1) although no specific diagnostic criteria of L-cell–type NETs exist.[20] Therefore, pathologists are confused about assigning behavior coding for rectal NETs as NET G1 (M8240/3) or L-cell–type NETs (M8152/1). In general, rectal NETs usually manifest as a single, smooth submucosal nodule or polyp with normal-appearing mucosa.[70] About 80% of rectal NETs are 1 cm or smaller.[71] The L-cell NETs are detected in 50% to 80% of rectal NETs with various combinations of L-cell markers, including GLP1, GLP2, PYY, and PPY.[71–74] Histologically, L-cell–type NETs have predominantly trabecular patterns (Figure 1, D). L-cell–type NETs are tumors with uncertain malignant potential in the 2010 WHO scheme.[20] Biologic behaviors of rectal NETs depend on the L-cell immune phenotype, tumor size (≤1 or >1 cm), tumor grade, extension, and lymph node metastasis.[71,74,75] Small (<1 cm) rectal NETs tend to have no recurrence, even with incomplete resection.[76] On the other hand, large rectal NETs (>1 cm) and non–L-cell phenotype tumors have an aggressive clinical behavior and worse prognosis.[71]
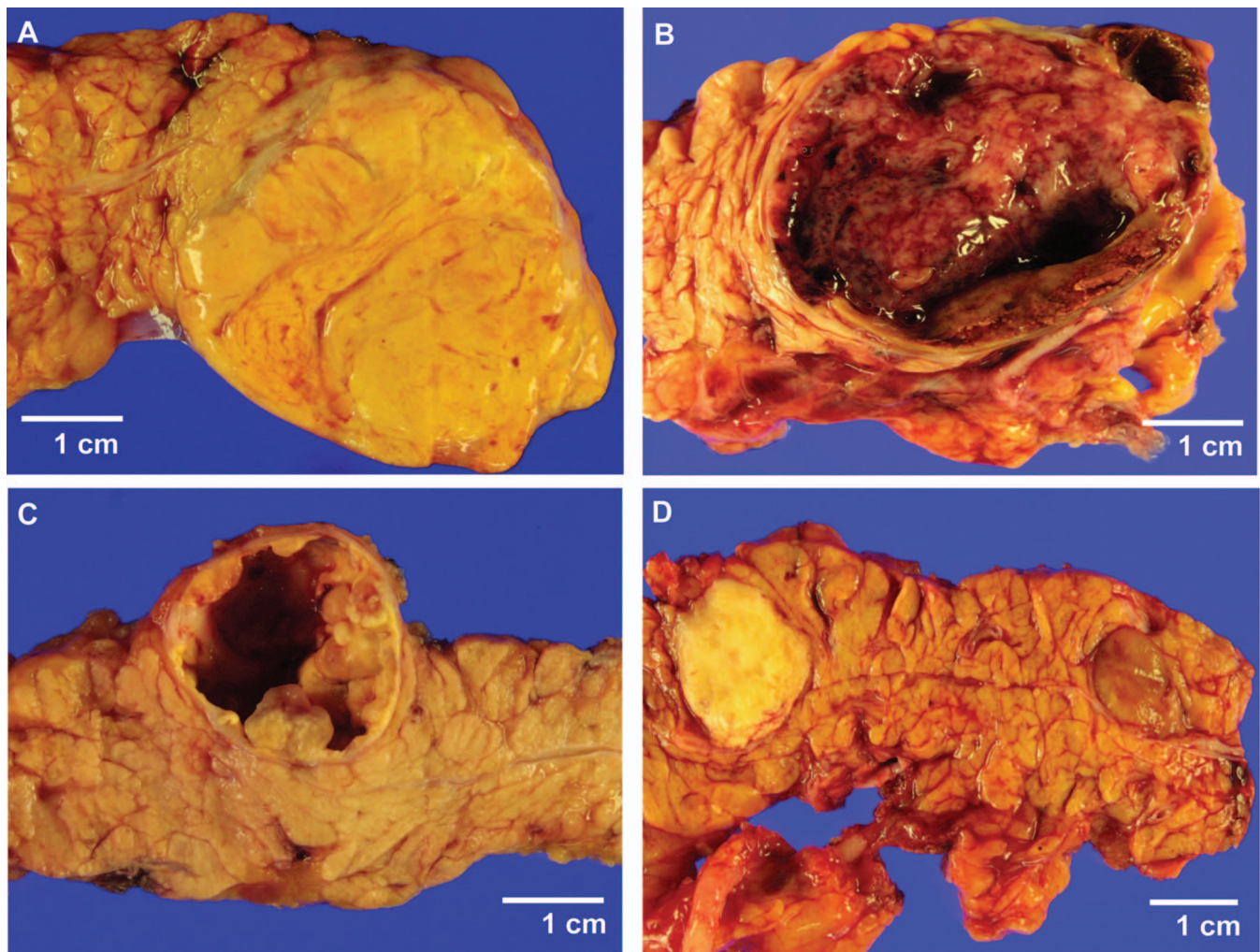
Pancreatic NETs

Pancreatic NETs account for about 3% of pancreatic neoplasms.[77,78] The tumors show an expansile growth pattern with pushing borders and have a yellow, fish-flesh, or tan-to-brown color (Figures 2, A and B).[79] Some tumors show peliosis or hemorrhage. Approximately 10% of pancreatic NETs are unilocular cystic tumors surrounded by fibrous rims and contain straw-colored cystic fluid (Figure 2, C).[80] Microscopically, cystic NETs are lined by thin fibrous bands.[80,81] Most sporadic pancreatic NETs are solitary, whereas some pancreatic NETs from patients with hereditary syndrome tend to have multiple tumors (Figure 2, D).[82]

