18 - 89 Gastrointestinal Neuroendocrine Tumors

89 Gastrointestinal Neuroendocrine Tumors

TABLE 88-4 Combination Chemotherapy Regimens That Have an Impact on Survival in Stage IV Disease NO. OF PATIENTS MEDIAN OVERALL SURVIVAL (MONTHS) STUDY DESIGN (AUTHOR/REF) Gemcitabine + erlotinib vs gemcitabine (Moore et al: J Clin Oncol 26:1960, 2007)

6.24 vs 5.91 (HR 0.82; 95% CI 0.69–0.99;

p = .038) FOLFIRINOX (folinic acid + 5-fluorouracil + irinotecan + oxaliplatin) vs gemcitabine (Conroy et al: N Engl J Med 364:1817, 2011)

11.1 vs 6.8 (HR 0.57; 95% CI 0.45–0.70;

p <.001) Nab-paclitaxel + gemcitabine vs gemcitabine (Von Hoff et al: N Eng J Med 369:1691, 2013)

8.5 vs 6.7 (HR 0.72; 95% CI 0.62–0.83;

p <.001a Nanoliposomal irinotecan, 5-fluorouracil + folinic acid vs nanoliposomal irinotecan monotherapy vs 5-fluorouracil + folinic acid (Wang-Gillam et al: Lancet 387:545, 2015)

6.1 vs 4.2 (HR 0.67; 95% CI 0.49–0.92;

p = .012b) NALIRIFOX (nanoliposomal irinotecan, 5-fluorouracil, folinic acid, oxaliplatin) vs nab-paclitaxel and gemcitabine (Wainberg et al: Lancet 402:1272, 2023)

11.1 vs 9.2 (HR 0.83; 95% CI 0.70–0.99;

p = .036) aThe 2-year survival rate with this regimen is 9%, and the 3+ year rate is 4%. Other studies have not reported on these parameters. bHR is for nanoliposomal irinotecan + 5-fluorouracil + folinic acid vs 5-fluorouracil + folinic acid. Abbreviations: CI, confidence interval; HR, hazard ratio. PART 4 Oncology and Hematology cancers); however, agents that target more common KRAS muta tions (G12D, G12V, G12R) are being evaluated in clinical trials and have high

potential to become part of standard treatment algorithms in the future. Other rare actionable alterations include oncogenic fusions in RET, ALK, MET, NRG-1, ROS, and BRAF V600E mutations, for which therapeutic agents are available and are in clinical trials. MAINTENANCE THERAPY FOR PATIENTS RESPONDING

TO TREATMENT For patients with a germline BRCA1 or BRCA2 mutation whose metastatic pancreatic cancer has not grown during an initial plati num-based regimen, the PARP inhibitor olaparib has been shown to improve progression-free survival (7.4 vs 3.8 months; HR 0.53; 95% CI 0.35–0.82; p = .004) and maintenance of quality of life, both relative to placebo. ■ ■FUTURE DIRECTIONS Multiple novel therapies are under development in pancreatic cancer. Immunotherapy using personalized neoantigen vaccines or using an antigenic target such as a “public” or shared neoantigen such as KRAS has demonstrated early promise following resection of pancreatic cancer as an adjunct to standard chemotherapy. Mid-phase trials are planned/underway to further explore these signals. KRAS has hereto fore been considered nondruggable; however, developments in organic chemistry, biosynthesis, and other innovations have led to a series of therapeutics directly targeting KRAS with promise that these agents in the proximate future will be integrated as part of standard therapy for pancreatic cancer. Multiple therapeutic approaches targeting the tumor immune microenvironment are being explored, capitalizing on an increased understanding of the pathobiology of this cancer. Other important developments include innovation in clinical trial design, novel approaches to screening and surveillance utilizing “liquid” bio markers (incorporating DNA fragments, methylation, and proteomic profiles), and other technologic developments. Acknowledgment Thank you to the American Joint Committee on Cancer for providing the tables. ■ ■FURTHER READING Conroy T et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817, 2011.

