MEN1, occurring in 44% of patients, followed by mutations in 43% of patients in genes encoding for two subunits of a transcription/chromatin remodeling complex consisting of DAXX (death-domain-associated protein) and ATRX (α-thalassemia/mental retardation syndrome X-linked) and in 15% of patients in the mTOR pathway. The presence of a number of these molecular alterations in pNETs or GI-NETs (carcinoids) correlates with tumor growth, tumor size, and disease extent or invasiveness and may have prognostic significance (Table 113-5).

GI-NETs (CARCINOIDS) AND CARCINOID SYNDROME

CHARACTERISTICS OF THE MOST COMMON GI-NETs (CARCINOIDS)

Appendiceal NETs (Carcinoids) Appendiceal NETs (carcinoids) occur in 1 in every 200–300 appendectomies, usually in the appendiceal tip, have an incidence of 0.15/100,000 per year, comprise 2–5% of all GI-NETs (carcinoids), and comprise 32–80% of all appendiceal tumors. Most (i.e., >90%) are <1 cm in diameter without metastases in older studies, but more recently, 2–35% have had metastases (Table 113-3). In the SEER data of 1570 appendiceal carcinoids, 62% were localized, 27% had regional metastases, and 8% had distant metastases. The risk of metastases increases with size, with those <1 cm having a 0 to <10% risk of metastases and those >2 cm having a 25–44% risk. Besides tumor size, other important prognostic factors for metastases include basal location, invasion of mesoappendix, poor differentiation, advanced stage or WHO/ENETS classification, older age, and positive resection margins. The 5-year survival is 88–100% for patients with localized disease, 78–100% for patients with regional involvement, and 12–28% for patients with distal metastases. In patients with tumors <1 cm in diameter, the 5-year survival is 95–100%, whereas it is 29% if tumors are >2 cm in diameter. Most tumors are well-differentiated G1 tumors (87%) (Table 113-4), with the remainder primarily well-differentiated G2 tumors (13%); poorly differentiated G3 tumors are uncommon (<1%). Their percentage of the total number of carcinoids decreased from 43.9% (1950–1969) to 2.4% (1992–1999). Appendiceal goblet cell (GC) NETs (carcinoids)/carcinomas are a rare subtype (<5%) that are mixed adeno-neuroendocrine carcinomas. They are malignant and are thought to comprise a distinct entity; they frequently present with advanced disease and are recommended to be treated as adenocarcinomas, not carcinoid tumors.

SMALL INTESTINAL NETs (CARCINOIDS)

Small intestinal (SI) NETs (carcinoids) have a reported incidence of 0.67/100,000 in the United States, 0.32/100,000 in England, and 1.12/100,000 in Sweden and comprise >50% of all SI tumors. There is a male predominance (1.5:1), and race affects frequency, with a lower frequency in Asians and greater frequency in African Americans. The mean age of presentation is 52–63 years, with a wide range (1–93 years). Familial SI carcinoid families exist but are very uncommon. These are frequently multiple; 9–18% occur in the jejunum, 70–80% are present in the ileum, and 70% occur within 6 cm (2.4 in.) of the ileocecal valve. Forty percent are <1 cm in diameter, 32% are 1–2 cm, and 29% are >2 cm. They are characteristically well differentiated; however, they are generally invasive, with 1.2% being intramucosal in location, 27% penetrating the submucosa, and 20% invading the muscularis propria. Metastases occur in a mean of 47–58% (range 20–100%). Liver metastases occur in 38%, to lymph nodes in 37% and more distant in 20–25%. They characteristically cause a marked fibrotic reaction, which can lead to intestinal obstruction. Tumor size is an important variable in the frequency of metastases. However, even small NETs (carcinoids) of the small intestine (<1 cm) have metastases in 15–25% of cases, whereas the proportion increases to 58–100% for tumors 1–2 cm in diameter. Carcinoids also occur in the duodenum, with 31% having metastases. Duodenal tumors <1 cm virtually never metastasize, whereas 33% of those >2 cm had metastases. SI NETs (carcinoids) are the most common cause (60–87%) of the carcinoid syndrome and are discussed in a later section (Table 113-7). Important prognostic factors are listed in (Table 113-5), and particularly important are the tumor extent, proliferative index by grading, and stage (Table 113-4). The overall survival at 5 years is 55–75%; however, it varies markedly with disease extent, being 65–90% with localized disease, 66–72% with regional involvement, and 36–43% with distant disease.

TABLE 113-7 CLINICAL CHARACTERISTICS IN PATIENTS WITH CARCINOID SYNDROME

	Percentage (Range)	
	At Presentation	During Course of Disease
Symptoms/signs		
Diarrhea	32–93%	68–100%
Flushing	23–100%	45–96%
Pain	10%	34%
Asthma/wheezing	4–14%	3–18%
Pellagra	0–7%	0–5%
None	12%	22%
Carcinoid heart disease present	11–40%	14–41%
Demographics		
Male	46–59%	46–61%
Age		
Mean	57 yrs	59.2 yrs
Range	25–79 yrs	18–91 yrs
Tumor location		
Foregut	5–14%	0–33%
Midgut	57–87%	60–100%
Hindgut	1–7%	0–8%
Unknown	2–21%	0–26%

Rectal NETs (Carcinoids) Rectal NETs (carcinoids) comprise 27% of all GI-NETs (carcinoids) and 16% of all NETs and are increasing in frequency. In the U.S. SEER data, they currently have an incidence of 0.86/100,000 per year (up from 0.2/100,000 per year in 1973) and represent 1–2% of all rectal tumors. They are found in approximately 1 in every 1500/2500 proctoscopies/colonoscopies or 0.05–0.07% of individuals undergoing these procedures. Nearly all occur between 4 and 13 cm above the dentate line. Most are small, with 66–80% being <1 cm in diameter, and rarely metastasize (5%). Tumors between 1 and 2 cm can metastasize in 5–30%, and those >2 cm, which are uncommon, in >70%. Most invade only to the submucosa (75%), with 2.1% confined to the mucosa, 10% to the muscular layer, and 5% to adjacent structures. Histologically, most are well differentiated (98%) with 72% ENETS/WHO grade G1 and 28% grade G2 (Table 113-4). Overall survival is 88%; however, it is very much dependent of the stage, with 5-year survival of 91% for localized disease, 36–49% for regional disease, and 20–32% for distant disease. Risk factors are listed in Table 113-5 and particularly include tumor size, depth of invasion, presence of metastases, differentiation, and recent TNM classification and grade.

Bronchial NETs (Carcinoids) Bronchial NETs (carcinoids) comprise 25–33% of all well-differentiated NETs and 90% of all the poorly differentiated NETs found, likely due to a strong association with smoking. Their incidence ranges from 0.2 to 2/100,000 per year in the United States and European countries and is increasing at a rate of 6% per year. They are slightly more frequent in females and in whites compared with those of Hispanic/Asian/African descent, and are most commonly seen in the sixth decade of life, with a younger age of presentation for typical carcinoids (45 years) compared to atypical carcinoids (55 years).

A number of different classifications of bronchial GI-NETs (carcinoids) have been proposed. In some studies, they are classified into four categories: typical carcinoid (also called bronchial carcinoid tumor, Kulchitsky cell carcinoma I [KCC-I]), atypical carcinoid (also called well-differentiated neuroendocrine carcinoma [KC-II]), intermediate small-cell neuroendocrine carcinoma, and small-cell neuroendocarcinoma