Well-differentiated pancreatic NETs can be classified into functioning and nonfunctioning tumors based on the clinical symptoms induced by hormonal hypersecretion. About one-half of pancreatic NETs are functioning tumors, and insulinomas are the most common, followed, in order of frequency, by glucagonomas, gastrinomas, and somatostatinomas. Occasional stromal or intracellular amyloid deposition is noted in many cases of insulinomas.[79] For functioning tumors, insulinomas have an indolent clinical behavior, whereas gastrinomas, glucagonomas, and somatostatinomas are associated with a high malignant potential.[83,84] Similarly, patients with insulin-immuno–labeled NETs have better survival, whereas those with gastrin-immuno–labeled NETs have worse survival, regardless of clinical symptoms.[85] In addition to the typical features of NETs, some pancreatic NETs show morphologic variations, including clear cell, oncocytic, and pleomorphic types. Clear cell NETs will be discussed in the section on von Hippel-Lindau syndrome (Figure 3, A). Oncocytic pancreatic NETs contain large polygonal cells with eosinophilic granular cytoplasm and prominent nucleoli (Figure 3, B). Some studies reported that oncocytic tumors have a malignant clinical behavior.[86,87] In the setting of liver metastasis of oncocytic pancreatic NETs, immunohistochemical staining with neuroendocrine markers can help to differentiate hepatocellular carcinomas. Pleomorphic NETs contain more than 20% of tumor cells with marked nuclear pleomorphism (Figure 3, C). A bizarre, pleomorphic nuclear appearance does not affect clinical behavior and patient survival.[88] Pleomorphic NETs can be misdiagnosed as ductal adenocarcinoma, and immunohistochemical staining is helpful for differential diagnosis. Serotonin-producing tumors account for about one-quarter of pancreatic NETs; the tumor cells show a predominantly trabecular pattern with stromal fibrosis and uniquely involve main pancreatic ducts (Figure 3, D).[89]

Poorly differentiated NECs are further classified as small cell carcinomas and large cell carcinomas. Abundant apoptotic bodies, mitosis, and extensive necrosis are commonly observed in poorly differentiated NECs. Small cell carcinomas are composed of sheets or nests of tumor cells with a high nuclear to cytoplasmic ratio, hyperchromatic nuclei, inconspicuous nucleoli, and nuclear molding (Figure 3, E). Large cell carcinomas consist of large polygonal cells with large nuclei and prominent nucleoli. Their tumor cells form solid or nested growth patterns (Figure 3, F). In the pancreas, large cell carcinomas are more common than small cell carcinomas.[90]

Gastrointestinal and Pancreatobiliary Neuroendocrine Tumors—Kim & Hong

Figure 2. *Representative gross images of pancreatic neuroendocrine tumors. A, A well-circumscribed, yellow, solid tumor. B, A well-circumscribed tumor with variegated appearance and focal cystic degeneration. C, A cystic neuroendocrine tumor showing a unilocular cyst with a thin, fibrous rim and remaining tumor at the periphery. D, Two neuroendocrine tumors in a patient with multiple endocrine neoplasia type 1.*

Extrahepatic Biliary Tract NETs

Extrahepatic biliary epithelia contain scattered endocrine cells, which are immunolabeled by neuroendocrine markers.[9] Biliary tract NETs are extremely rare, and only one-fifth of these tumors are well-differentiated NETs.[91,92] Similarly, high-grade tumors, such as NECs and mixed adenoneuroendocrine carcinomas, are more common than either NET G1 or G2 tumors in the biliary tract.[1] The common locations of biliary NETs include the common hepatic and proximal common bile ducts.[91] The growth patterns of biliary tract NETs are either nodular or polypoid. In contrast to pancreatic NETs, biliary tract NETs do not have functioning tumors. However, a few biliary NETs express gastrin, serotonin, PP, or somatostatin.[92] Larger tumors (>2 cm) are associated with aggressive behavior.[92]

HEREDITARY SYNDROMES ASSOCIATED WITH GI AND PANCREATOBILIARY TRACT NEUROENDOCRINE TUMORS

Some GI tract and pancreatic NETs are associated with hereditary syndromes, including MEN1, von Hippel-Lindau syndrome, neurofibromatosis 1, and tuberous sclerosis.[93] The genes, clinical manifestations, and tumors involved in the GI and pancreatobiliary tracts and other organs are summarized in Table 5. All 4 hereditary syndromes are inherited in an autosomal-dominant manner.

MEN1 is a multiple-organ–involving endocrine neoplastic disorder with autosomal-dominant inheritance, characterized by multiple neoplasms in the pituitary glands, parathyroid glands, pancreas, adrenal glands, stomach, duodenum, thymus, and lung. Loss of *MEN1* heterozygosity is associated with the generation of multiple tumors. Multiple histamine-producing gastric tumors, multiple gastrin-producing duodenal tumors; and multiple insulin- or gastrin-producing pancreatic NETs are associated with MEN1.[83,94] Numerous endocrine precursor lesions, such as islet hyperplasia and dysplasia, and microadenomas are observed in the pancreas of MEN1 patients.[90]

