TABLE 113-3 GI-NET (CARCINOID) LOCATION, FREQUENCY OF METASTASES, AND ASSOCIATION WITH THE CARCINOID SYNDROME

	Location (% of Total)	Incidence of Metastases	Incidence of Carcinoid Syndrome
Foregut			
Esophagus	<0.1	—	—
Stomach	4.6	10	9.5
Duodenum	2.0	—	3.4
Pancreas	0.7	71.9	20
Gallbladder	0.3	17.8	5
Bronchus, lung, trachea	27.9	5.7	13
Midgut			
Jejunum	1.8	{58.4	9
Ileum	14.9		9
Meckel's diverticulum	0.5	—	13
Appendix	4.8	38.8	<1
Colon	8.6	51	5
Liver	0.4	32.	—
Ovary	1.0	2 32	50
Testis	<0.1	—	50
Hindgut			
Rectum	13.6	3.9	—

Abbreviation: GI-NET, gastrointestinal neuroendocrine tumor.

Source: Location is from the PAN-SEER data (1973–1999), and incidence of metastases is from the SEER data (1992–1999), reported by IM Modlin et al: Cancer 97:934, 2003. Incidence of carcinoid syndrome is from 4349 cases studied from 1950–1971, reported by JD Godwin: Cancer 36:560, 1975.

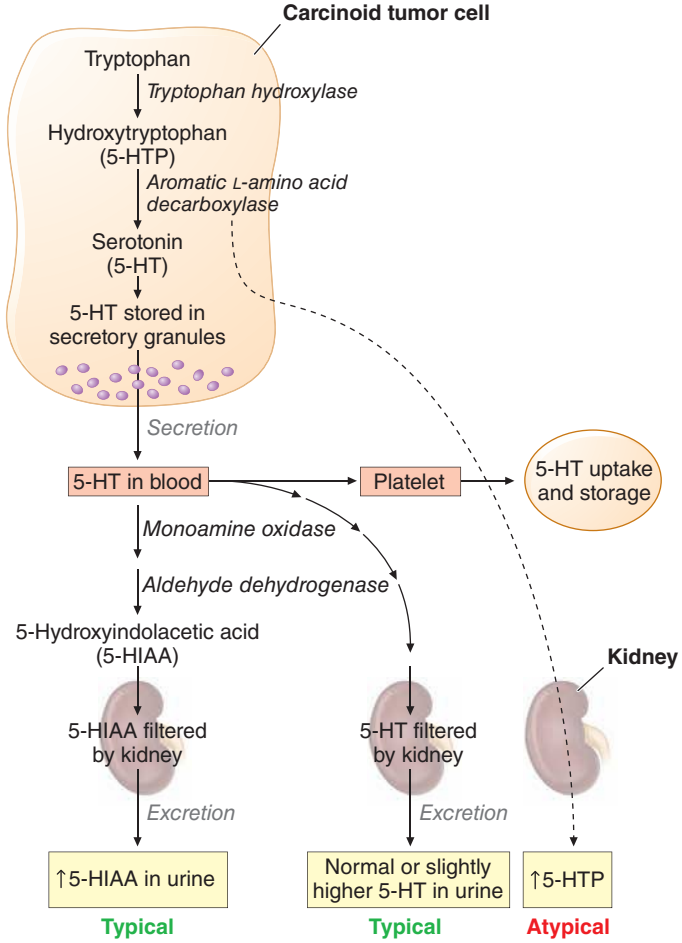

FIGURE 113-1 Synthesis, secretion, and metabolism of serotonin (5-HT) in patients with typical and atypical carcinoid syndromes. 5-HIAA, 5-hydroxyindolacetic acid.

Because a large proportion of nonfunctional pNETs (60–90%) secrete PP, these tumors are often referred to as PPomas (Table 113-2).

GI-NETs (carcinoids) can occur in almost any GI tissue (Table 113-3); however, at present, most (70%) have their origin in one of three sites: bronchus, jejunoileum, or colon/rectum. In the past, GI-NET (carcinoids) most frequently were reported in the appendix (i.e., 40%); however, the bronchus/lung, rectum, and small intestine are now the most common sites. Overall, the GI tract is the most common site for these tumors, accounting for 64%, with the respiratory tract a distant second at 28%. Both race and sex can affect the frequency as well as the distribution of GI-NETs (carcinoids). African Americans have a higher incidence of carcinoids. Race is particularly important for rectal carcinoids, which are found in 41% of Asians/Pacific Islanders with NETs compared to 32% of American Indians/Alaskan natives, 26% of African Americans, and 12% of white Americans. Females have a lower incidence of small intestinal and pancreatic carcinoids.

The term *pancreatic neuroendocrine* or *endocrine tumor*, although widely used and therefore retained here, is also a misnomer, strictly speaking, because these tumors can occur either almost entirely in the pancreas (insulinomas, glucagonomas, nonfunctional pNETs, pNETs causing hypercalcemia) or at both pancreatic and extrapancreatic sites (gastrinomas, VIPomas [vasoactive intestinal peptide], somatostatinomas, GRFomas [growth hormone–releasing factor]). pNETs are also called islet cell tumors; however, the use of this term is discouraged because it is not established that they originate from the islets, and many can occur at extrapancreatic sites.

Whereas the classification of GI neuroendocrine tumors into foregut, midgut, or hindgut is widely used and generally useful because the NETs within these areas have many similarities, they also have marked differences, particularly in biologic behavior, and it has not proved useful for prognostic purposes. More general classifications have been developed that allow NETs with similar features in different locations to be compared, have proven prognostic value, and are widely used. New classification systems have been developed for both GI-NETs (carcinoids) and pNETs by the World Health Organization (WHO), European Neuroendocrine Tumor Society (ENETS), and the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC). Although there are some differences between these different classification systems, each uses similar information, and it is now recommended that the basic data underlying the classification be included in all standard pathology reports. These classification systems divide NETs from all sites into those that are well differentiated (low grade [G1] or intermediate grade [G2]) and those that are poorly differentiated (high grade [G3] divided into either small-cell carcinoma or large-cell neuroendocrine carcinoma). In these classification systems, both pNETs and GI-NETs (carcinoids) are classified as neuroendocrine tumors, and the old term of carcinoid is equivalent to well-differentiated neuroendocrine tumors of the GI tract. These classification systems are based on not only the differentiation of the NET, but also a grading system assessing proliferative indices (Ki-67 and the mitotic count). NETs are considered low grade (ENETS G1) if the Ki-67 is <3% and the mitotic count is <2 mitoses/high-power field (HPF), intermediate grade (ENETS G2) if the Ki-67 is 3–20% and the mitotic count is 2–20 mitoses/HPF, and high grade (ENETS G3) if the Ki-67 is >20% and the mitotic count is >20 mitoses/HPF. In addition to the grading system, a TNM classification has been proposed that is based on the level of tumor invasion, tumor size, and tumor extent (see Table 113-4 for an example with pNETs and appendiceal GI-NETs [carcinoids]). Because of the proven prognostic value of these classification and grading systems, as well as the fact that NETs with different classifications/grades respond differently to treatments, the systems are now essential for the management of all NETs.

In addition to these classification/grading systems, a number of other factors have been identified that provide important prognostic information that can guide treatment (Table 113-5).

The exact incidence of GI-NETs (carcinoids) or pNETs varies according to whether only symptomatic tumors or all tumors are considered. The incidence of clinically significant carcinoids is 7–13 cases/million population per year, whereas any malignant carcinoids