Conroy T et al: FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 379:2395, 2018. Golan T et al: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 381:317, 2019. Hu ZI, O’Reilly EM: Therapeutic developments in pancreatic cancer. Nat Rev Gastroenterol Hepatol 21:7, 2024. Hruban RJ et al: Genetic progression in the pancreatic ducts. Am J Pathol 156:1821, 2000. Park W et al: Pancreatic cancer: A review. JAMA 326:851, 2021. Rahib L et al: Evaluation of pancreatic cancer clinical trials and benchmarks for clinically meaningful future trials: A systemic review. JAMA Oncol 2:1209, 2016. Rawla P et al: Epidemiology of pancreatic cancer: Global trends, etiology, and risk factors. World J Oncol 10:10, 2019. Solomon S et al: Inherited pancreatic cancer syndromes. Cancer J 18:485, 2012. Von Hoff D et al: Increased survival in pancreatic cancer with nabpaclitaxel plus gemcitabine. N Engl J Med 369:1691, 2013. Wainberg Z et al: NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adeno carcinoma (NAPOLI 3): A randomised, open-label, phase 3 trial. Lancet 402:1272, 2023. Yuan C et al: Diabetes, weight change, and pancreatic cancer risk. JAMA Oncol 6:e202948, 2020. Matthew H. Kulke

Gastrointestinal

Neuroendocrine Tumors Gastrointestinal (GI) neuroendocrine tumors (NETs) can be broadly grouped according to their site of origin as either extrapancreatic NETs, historically called carcinoid tumors, or pancreatic NETs. While NETs can pursue a broad range of clinical behaviors, they classically follow a course that is more indolent than many other malignancies. NETs also have the

ability to synthesize peptides, growth factors, and bioactive amines that may be ectopically secreted, giving rise to a range of unique clinical syndromes. INCIDENCE AND PREVALENCE The diagnosed incidence of NETs has been steadily increasing over the past several decades. An analysis of data from the Surveillance, Epidemi ology, and End Results (SEER) program, comprising population-based data in the United States from 1973 to 2012, showed that the overall inci dence had increased 6.4-fold over this time period and that the estimated prevalence of patients who had been diagnosed with a NET was >170,000. Gastroenteropancreatic neuroendocrine tumors comprise the majority of neuroendocrine tumors, and recent analyses suggest the incidence in this subgroup has risen proportionately and continues to rise (Fig. 89-1). These same studies have also found that overall survival durations for patients with NETs have improved significantly over time. The increasing incidence and improved survival durations for patients with NETs likely reflect, at least in part, advances in both diagnosis and treatment. While environmental or other factors leading to an increased inci dence of NETs cannot be excluded, common cancer risk factors such as tobacco or alcohol use and dietary patterns have not been clearly linked to NET development. A minority of NETs develop in the context of autosomal inherited genetic syndromes associated with mutations in specific tumorsuppressor genes. The most common of these is multiple endocrine neoplasia type 1 (MEN 1), due to mutation and loss of function of the menin gene, located on chromosome 11q13 (Chap. 400). Patients

Age adjusted incidence of neuroendocrine tumors in U.S. (per 100,000) Age adjusted incidence of all malignancies in the U.S. (per 100,000) A B

FIGURE 89-1 Incidence of gastroenteropancreatic neuroendocrine tumors (NETs). The incidence of gastroenteropancreatic neuroendocrine tumors has been increasing over the past several decades, an observation that has been attributed in part to improved diagnosis and classification. (Adapted from Z Xu et al: Epidemiologic trends of and factors associated with overall survival for patients with gastroenteropancreatic neuroendocrine tumors in the United States. JAMA Network Open 4:e2124750, 2021, Figure 1A.) with MEN 1 are at risk for developing pancreatic NETs as well as hyperparathyroidism and pituitary adenomas; less commonly, they may develop bronchial and thymic NETs. Other inherited syndromes associated with NETs include von Hippel–Lindau disease (VHL), von Recklinghausen’s disease (neurofibromatosis type 1), and tuberous sclerosis (Bourneville’s disease). Inherited mutations in the VHL gene, located on chromosome 3p25, are associated with the development of cerebellar hemangioblastomas, renal cancer, and pheochromocytomas and, less commonly, pancreatic NETs. Mutations in neurofibromin (NF1) are associated with neurofibromatosis (von Recklinghausen’s disease); patients with neurofibromatosis are at risk of developing both pancreatic and extrapancreatic NETs. Tuberous sclerosis is caused by mutations that alter either hamartin (TSC1) or tuberin (TSC2). Both hamartin and tuberin function as inhibitors of the phosphatidylinositol 3-kinase and the mechanistic target of rapamycin (mTOR) signaling cascades, and pancreatic NETs have been reported in these patients. Rare cases of familial small intestine NETs have also been reported; in these cases, multiple synchronous tumors generally arise within the small intestine. A characteristic inherited mutation has not been iden tified to date in the majority of these cases. HISTOLOGIC CLASSIFICATION AND MOLECULAR FEATURES The histologic features of NETs vary widely and are one of the most important determinants of both clinical behavior and treatment. NETs are classified based on the degree tumor differentiation (well or poorly TABLE 89-1 Histologic Classification of Neuroendocrine Tumors CLASSIFICATION DIFFERENTIATION GRADE MITOTIC COUNT KI-67 Neuroendocrine tumor Well