Von Hippel-Lindau syndrome is an autosomal-dominant familial cancer syndrome caused by germline *VHL* mutation and characterized by clear cell tumors that affect multiple organs, such as hemangioblastomas of the central nervous system and retina, renal cell carcinomas, pheochromocytomas, and adrenal cortical adenomas. The NETs involving the GI tract have not been described,[94] whereas pancreatic lesions are associated with von Hippel-Lindau syndrome,
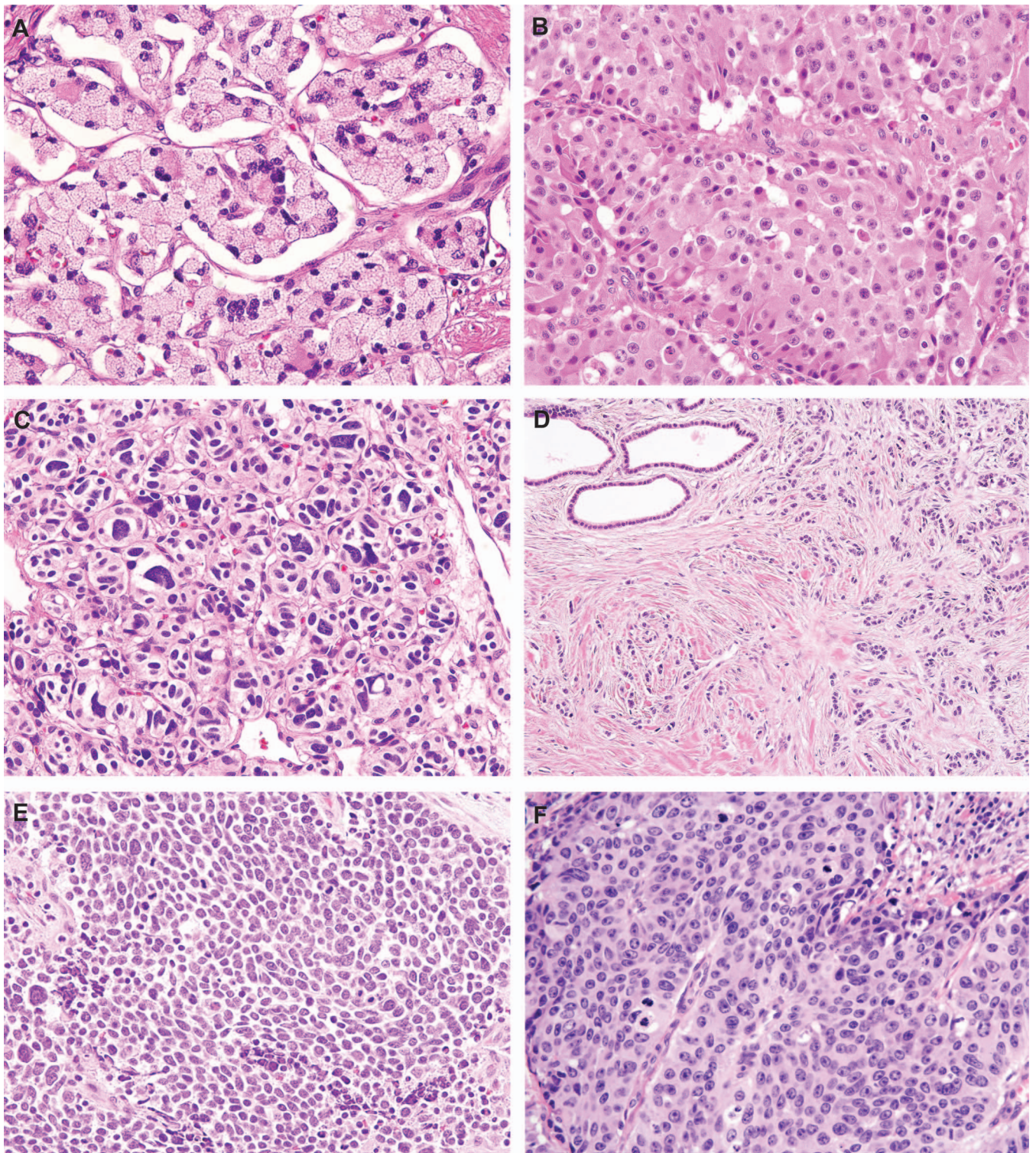
Figure 3. *Representative microscopic images of pancreatic neuroendocrine tumors. A, A clear cell variant of pancreatic neuroendocrine tumor. B, An oncocytic variant of pancreatic neuroendocrine tumor containing abundant eosinophilic granular cytoplasm with prominent nucleoli. C, A pleomorphic variant of pancreatic neuroendocrine tumor showing bizarre pleomorphic nuclei. D, A serotonin-producing neuroendocrine tumor showing a predominantly trabecular pattern with stromal fibrosis and uniquely involving pancreatic ducts. E, A small cell type of poorly differentiated neuroendocrine carcinoma with a high nuclear to cytoplasmic ratio, hyperchromatic nuclei, inconspicuous nucleoli, and nuclear molding. F, A large cell type of poorly differentiated neuroendocrine carcinoma with large, polygonal cytoplasm; large nuclei; and prominent nucleoli (hematoxylin-eosin, original magnifications ×400 [A, B, and D through F] and ×200 [C]).*

Table 5. Hereditary Syndromes Associated With Gastrointestinal (GI) and Pancreatobiliary Tract Neuroendocrine Tumors (NETs)[a]

