Biochemical Diagnosis and Preoperative Imaging of Gastroenteropancreatic Neuroendocrine Tumors

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KEYWORDS

• Pancreas neuroendocrine tumors • Carcinoid • OctreoScan • Gut hormones

KEY POINTS

- Many neuroendocrine tumors (NETs) secrete substances that can cause symptoms, but also aid biochemical diagnosis and localization of the primary tumor.
- There are many foods and medications that can interfere with biomarker assays.
- In cases where a pancreas neuroendocrine tumor is suspected, pancreatic polypeptide, chromogranin A (CgA), calcitonin, parathyroid hormone-related peptide, and growth hormone releasing hormone should be drawn during the patient's initial visit.
- When a gastrointestinal NET is suspected, CgA and serotonin levels should be obtained.
- Molecular testing may be used to identify an unknown metastasis as a NET and can be more accurate than traditional histologic procedures in differentiating between primary tumor sites.

INTRODUCTION

There has been a marked increase in the incidence of neuroendocrine tumors (NETs) over the past several decades, from approximately 1 case per 100,000 in 1973 to 5 cases per 100,000 in 2004.[1] The reasons for this increase are unclear and could be

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due to increased environmental exposures, a greater understanding and awareness of these tumors, and the parallel, marked increased use of anatomic imaging studies over this period. Regardless of the cause, these tumors have gone from rare to commonplace, and clinicians need tools to help differentiate NETs from other neoplasms. Furthermore, 30% of patients with small bowel (SBNETs) and 64% of pancreatic NETs (PNETs) present with metastatic disease,[1] and determining the primary NET site of origin is critical for guiding future surgical and medical therapy. This review describes the different modalities commonly used in the diagnosis and follow-up of gastroenteropancreatic (GEP) NETs, including biochemical markers, gene expression tests, and radiologic and nuclear medicine imaging.

BIOCHEMICAL MARKERS FOR GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS

Approximately 50 years ago, Pearse[2] proposed that all peptide-producing cells of the gut, pancreas, and to a lesser extent, the anterior pituitary gland, belonged to a larger system that shared similar chemical, ultrastructural, and functional characteristics. This system was called the diffuse neuroendocrine cell system, and Pearse held that all of these cells were of neural crest origin. GEP NETs were postulated to derive from a common endocrine progenitor termed amine precursor uptake and decarboxylation cell. Neoplasms arising from this system are defined as epithelial neoplasms with predominant neuroendocrine differentiation.[3] One property shared by these cells and their respective tumors is staining with neuroendocrine immunohistochemical (IHC) markers CgA and synaptophysin.[4] Another property is that approximately 80% of NETs express the somatostatin subtype 2 receptors (SSTR2),[5,6] allowing for the use of synthetic somatostatin (congeners) in the diagnosis and management of these NETs.[5–9] It has been suggested that the long latency period of NETs (up to 9 years for midgut carcinoids)[10] may be related to the inhibitory and antiproliferative action of native somatostatin and its congeners via membrane receptor coupling.[5,7,8,11]

NETs may occur throughout the body, including the lung (bronchial carcinoids), thyroid (medullary thyroid cancer), adrenal gland (pheochromocytoma), gastrointestinal (GI) tract (stomach, duodenum, jejunum, ileum, colon, and rectum), pancreas, and the skin (Merkel cell carcinoma). This occurrence throughout the body is not surprising because the cells of the diffuse neuroendocrine system have come to reside normally in these various organs and tissues. These tumors produce amines and peptides that can be exploited for diagnosis and followed for response to therapy (**Table 1**). These secreted substances may cause symptoms that give clues as to tumor location and are ideal markers to be selected for biochemical testing.[10] This review focuses on NETs of the GEP system, which may be functional (cause symptoms) or nonfunctional. The most frequently encountered GEP NETs are of the small bowel (SBNETs, or carcinoid tumors) and pancreas (PNETs), which account for approximately 70% to 75% of all tumors of the diffuse neuroendocrine system in humans.

Gastrointestinal Neuroendocrine Tumors

The derivation of the term “carcinoid” (carcinoma-like, karzinoide) is credited to Oberndorfer, whose series of 6 cases published in 1907 identified what was thought to be a form of benign neoplasia.[12,13] Carcinoid tumors of the small intestine account for approximately 55% of all adult NETs,[10] and 28% to 44% of all malignant tumors of the small bowel.[14,15] Its incidence has increased 4-fold between 1973 and 2004 (from 2.1 to 9.3 cases per million), and it has transcended adenocarcinoma as the most common cancer type of the small bowel in 2000.[15] The neuroendocrine cell giving