TABLE 113-4 COMPARISON OF THE CRITERIA FOR THE TUMOR CATEGORY IN THE ENETS AND SEVENTH EDITION AJCC TNM CLASSIFICATIONS OF PANCREATIC AND APPENDICEAL NETs

	ENETS TNM	AJCC/UICC TNM
pNETs		
T1	Confined to pancreas, <2 cm	Confined to pancreas, <2 cm
T2	Confined to pancreas, 2–4 cm	Confined to pancreas, >2 cm
T3	Confined to pancreas, >4 cm, or invasion of duodenum or bile duct	Peripancreatic spread, but without major vascular invasion (truncus coeliacus, superior mesenteric artery)
T4	Invasion of adjacent organs or major vessels	Major vascular invasion
Appendiceal NETs		
T1	≤1 cm; invasion of muscularis propria	T1a, ≤1 cm; T1b, >1–2 cm
T2	≤2 cm and <3 mm invasion of subserosa/mesoappendix	>2–4 cm or invasion of cecum
T3	>2 cm or >3 mm invasion of subserosa/mesoappendix	>4 cm or invasion of ileum
T4	Invasion of peritoneum/ other organs	Invasion of peritoneum/ other organs

Abbreviations: AJCC, American Joint Committee on Cancer; ENETS, European Neuroendocrine Tumor Society; NET, neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; TNM, tumor, node, metastasis; UICC, International Union Against Cancer.

Source: Modified from DS Klimstra: Semin Oncol 40:23, 2013 and G Kloppel et al: Virchow Arch 456:595, 2010.

at autopsy are reported in 21–84 cases/million population per year. The incidence of GI-NETs (carcinoids) is approximately 25–50 cases per million in the United States, which makes them less common than adenocarcinomas of the GI tract. However, their incidence has increased sixfold in the last 30 years. In an analysis of 35,825 GI-NETs (carcinoids) (2004) from the U.S. Surveillance, Epidemiology, and End Results (SEER) database, their incidence was 5.25/100,000 per year, and the 29-year prevalence was 35/100,000. Clinically significant pNETs have a prevalence of 10 cases/million population, with insulinomas, gastrinomas, and nonfunctional pNETs having an incidence of 0.5–2 cases/million population per year (Table 113-2). pNETs account for 1–10% of all tumors arising in the pancreas and 1.3% of tumors in the SEER database, which consists primarily of malignant tumors. VIPomas are 2–8 times less common, glucagonomas are 17–30 times less common, and somatostatinomas are the least common. In autopsy studies, 0.5–1.5% of all cases have a pNET; however, in less than 1 in 1000 cases was a functional tumor thought to occur.

Both GI-NETs (carcinoids) and pNETs commonly show malignant behavior (Tables 113-2 and 113-3). With pNETs, except for insulinomas in which <10% are malignant, 50–100% in different series are malignant. With GI-NETs (carcinoids), the percentage showing malignant behavior varies in different locations (Table 113-3). For the three most common sites of occurrence, the incidence of metastases varies greatly from the jejunoileum (58%), lung/bronchus (6%), and rectum (4%) (Table 113-3). With both GI-NETs (carcinoids) and pNETs, a number of factors (Table 113-5) are important prognostic factors in determining survival and the aggressiveness of the tumor. Patients with pNETs (excluding insulinomas) generally have a poorer prognosis than do patients with GI-NETs (carcinoids). The presence of liver metastases is the single most important prognostic factor in single and multivariate analyses for both GI-NETs (carcinoids) and pNETs. Particularly important in the development of liver metastases is the size of the primary tumor. For example, with small intestinal carcinoids, which are the most common cause of the carcinoid syndrome due to metastatic disease in the liver (Table 113-2), metastases occur in 15–25% if the tumor is <1 cm in diameter, 58–80% if it is 1–2 cm in diameter, and >75% if it is >2 cm in diameter. Similar data exist for gastrinomas and other pNETs; the size of the primary tumor is an independent predictor of the development of liver metastases.