Syndrome	Inheritance	Chromosomal Band Location	Gene/ Protein Involved	GI and Pancreatobiliary Tract NETs	Other Tumors in GI and Pancreatobiliary Tracts	Clinical Presentation Outside GI and Pancreatobiliary Tracts
Multiple endocrine neoplasia 1	AD	11q13.1	MEN1/ menin	Multiple gastric, duodenal, and pancreatic NETs	Esophageal leiomyoma	Pituitary adenoma, parathyroid hyperplasia, bronchial and thymic NETs, adrenal cortical adenoma
von Hippel-Lindau	AD	3p25.3	VHL/ VHL	Pancreatic clear cell NETs	Pancreas serous cyst adenomas	Hemangioblastomas of the CNS and retina, renal clear cell carcinomas, pheochromocytomas, adrenal cortical adenomas
Neurofibromatosis 1	AD	17q11.2	NF1/ neurofibromin	Duodenal and pancreatic somatostatin-producing NETs	GIST, neurofibromas	Neurofibromatosis, café au lait spots, optic nerve gliomas
Tuberous sclerosis	AD	9q34.13	TSC1/ hamartin	Pancreatic insulin- and somatostatin-producing NETs	Hamartomatous polyp	Multiple organ hamartomas
		16p13.3	TSC2/ tuberin			

Abbreviations: AD, autosomal dominant; CNS, central nervous system; GIST, gastrointestinal stromal tumor; MEN1, multiple endocrine neoplasia type 1; NF1, neurofibromatosis type 1; TSC1, tuberous sclerosis complex 1; TSC2, tuberous sclerosis complex 2; VHL, von Hippel-Lindau.

[a] Modified with permission from Elsevier: [90]Shi C, Klimstra DS. *Semin Diagn Pathol.* 2014;31(6):498–511.

including multiple clear cell NETs, serous cystadenomas, and benign serous cysts.[90,94] Clear cells in pancreatic NETs show a trabecular, glandular, or solid pattern and have a multivesicular, clear cytoplasm (Figure 3, A). These features are frequently seen not only in von Hippel-Lindau syndrome but also in sporadic pancreatic NETs and in association with MEN1 syndrome.[95] Differential diagnosis of clear cell pancreatic NETs includes metastatic renal cell carcinomas, especially in the setting of patients with von Hippel-Lindau syndrome.[90]

Neurofibromatosis type 1, also known as *von Reckling-hausen disease*, is an autosomal-dominant disorder characterized by café au lait spots, neurofibromas, optic nerve gliomas, and malignant peripheral nerve sheath tumors.[94] Occasional duodenal or ampullary NETs and rare pancreatic somatostatin-producing NETs are noted with characteristic glandular patterns and psammoma bodies.[4]

PROGNOSTIC MARKERS OF GI AND PANCREATOBILIARY TRACT NEUROENDOCRINE TUMORS

In addition to their use in the grading and staging of GI and pancreatobiliary tract NETs, several biomarkers were reported to be prognostic factors in GI and pancreatobiliary tract NETs.

In well-differentiated pancreatic NETs, a recent whole-exome sequencing study[96] revealed the genomic landscape of pancreatic NETs and the higher frequency of mutations in MEN1, ATRX (alpha thalassemia/mental retardation syndrome X-linked), and DAXX (death-domain associated protein) and a low frequency of mutations in several genes in the mTOR pathways, such as PTEN, TSC2, and PIC3CA. The protein expression status of some of these genes affects the survival of patients with pancreatic NETs.[97,98] For example, loss of PTEN, ATRX, and DAXX expression has

been related to worse survival.[97,98] Although cytokeratin 19 was initially proposed as a powerful worse prognostic indicator,[99] controversy remains: some studies showed that cytokeratin 19 expression correlated with worse survival,[100,101] but others did not find significant prognostic differences according to cytokeratin 19 expression in patients with pancreatic NETs.[102–104] Similarly, there have been controversies about the prognostic significance of KIT expression: a few groups showed that KIT-expressing pancreatic NETs had poor survival,[102,105] whereas another group observed no survival difference.[100] In addition, one study[97] showed that progesterone receptor negativity was associated with worse survival and that combined negative progesterone receptor/low PTEN was a worse prognostic indicator in patients with pancreatic NET. Another study[85] showed that insulin, GLP1, and increased numbers of peptide hormonal expression were associated with better survival in patients with pancreatic NET, whereas gastrin expression was associated with worse survival. Similarly, expression of cyclooxygenase-2, p21, p18, RB, and thymidylate synthetase and loss of somatostatin receptor 2 expression was related to poorer survival in GI and pancreatobiliary tract NETs.[106–108] Loss of p27 was reported to be a negative prognostic indicator in GI and pancreatobiliary tract NETs.[108]

SUMMARY

The incidence of NETs from the GI and pancreatobiliary tracts are continuously increasing: small intestinal NETs are the most common type among patients in the United States, whereas rectal NETs are the most frequent among patients in Korea. At least 15 types of neuroendocrine cells are distributed in the GI and pancreatobiliary tracts, and there is a correlation between the distributions of specific endocrine cells and the preferential location of specific hormone-

producing NETs in the GI and pancreatobiliary tracts, although there are some aberrations. The current 2010 WHO classification scheme includes histologic grading based on mitotic counts and the Ki-67 labeling index. Manual counting of camera-captured or printed images is the recommended practical method for the calculation of Ki-67 labeling. The presence of heterogeneity in G3 NETs—well-differentiated tumors with a high Ki-67 index and poorly differentiated tumors with different histologic and immunohistochemical characteristics and responses to platinum-based treatment—may indicate the need for further classification of these tumor groups. Several prognostic factors have been proposed, but most require further validation studies to stratify the survival of patients with GI and pancreatobiliary tract NETs.

