FEATURE

Updated Guidelines for Classifying Gastroenteropancreatic Neuroendocrine Neoplasms

Written by Nicola Parry

Robert Yoshiyuki Osamura, MD, PhD, International University of Health and Welfare, Tokyo, Japan, discussed the nomenclature of neuroendocrine tumors (NETs), according to the updated 2010 World Health Organization (WHO) classification. This scheme classifies NETs based on prognostication by their proliferative activities, with respect to mitotic rate and Ki-67 labeling index. Since this accounts for tumor grading and prognosis, it facilitates development of treatment strategies, with somatostatin receptor (SSTR) 2a-positive tumors in particular demonstrating improved response to therapy with somatostatin analogs (SAs).

NETs constitute a heterogeneous group of neoplasms considered to originate from a common precursor cell population found in endocrine glands, neuroendocrine tissues, pancreatic endocrine islets scattered between exocrine cells within glandular tissue. Tumors in this group include insulinoma, glucagonoma, and historically used misnomer "carcinoid." Yet, although NETs have a wide spectrum of malignancy, these terminologies are somewhat problematic because they do not adequately convey the potential for malignant behavior that is associated with many of these tumors. Thus, NETs now are subdivided into NET G1, NET G2 and NEC.

Accordingly, in 2010, however, a new WHO classification was established, that is more definitive than its earlier counterparts, no longer uses the terminology "carcinoid," and has prognostic and predictive value (Table 1). In this scheme, gastrointestinal and pancreatic tumors of endocrine and neuroendocrine origin are designated as gastroenteropancreatic neuroendocrine neoplasms (NENs), and are further subdivided into NETs (well-differentiated NENs) and neuroendocrine carcinomas (NECs; poorly differentiated NENs). NETs are further classified as grade Grade 1 (G1) or G2 tumors, according to their proliferative activity with respect to mitotic rate and Ki-67 labeling index (Table 2).

Table 1. WHO Classification

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	1. Well-differentiated endocrine tumor 2. Well-differentiated endocrine carcinoma 3. Poorly differentiated endocrine carcinoma/ small cell carcinoma	1. NET G1 2. NET G2 3. NEC (large cell or small cell type)
II. Mucocarcinoid III. Mixed forms carcinoid-adenocarcinoma	4. Mixed exocrine-carcinoma	4. Mixed adenoneuroendocrine carcinoma
IV. Pseudotumor lesions	5. Tumor-like lesions	5. Hyperplastic and preneoplastic lesions

G=grade; NEC=neuroendocrine carcinoma; NET=neuroendocrine tumor.

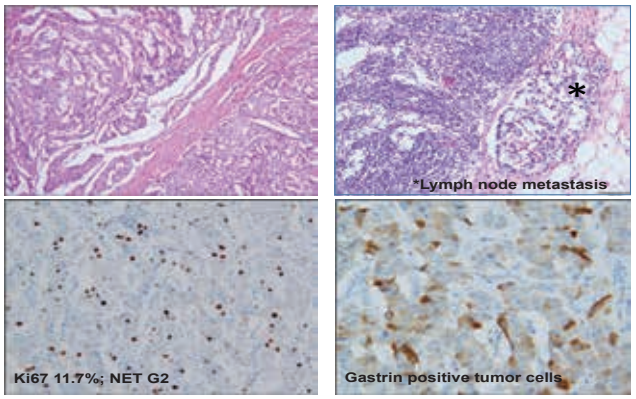
Table 2. Ki67 Index

Grade	Mitotic Count (10HPF)*	Ki-67 Index (%)**
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

*10HPF=2 mm^2, at least 40 fields (at 40x magnification) evaluated in areas of highest mitotic density; **MIVI antibody; Percent of 2000 tumor cells in areas of highest nuclear labeling.

Mixed adenoneuroendocrine carcinoma, and hyperplastic and preneoplastic lesions comprise additional special groups. Figure 1 indicates a pancreatic NET G2 with gastric production.