differentiated Low grade (grade 1) <2 per 10 HPF <3% Neuroendocrine tumor Well differentiated Intermediate grade (grade 2) 2–20 per 10 HPF 3–20% Neuroendocrine tumor Well differentiated High grade (grade 3)

> 20 per 10 HPF 20% Neuroendocrine carcinoma Poorly differentiated High grade (grade 3) 20 per 10 HPF 20% Abbreviation: HPF, high-power field.

differentiated), as assessed by a pathologist, and tumor grade (grades 1–3) (Table 89-1). Tumor grade closely correlates with mitotic count and Ki-67 proliferative index. Classic, well-differentiated NETs are composed of monotonous sheets of small round cells with uniform nuclei and only rare mitoses. Immunocytochemical staining for chromogranins and synaptophysin is typical. Ultrastructurally, these tumors contain electron-dense neurosecretory granules containing peptides and bio active amines that may be ectopically secreted, giving rise to a range of clinical syndromes. These classic well-

differentiated NETs have low-grade features and gener ally have a mitotic index of <2 mitoses per 10 high-power fields (HPFs) and a Ki-67 proliferative index of <3%. Less commonly, well-differentiated NETs have an intermedi ate histologic grade and pursue a somewhat more aggres sive clinical course. Intermediate-grade tumors typically have a mitotic count of 2–20 per 10 HPF and a mitotic index of 3–20%. Well-differentiated high-grade tumors are rare and have mitotic counts that exceed 20 per 10 HPF and a Ki-67 proliferative index of >20%. Poorly dif ferentiated high-grade tumors form the most clinically aggressive category; prognosis and treatment for these tumors differ markedly from their well-differentiated counterparts.

CHAPTER 89 Whole exome sequencing of sporadic pancreatic NETs has shown that the most frequently altered gene was MEN1, occurring in 44% of tumors. In addition, 43% of tumors had mutations in genes encoding two sub units of a transcription/chromatin remodeling complex consisting of DAXX (death-domain-associated protein) and ATRX (α-thalassemia/mental retardation syndrome X-linked). Mutations in genes associated with the mTOR pathway were identified in 15% of tumors. In contrast, recurrent mutations in extrapancreatic NETs appear to be rare. In one study that evaluated 180 small intestinal NETs using a combination of whole exome and more targeted genome-sequencing analysis, recurrent mutations were only observed in the CDKN1B gene (cyclin-dependent kinase inhibitor 1B [p27Kip1]) in 8% of cases. Loss of chromosome 18 is a common finding in small-bowel NETs. Small-intestinal GI carcinoids commonly have epigenetic changes; however, the clinical significance of these alterations remains uncertain. Gastrointestinal Neuroendocrine Tumors CLINICAL PRESENTATION AND MANAGEMENT OF LOCALIZED PANCREATIC NEUROENDOCRINE TUMORS Pancreatic NETs have been subcategorized as either “functional,” meaning associated with symptoms of hormone secretion, or non functional, in which case they may be clinically silent until they cause anatomic symptoms. The clinical presentation of functional pancreatic NETs depends on the type of hormone secreted and can sometimes lead to dramatic clinical presentations (Table 89-2). The most com mon functional pancreatic NETs are insulinomas, followed in inci dence by glucagonomas and gastrinomas. Pancreatic NETs secreting other hormones, including somatostatin, vasoactive intestinal pep tide (VIP), adrenocorticotropic hormone (ACTH), and parathyroid hormone (PTH), have also been described but are uncommon.