References

1. Cho MY, Kim JM, Sohn JH, et al; Gastrointestinal Pathology Study Group of Korean Society of Pathologists. Current trends of the incidence and pathological diagnosis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in Korea 2000–2009: multicenter study. *Cancer Res Treat*. 2012;44(3):157–165.

2. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas*. 2010;39(6):707–712.

3. Klöppel G, Couvelard A, Perren A, et al; Mallorca Consensus Conference participants; European Neuroendocrine Tumor Society. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. *Neuroendocrinology*. 2009;90(2): 162–166.

4. Klöppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann N Y Acad Sci*. 2004;1014:13–27.

5. Mocellin S, Nitti D. Gastrointestinal carcinoid: epidemiological and survival evidence from a large population-based study (n = 25 531). *Ann Oncol*. 2013;24(12):3040–3044.

6. Schonhoff SE, Giel-Moloney M, Leiter AB. Minireview: development and differentiation of gut endocrine cells. *Endocrinology*. 2004;145(6):2639–2644.

7. Schimmack S, Svejda B, Lawrence B, Kidd M, Modlin IM. The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors. *Langenbecks Arch Surg*. 2011;396(3):273–298.

8. Klimstra DS, Hruban RH, Pitman MB. Pancreas. In: Mills SE, ed. *Histology for Pathologists*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012: 777–816.

9. Stelow EB, Hong SM, Frierson HF. Gallbladder and extrahepatic biliary system. In: Mills SE, ed. *Histology for Pathologists*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012:759–776.

10. Solcia E, Vanoli A. Histogenesis and natural history of gut neuroendocrine tumors: present status. *Endocr Pathol*. 2014;25(2):165–170.

11. Klimstra DS, Modlin IR, Adsay NV, et al. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. *Am J Surg Pathol*. 2010;34(3): 300–313.

12. La Rosa S, Rigoli E, Uccella S, Chiaravalli AM, Capella C. CDX2 as a marker of intestinal EC-cells and related well-differentiated endocrine tumors. *Virchows Arch*. 2004;445(3):248–254.

13. Schmitt AM, Riniker F, Anlauf M, et al. Islet 1 (Isl1) expression is a reliable marker for pancreatic endocrine tumors and their metastases. *Am J Surg Pathol*. 2008;32(3):420–425.

14. Agaimy A, Erlenbach-Wunsch K, Konukiewitz B, et al. ISL1 expression is not restricted to pancreatic well-differentiated neuroendocrine neoplasms, but is also commonly found in well and poorly differentiated neuroendocrine neoplasms of extrapancreatic origin. *Mod Pathol*. 2013;26(7):995–1003.

15. Graham RP, Shrestha B, Caron BL, et al. Islet-1 is a sensitive but not entirely specific marker for pancreatic neuroendocrine neoplasms and their metastases. *Am J Surg Pathol*. 2013;37(3):399–405.

16. Koo J, Zhou X, Moschiano E, De Peralta-Venturina M, Mertens RB, Dhall D. The immunohistochemical expression of islet 1 and PAX8 by rectal neuroendocrine tumors should be taken into account in the differential diagnosis of metastatic neuroendocrine tumors of unknown primary origin. *Endocr Pathol*. 2013;24(4):184–190.

17. Weissferdt A, Tang X, Wistuba II, Moran CA. Comparative immunohistochemical analysis of pulmonary and thymic neuroendocrine carcinomas using PAX8 and TTF-1. *Mod Pathol*. 2013;26(12):1554–1560.

18. Hermann G, Konukiewitz B, Schmitt A, Perren A, Klöppel G. Hormonally defined pancreatic and duodenal neuroendocrine tumors differ in their transcription factor signatures: expression of ISL1, PDX1, NGN3, and CDX2. *Virchows Arch*. 2011;459(2):147–154.

19. Yachida S, Vakiani E, White CM, et al. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. *Am J Surg Pathol*. 2012;36(2):173–184.

20. Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. *WHO Classification of Tumours of the Digestive System*. 4th ed. Lyon, France: IARC Press; 2010. *World Health Organization Classification of Tumours*; vol 3.

21. Rindi G, Klöppel G, Couvelard A, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch*. 2007;451(4):757–762.

22. McCall CM, Shi C, Cornish TC, et al. Grading of well-differentiated pancreatic neuroendocrine tumors is improved by the inclusion of both Ki67 proliferative index and mitotic rate. *Am J Surg Pathol*. 2013;37(11):1671–1677.

23. Hochwald SN, Zee S, Conlon KC, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol*. 2002;20(11):2633–2642.

24. Pape UF, Jann H, Müller-Nordhorn J, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. *Cancer*. 2008;113(2):256–265.

25. Voss SM, Riley MP, Lokhandwala PM, Wang M, Yang Z. Mitotic count by phosphohistone H3 immunohistochemical staining predicts survival and improves interobserver reproducibility in well-differentiated neuroendocrine tumors of the pancreas. *Am J Surg Pathol*. 2015;39(1):13–24.

26. Reid MD, Balci S, Saka B, Adsay NV. Neuroendocrine tumors of the pancreas: current concepts and controversies. *Endocr Pathol*. 2014;25(1):65–79.

27. Cross SS, Start RD, Smith JH. Does delay in fixation affect the number of mitotic figures in processed tissue? *J Clin Pathol*. 1990;43(7):597–599.

