Neuroendocrine Tumors: Current Recommendations for Diagnosis and Surgical Management

Saju Joseph, MD[a,b], Yi-Zarn Wang, MD[a,c], J. Philip Boudreaux, MD[a,c,d], Lowell B. Anthony, MD[e,f], Richard Campeau, MD[g,h], Daniel Raines, MD[i], Thomas O'Dorisio, MD[j], Vay Liang Go, MD[k], Aaron I. Vinik, MD, PhD, FCP, MACP[l], Jason Cundiff, MD[a], Eugene A. Woltering, MD[a,c,*]

KEYWORDS

• Neuroendocrine tumors • Imaging • Surgery • Chemotherapy • Radiation therapy • Foregut • Hindgut • Midgut • Biochemical markers • Tumor markers

[a] Section of Endocrine Surgery, Department of Surgery, Louisiana State University Health Sciences Center, 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065, USA
[b] Section of Hepatobiliary Surgery, Department of Surgery, Louisiana State University Health Sciences Center, 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065, USA
[c] Section of Surgical Oncology, Department of Surgery, Louisiana State University Health Sciences Center, 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065, USA
[d] Section of Transplant Surgery, Department of Surgery, Louisiana State University Health Sciences Center, 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065, USA
[e] Section of Hematology and Oncology, Department of Medicine, Louisiana State University Health Sciences Center, 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065, USA
[f] Section of Medical Oncology, Department of Medicine, Louisiana State University Health Sciences Center, 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065, USA
[g] Section of Radiation Oncology, Department of Radiology, Louisiana State University Health Sciences Center, 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065, USA
[h] Section of Radiation Oncology, Department of Medicine, Louisiana State University Health Sciences Center, 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065, USA
[i] Section of Gastroenterology, Department of Medicine, Louisiana State University Health Sciences Center, 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065, USA
[j] Carver College of Medicine at the University of Iowa, University of Iowa Hospitals and Clinics, 200 Hawkins Drive E419GH, Iowa City, IA 52242, USA
[k] UCLA Center for Excellence in Pancreatic Diseases, David Geffen School of Medicine at UCLA, 900 Veteran Avenue, 13-146 Warren Hall, Los Angeles, CA 90095–1742, USA
[l] Eastern Virginia Medical School, Strelitz Diabetes Center, 855 West Brambleton Avenue, Norfolk, VA 23510, USA
* Corresponding author. 200 West Esplanade Avenue, Suite 200, Kenner, LA 70065.
E-mail address: ewolte@lsuhsc.edu

Endocrinol Metab Clin N Am 40 (2011) 205–231
doi:10.1016/j.ecl.2010.08.004 **endo.theclinics.com**
0889-8529/11/$ – see front matter

The diverse clinical and histologic nature of neuroendocrine tumors (NETs) and the relative paucity of adequately powered studies make it difficult to formulate a consistent diagnosis and treatment strategy. In addition, the rapid emergence and incorporation of new technologies into the clinical arena makes defining a "static" gold standard for diagnosis or treatment difficult.

Based on the expertise of the Inter-Science Institute's GI council and the expertise of the Louisiana State University Neuroendocrine tumor group's extensive experience, the authors compiled recommendations for the diagnostic work-up of patients with suspected NETs. These recommendations are presented in tabular form to make it easier for clinical reference. The guidelines help serve as an aggregate of the available consensus reports and reflect a practical, but academically oriented, approach to these tumors. These recommendations are from diverse areas of clinical practice including surgery, endocrinology, oncology, and gastroenterology.

TUMOR CLASSIFICATION

The most recent World Health Organization classification described three general categories of NETs: (1) well-differentiated NETs, which exhibit uncertain malignant potential; (2) well-differentiated NE carcinomas, which are low-grade malignancies; and (3) poorly differentiated NE carcinomas, which are high-grade malignancies.[1] Currently, the term "carcinoid" is commonly used to refer to well-differentiated tumors of the bronchus, thymus, ovary, or gut. The term "islet cell tumor" commonly refers to well-differentiated adenoma-like lesions that behave in a benign fashion. Likewise, the term "islet cell carcinoma" commonly refers to a well-differentiated neuroendocrine carcinoma that arises from the pancreas or periampullary region.[2] In all of these tumors, therapeutic decisions are influenced by the degree of cellular differentiation. The standard criteria for classifying these tumors are based on the histologic characteristics of the tumor. The microscopic assessment of tumor differentiation is commonly supplemented by immunohistochemical stains, such as Ki-67, chromogranin A (CgA), and synaptophysin. Other stains, such as neuron-specific enolase and specific stains for multiple peptides in pancreatic or duodenal tumors, are commonly used in the classification of NETs. Ultimately, the rationale for classification of these tumors is to provide the clinician with a framework for the prediction of a tumor's behavior. These "islet" cell tumors commonly stain positively for gastrin, glucagon, somatostatin, vasoactive intestinal peptide, pancreatic polypeptide, insulin, and C-peptide. It is critical to note that the presence of a positive peptide or amine stain in these pancreatic-duodenal tumors often leads to the mistaken diagnosis of a specific functional tumor type. The ultimate diagnosis of the functionality of these tumors is solely dependent on hypersecretion of peptide being documented in the serum, plasma, or urine. All NETs should undergo histologic evaluation by an experienced pathologist with extensive experience in NETs. These pathologists should determine the tumor's degree of differentiation. This should be determined by visual examination of the tumor and the selective use of stains, such as Ki-67, CgA, synaptophysin, and others as needed to assist the pathologist in determination of the proper classification.[1]

More recently, within the appendiceal carcinoid specimens, the terms "adenocarcinoid" or "mucinous carcinoid" have been used. It is the authors' opinion that these tumors represent a subset of carcinoid tumors that exhibit macroscopic similarities to carcinoids but morphologically also possess glandular structures that produce mucin. Their behavior mimics that of a classic adenocarcinoma rather than an NET.