Figure 1. Pancreatic Tumor NET G2 With Lymph Node Metasasis



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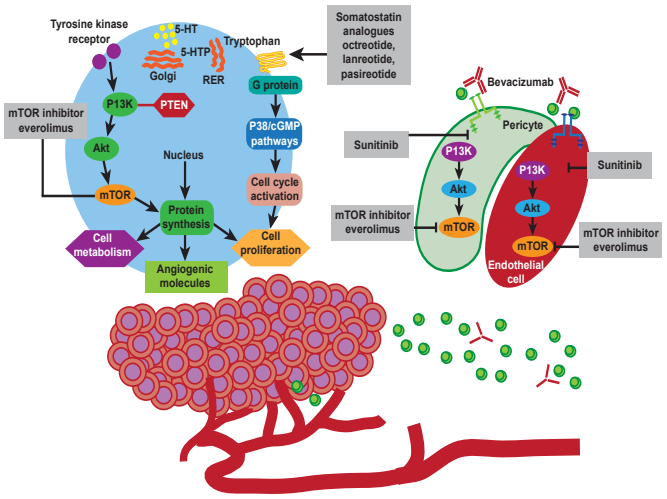
Although historically a difficult group of tumors to treat, in the current era of molecular targeted therapy, emerging novel strategies now hold promise for managing patients with advanced NETs (Figure 2) [Dong M et al. *Clin Cancer Res* 2012].

Various neuroendocrine markers and hormonal receptors with diagnostic, prognostic, and therapeutic implications have been described in NENs. These include SSTRs that mediate intracellular signaling pathways in cell proliferation and hormone secretion.

Figure 2. Strategies for Treatment of Patients With NETs



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Immunohistochemical profiling of various SSTR subtypes in NETs now represents part of the routine diagnostic assessment of these tumors, serving as a useful predictor of responsiveness to various SAs, such as octreotide and pasireotide. These have been shown to block different SSTRs (SSTR1 to SSTR5; Figure 3), reduce the release of bioactive peptides and neuroamines, and delay NET growth. The multitargeted tyrosine kinase inhibitor sunitinib [Raymond E et al. *N Engl J Med* 2011], as well as the mammalian target of rapamycin (mTOR) inhibitor everolimus [Yao JC et al. *N Engl J Med* 2011], have also been demonstrated to improve progression-free survival in pancreatic NETs, confirming the importance of the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway and angiogenesis in tumorigenesis, as well as important targets for further therapeutic advances [Dong M et al. *Clin Cancer Res* 2012]. It is also proposed that SSTR2a-positive NECs with NET histological features could be classified as NET G3, and may also respond to octreotide therapy.

Figure 3. Binding Affinities of Somatostatin and Its Analogs to Somatostatin Receptors

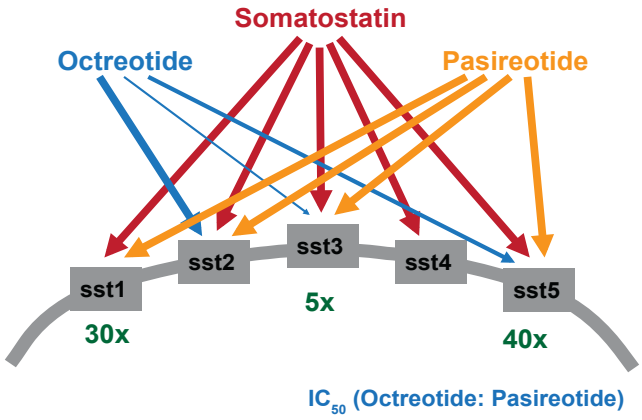

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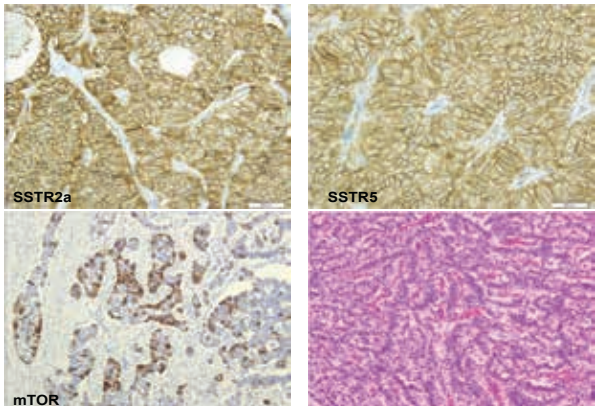
Figure 4 reveals a pancreatic NET with positive SSTR2a, SSTR5, and mTOR which may suggest various therapeutic possibiiies. Ki67 index is 11.7% and had a metastasis in a lymph node.

Figure 4. Pancreatic NET Positive for SSTR2a, SSTR5, and mTOR



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Prof. Osamura therefore concluded that the WHO 2010 classification scheme should be recommended for diagnosis of pancreatic and gastrointestinal NETs G1 and G2, and NECs, and that since it incorporates with grading and staging, it provides a useful basis for prognostic prediction and treatment stratification.