TABLE 113-5 PROGNOSTIC FACTORS IN NEUROENDOCRINE TUMORS

I. Both GI-NETs (carcinoids) and pNETs
Symptomatic presentation (p <.05)
Presence of liver metastases (*p* <.001)
Extent of liver metastases (*p* <.001)
Presence of lymph node metastases (*p* <.001)
Development of bone or extrahepatic metastases (*p* <.01)
Depth of invasion (*p* <.001)
Rapid rate of tumor growth
Elevated serum alkaline phosphatase levels (*p* = .003)
Primary tumor site (*p* <.001)
Primary tumor size (*p* <.005)
High serum chromogranin A level (*p* <.01)
Presence of one or more circulating tumor cells (*p* <.001)
Various histologic features
Tumor differentiation (*p* <.001)
High growth indices (high Ki-67 index, PCNA expression)
High mitotic counts (*p* <.001)
Necrosis present
Presence of cytokeratin 19 (*p* <.02)
Vascular or perineural invasion
Vessel density (low microvessel density, increased lymphatic density)
High CD10 metalloproteinase expression (in series with all grades of NETs)
Flow cytometric features (i.e., aneuploidy)
High VEGF expression (in low-grade or well-differentiated NETs only)
WHO, ENETS, AJCC/UICC, and grading classification
Presence of a pNET rather than GI-NET associated with poorer prognosis (*p* = .0001)
Older age (*p* <.01)
II. GI-NETs (Carcinoids)
Location of primary: appendix < lung, rectum < small intestine < pancreas
Presence of carcinoid syndrome
Laboratory results (urinary 5-HIAA levels [*p* <.01], plasma neuropeptide K [*p* <.05], serum chromogranin A [*p* <.01])
Presence of a second malignancy
Male sex (*p* <.001)
Molecular findings (TGF-α expression [*p* <.05], chr 16q LOH or gain chr 4p [*p* <.05])
WHO, ENETS, AJCC/UICC, and grading classification
Molecular findings (gain in chr 14, loss of 3p13 [ileal carcinoid], upregulation of Hoxc6)
III. pNETs
Location of primary: duodenal (gastrinoma) better than pancreatic
Ha-*ras* oncogene or p53 overexpression
Female gender
MEN 1 syndrome absent
Presence of nonfunctional tumor (some studies, not all)
WHO, ENETS, AJCC/UICC, and grading classification
Various histologic features: IHC positivity for c-KIT, low cyclin B1 expression (*p* <.01), loss of PTEN or of tuberous sclerosis-2 IHC, expression of fibroblast growth factor-13
Laboratory findings (increased chromogranin A in some studies; gastrinomas—increased gastrin level)
Molecular findings (increased HER2/*neu* expression [*p* = .032], chr 1q, 3p, 3q, or 6q LOH [*p* = .0004], EGF receptor overexpression [*p* = .034], gains in chr 7q, 17q, 17p, 20q; alterations in the VHL gene [deletion, methylation]; presence of FGFR4-G388R single-nucleotide polymorphism)

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; AJCC, American Joint Committee on Cancer; chr, chromosome; EGF, epidermal growth factor; FGFR, fibroblast growth factor receptor; GI-NET, gastrointestinal neuroendocrine tumor; IHC, immunohistochemistry; Ki-67, proliferation-associated nuclear antigen recognized by Ki-67 monoclonal antibody; LOH, loss of heterozygosity; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumors; PCNA, proliferating cell nuclear antigen; pNET, pancreatic neuroendocrine tumor; PTEN, phosphatase and tensin homologue deleted from chromosome 10; TGF-α, transforming growth factor α; TNM, tumor, node, metastasis; UICC, International Union Against Cancer; VEGF, vascular endothelial growth factor; WHO, World Health Organization.