28. Kroneman TN, Voss JS, Lohse CM, Wu TT, Smyrk TC, Zhang L. Comparison of three Ki-67 index quantification methods and clinical significance in pancreatic neuroendocrine tumors. *Endocr Pathol*. 2015;26(3):255–262.

29. Tang LH, Gonen M, Hedvat C, Modlin IM, Klimstra DS. Objective quantification of the Ki67 proliferative index in neuroendocrine tumors of the gastroenteropancreatic system: a comparison of digital image analysis with manual methods. *Am J Surg Pathol*. 2012;36(12):1761–1770.

30. Reid MD, Bagci P, Ohike N, et al. Calculation of the Ki67 index in pancreatic neuroendocrine tumors: a comparative analysis of four counting methodologies. *Mod Pathol*. 2015;28(5):686–694.

31. Basturk O, Yang Z, Tang LH, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol*. 2015;39(5):683–690.

32. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer*. 2014;120(18):2814–2823.

33. La Rosa S, Vanoli A. Gastric neuroendocrine neoplasms and related precursor lesions. *J Clin Pathol*. 2014;67(11):938–948.

34. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–1474.

35. Rindi G, Klöppel G, Alhman H, et al; all other Frascati Consensus Conference participants; European Neuroendocrine Tumor Society (ENETS). TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch*. 2006;449(4):395–401.

36. Klöppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer*. 2011;18(suppl 1):S1–S16.

37. Klöppel G, Rindi G, Perren A, Komminoth P, Klimstra DS. The ENETS and AJCC/UICC TNM classifications of the neuroendocrine tumors of the gastrointestinal tract and the pancreas: a statement. *Virchows Arch*. 2010;456(6):595–597.

38. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti AI, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer 2010.

39. Cho MY, Sohn JH, Jin SY, et al; Gastrointestinal Pathology Study Group of Korean Society of Pathologists. Proposal for a standardized pathology report of gastroenteropancreatic neuroendocrine tumors: prognostic significance of pathological parameters. *Korean J Pathol*. 2013;47(3):227–237.

40. Rindi G, Falconi M, Klersy C, et al. TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst*. 2012;104(10):764–777.

41. Strosberg JR, Cheema A, Weber J, Han G, Coppola D, Kvols LK. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. *J Clin Oncol*. 2011;29(22): 3044–3049.

42. Rindi G, Paolotti D, Fiocca R, Wiedenmann B, Henry JP, Solcia E. Vesicular monoamine transporter 2 as a marker of gastric enterochromaffin-like cell tumors. *Virchows Arch*. 2000;436(3):217–223.

43. Eissele R, Anlauf M, Schafer MK, Eiden LE, Arnold R, Weihe E. Expression of vesicular monoamine transporters in endocrine hyperplasia and endocrine tumors of the oxyntic stomach. *Digestion*. 1999;60(5):428–439.

44. La Rosa S, Inzani F, Vanoli A, et al. Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. *Hum Pathol*. 2011;42(10):1373–1384.

45. Bale SJ, Bale AE, Stewart K, et al. Linkage analysis of multiple endocrine neoplasia type 1 with INT2 and other markers on chromosome 11. *Genomics*. 1989;4(3):320–322.

46. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science*. 1997;276(5311):404–407.

47. Debelenko LV, Emmert-Buck MR, Zhuang Z, et al. The multiple endocrine neoplasia type I gene locus is involved in the pathogenesis of type II gastric carcinoids. *Gastroenterology*. 1997;113(3):773–781.

48. Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjöld M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. *Nature*. 1988;332(6159):85–87.

49. Agarwal SK, Guru SC, Heppner C, et al. Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription. *Cell*. 1999; 96(1):143–152.

50. Dayal Y, Tallberg KA, Nunnemacher G, DeLellis RA, Wolfe HJ. Duodenal carcinoids in patients with and without neurofibromatosis: a comparative study. *Am J Surg Pathol*. 1986;10(5):348–357.

51. Garbrecht N, Anlauf M, Schmitt A, et al. Somatostatin-producing neuroendocrine tumors of the duodenum and pancreas: incidence, types, biological behavior, association with inherited syndromes, and functional activity. *Endocr Relat Cancer*. 2008;15(1):229–241.

52. Hartel M, Wente MN, Sido B, Friess H, Büchler MW. Carcinoid of the ampulla of Vater. *J Gastroenterol Hepatol*. 2005;20(5):676–681.

53. Stamm B, Hedinger CE, Saremaslani P. Duodenal and ampullary carcinoid tumors: a report of 12 cases with pathological characteristics, polypeptide content and relation to the MEN I syndrome and von Recklinghausen's disease (neurofibromatosis). *Virchows Arch A Pathol Anat Histopathol*. 1986;408(5):475–489.

54. Okubo Y, Nemoto T, Wakayama M, et al. Gangliocytic paraganglioma: a multi-institutional retrospective study in Japan. *BMC Cancer*. 2015;15:269.

55. Büchler M, Malfertheiner P, Baczako K, Krautzberger W, Beger HG. A metastatic endocrine-neurogenic tumor of the ampulla of Vater with multiple endocrine immunoreaction—malignant paraganglioma? *Digestion*. 1985;31(1): 54–59.

56. Inai K, Kobuke T, Yonehara S, Tokuoka S. Duodenal gangliocytic paraganglioma with lymph node metastasis in a 17-year-old boy. *Cancer*. 1989; 63(12):2540–2545.

57. Modlin IM, Champaneria MC, Chan AK, Kidd M. A three-decade analysis of 3,911 small intestinal neuroendocrine tumors: the rapid pace of no progress. *Am J Gastroenterol*. 2007;102(7):1464–1473.

58. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg*. 2004;240(1):117–122.

59. Burke AP, Thomas RM, Elsayed AM, Sobin LH. Carcinoids of the jejunum and ileum: an immunohistochemical and clinicopathologic study of 167 cases. *Cancer*. 1997;79(6):1086–1093.

60. Moertel CG, Sauer WG, Dockerty MB, Baggenstoss AH. Life history of the carcinoid tumor of the small intestine. *Cancer*. 1961;14(5):901–912.

61. Strodel WE, Talpos G, Eckhauser F, Thompson N. Surgical therapy for small-bowel carcinoid tumors. *Arch Surg*. 1983;118(4):391–397.

62. Deschamps L, Couvelard A. Endocrine tumors of the appendix: a pathologic review. *Arch Pathol Lab Med*. 2010;134(6):871–875.

63. Burke AP, Sobin LH, Federspiel BH, Shekitka KM, Helwig EB. Goblet cell carcinoids and related tumors of the vermiform appendix. *Am J Clin Pathol*. 1990; 94(1):27–35.

64. Hofler H, Kloppel G, Heitz PU. Combined production of mucus, amines and peptides by goblet-cell carcinoids of the appendix and ileum. *Pathol Res Pract*. 1984;178(6):555–561.

65. Isaacson P. Crypt cell carcinoma of the appendix (so-called adenocarcinoid tumor). *Am J Surg Pathol*. 1981;5(3):213–224.

66. van Eeden S, Offerhaus GJ, Hart AA, et al. Goblet cell carcinoid of the appendix: a specific type of carcinoma. *Histopathology*. 2007;51(6):763–773.

67. Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. *Am J Surg Pathol*. 2008;32(10):1429–1443.

68. McGory ML, Maggard MA, Kang H, O'Connell JB, Ko CY. Malignancies of the appendix: beyond case series reports. *Dis Colon Rectum*. 2005;48(12): 2264–2271.

69. Hristov AC, Young RH, Vang R, Yemelyanova AV, Seidman JD, Ronnett BM. Ovarian metastases of appendiceal tumors with goblet cell carcinoidlike and signet ring cell patterns: a report of 30 cases. *Am J Surg Pathol*. 2007;31(10): 1502–1511.

70. Shim KN, Yang SK, Myung SJ, et al. Atypical endoscopic features of rectal carcinoids. *Endoscopy*. 2004;36(4):313–316.

71. Kim JY, Kim KS, Kim KJ, et al. Non–L-cell immunophenotype and large tumor size in rectal neuroendocrine tumors are associated with aggressive clinical behavior and worse prognosis. *Am J Surg Pathol*. 2015;39(5):632–643.

72. Fiocca R, Rindi G, Capella C, et al. Glucagon, glicentin, proglucagon, PYY, PP, and proPP-icosapeptide immunoreactivities of rectal carcinoid tumors and related non-tumor cells. *Regul Pept*. 1987;17(1):9–29.

73. O'Briain DS, Dayal Y, DeLellis RA, Tischler AS, Bendon R, Wolfe HJ. Rectal carcinoids as tumors of the hindgut endocrine cells: a morphological and immunohistochemical analysis. *Am J Surg Pathol*. 1982;6(2):131–142.

74. Sohn JH, Cho MY, Park Y, et al. Prognostic significance of defining L-cell type on the biologic behavior of rectal neuroendocrine tumors in relation with pathological parameters. *Cancer Res Treat*. 2015;47(4):813–822.

75. Lee SH, Kim BC, Chang HJ, et al. Rectal neuroendocrine and L-cell tumors: diagnostic dilemma and therapeutic strategy. *Am J Surg Pathol*. 2013; 37(7):1044–1052.

76. Kim GU, Kim KJ, Hong SM, et al. Clinical outcomes of rectal neuroendocrine tumors ≤10 mm following endoscopic resection. *Endoscopy*. 2013;45(12):1018–1023.

77. Fischer L, Kleeff J, Esposito I, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. *Br J Surg*. 2008;95(5):627–635.

78. Tsutsumi K, Ohtsuka T, Mori Y, et al. Analysis of lymph node metastasis in pancreatic neuroendocrine tumors (PNETs) based on the tumor size and hormonal production. *J Gastroenterol*. 2012;47(6):678–685.

79. Hruban RH, Pitman MB, Klimstra DS. *Tumors of the Pancreas*. Washington, DC: American Registry of Pathology; 2007. *AFIP Atlas of Tumor Pathology*; 4th series, fascicle 6.

80. Singhi AD, Chu LC, Tatsas AD, et al. Cystic pancreatic neuroendocrine tumors: a clinicopathologic study. *Am J Surg Pathol*. 2012;36(11):1666–1673.

81. Kawamoto S, Johnson PT, Shi C, et al. Pancreatic neuroendocrine tumor with cystlike changes: evaluation with MDCT. *AJR Am J Roentgenol*. 2013; 200(3):W283–W290.

82. Lubensky IA, Pack S, Ault D, et al. Multiple neuroendocrine tumors of the pancreas in von Hippel-Lindau disease patients: histopathological and molecular genetic analysis. *Am J Pathol*. 1998;153(1):223–231.

83. Alexakis N, Neoptolemos JP. Pancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol*. 2008;22(1):183–205.

84. Kulke MH, Shah MH, Benson AB, III, et al; National Comprehensive Cancer Network. Neuroendocrine tumors, version 1.2015. *J Natl Compr Canc Netw*. 2015;13(1):78–108.

85. Kim JY, Kim MS, Kim KS, et al. Clinicopathologic and prognostic significance of multiple hormone expression in pancreatic neuroendocrine tumors. *Am J Surg Pathol*. 2015;39(5):592–601.

86. Sugihara A, Nakasho K, Ikuta S, et al. Oncocytic non-functioning endocrine tumor of the pancreas. *Pathol Int*. 2006;56(12):755–759.

87. Volante M, La Rosa S, Castellano I, Finzi G, Capella C, Bussolati G. Clinico-pathological features of a series of 11 oncocytic endocrine tumours of the pancreas. *Virchows Arch*. 2006;448(5):545–551.

88. Zee SY, Hochwald SN, Conlon KC, Brennan MF, Klimstra DS. Pleomorphic pancreatic endocrine neoplasms: a variant commonly confused with adenocarcinoma. *Am J Surg Pathol*. 2005;29(9):1194–1200.

89. McCall CM, Shi C, Klein AP, et al. Serotonin expression in pancreatic neuroendocrine tumors correlates with a trabecular histologic pattern and large duct involvement. *Hum Pathol*. 2012;43(8):1169–1176.

90. Shi C, Klimstra DS. Pancreatic neuroendocrine tumors: pathologic and molecular characteristics. *Semin Diagn Pathol*. 2014;31(6):498–511.

91. Michalopoulos N, Papavramidis TS, Karayannopoulou G, Pliakos I, Papavramidis ST, Kanellos I. Neuroendocrine tumors of extrahepatic biliary tract. *Pathol Oncol Res*. 2014;20(4):765–775.

92. Noronha YS, Raza AS. Well-differentiated neuroendocrine (carcinoid) tumors of the extrahepatic biliary ducts. *Arch Pathol Lab Med*. 2010;134(7): 1075–1079.

93. Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer*. 2008;113(7 suppl):1807–1843.

94. Anlauf M, Garbrecht N, Bauersfeld J, et al. Hereditary neuroendocrine tumors of the gastroenteropancreatic system. *Virchows Arch*. 2007;451(suppl 1): S29–S38.

95. Nunobe S, Fukushima N, Yachida S, Shimada K, Kosuge T, Sakamoto M. Clear cell endocrine tumor of the pancreas which is not associated with von Hippel-Lindau disease: report of a case. *Surg Today*. 2003;33(6):470–474.

96. Jiao Y, Shi C, Edil BH, et al. *DAXX/ATRX, MEN1*, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science*. 2011; 331(6021):1199–1203.

97. Estrella JS, Broaddus RR, Mathews A, et al. Progesterone receptor and PTEN expression predict survival in patients with low- and intermediate-grade pancreatic neuroendocrine tumors. *Arch Pathol Lab Med*. 2014;138(8):1027–1036.

98. Marinoni I, Kurrer AS, Vassella E, et al. Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. *Gastroenterology*. 2014;146(2):453–460 e455.

99. Deshpande V, Fernandez-del Castillo C, Muzikansky A, et al. Cytokeratin 19 is a powerful predictor of survival in pancreatic endocrine tumors. *Am J Surg Pathol*. 2004;28(9):1145–1153.

100. Han X, Zhao J, Ji Y, Xu X, Lou W. Expression of CK19 and KIT in resectable pancreatic neuroendocrine tumors. *Tumour Biol*. 2013;34(5):2881–2889.

101. La Rosa S, Rigoli E, Uccella S, Novario R, Capella C. Prognostic and biological significance of cytokeratin 19 in pancreatic endocrine tumours. *Histopathology*. 2007;50(5):597–606.

102. Son EM, Kim JY, An S, et al. Clinical and prognostic significances of cytokeratin 19 and KIT expression in surgically resectable pancreatic neuroendocrine tumors. *J Pathol Transl Med*. 2015;49(1):30–36.

103. Ali A, Serra S, Asa SL, Chetty R. The predictive value of CK19 and CD99 in pancreatic endocrine tumors. *Am J Surg Pathol*. 2006;30(12):1588–1594.

104. Schmitt AM, Anlauf M, Rousson V, et al. WHO 2004 criteria and CK19 are reliable prognostic markers in pancreatic endocrine tumors. *Am J Surg Pathol*. 2007;31(11):1677–1682.

105. Zhang L, Smyrk TC, Oliveira AM, et al. KIT is an independent prognostic marker for pancreatic endocrine tumors: a finding derived from analysis of islet cell differentiation markers. *Am J Surg Pathol*. 2009;33(10):1562–1569.

106. Lee HS, Chen M, Kim JH, et al. Analysis of 320 gastroenteropancreatic neuroendocrine tumors identifies TS expression as independent biomarker for survival. *Int J Cancer*. 2014;135(1):128–137.

107. Kim HS, Lee HS, Kim WH. Clinical significance of protein expression of cyclooxygenase-2 and somatostatin receptors in gastroenteropancreatic neuroendocrine tumors. *Cancer Res Treat*. 2011;43(3):181–188.

108. Kim HS, Lee HS, Nam KH, Choi J, Kim WH. p27 loss is associated with poor prognosis in gastroenteropancreatic neuroendocrine tumors. *Cancer Res Treat*. 2014;46(4):383–392.

109. Furness JB, Rivera LR, Cho HJ, Bravo DM, Callaghan B. The gut as a sensory organ. *Nat Rev Gastroenterol Hepatol*. 2013;10(12):729–740.