Only ~20% of pancreatic NETs are associated with symptoms of hormone

TABLE 89-2 Clinical Presentation and Management of Secretory Syndromes Associated with Neuroendocrine Tumors TREATMENT OPTIONS TO CONTROL SECRETORY SYMPTOMS CLINICAL SYMPTOMS AND MANIFESTATIONS Pancreatic Neuroendocrine Tumors Gastrinoma (generally located in “gastrinoma triangle”) Zollinger-Ellison syndrome: gastroesophageal reflux, peptic ulcer disease, diarrhea Proton pump inhibitors, somatostatin analogues Insulinoma Hypoglycemia leading to confusion, lethargy, coma; weight gain Diazoxide, everolimusa Glucagonoma Skin rash (necrolytic migratory erythema), glucose intolerance, weight loss Somatostatin analogues VIPoma Verner-Morrison syndrome: watery diarrhea, hypokalemia, achlorhydria Somatostatin analogues ACTHoma Cushing’s syndrome: hyperglycemia, weight gain, hypokalemia Ketoconazole, metyrapone, consider adrenalectomy PART 4 Oncology and Hematology Extrapancreatic Gastrointestinal Neuroendocrine Tumors Typically in setting of advanced disease from small intestine or appendiceal primary tumors Carcinoid syndrome: flushing, diarrhea, rightsided valvular heart disease, mesenteric fibrosis Somatostatin analogues, telotristat ethyl aSuccessful use of monoclonal anti-insulin receptor antibodies to treat insulininduced hypoglycemia has been reported but remains investigational. Abbreviations: ACTH, adrenocorticotropic hormone; VIP, vasoactive intestinal peptide. hypersecretion; the majority of pancreatic NETs are “nonfunctional” and are diagnosed either incidentally or after patients present with abdominal pain, weight loss, or other anatomic symptoms related to tumor bulk. ■ ■GASTRINOMA Patients with gastrinoma typically present with Zollinger-Ellison syn drome (ZES) (Chap. 335). The most common symptoms associated with this syndrome are abdominal pain, diarrhea, gastroesophageal reflux disease (GERD), and peptic ulcer disease. Peptic ulcer disease manifesting as multiple ulcers with associated diarrhea is a classic pre sentation. Up to 25% of patients with ZES have MEN 1, and a diagnosis of gastrinoma should prompt a family history as well as an assessment for concurrent hyperparathyroidism. Fasting hypergastrinemia is a nearly universal finding in patients with gastrinoma. Importantly, however, proton pump inhibitors (PPIs) can suppress acid secretion sufficiently to cause hypergastrinemia and can confound the diagno sis. Achlorhydria, usually in the context of chronic atrophic gastritis, will also elevate serum gastrin levels but can usually be easily distin guished from gastrinoma given the absence of other evidence of acid hypersecretion. While often classified as pancreatic NETs, the majority of gastri nomas in fact arise in the “gastrinoma triangle,” an anatomic region bounded by the duodenum, pancreas, and confluence of the cystic and common bile ducts. Most gastrinomas (50–90%) in sporadic ZES arise in the duodenum. They are frequently small and may be dif ficult to localize. Imaging studies generally include either computed tomography (CT) or magnetic resonance imaging (MRI); endoscopic ultrasound or somatostatin scintigraphy may also be helpful. PPIs are generally highly effective in the treatment of symptoms related to gastrinoma and are considered the initial treatment of choice. Rapid resolution of both abdominal pain and diarrhea related to acid hypersecretion is common. Somatostatin analogues may also be helpful

in controlling symptoms in refractory cases. Once symptoms are con trolled, surgical resection is generally recommended for patients with sporadic gastrinomas, both to eliminate the cause of gastrin secretion and to decrease the risk of developing metastatic disease. The tech nique used for resection depends in large part on the precise location of the tumor. In some cases where preoperative imaging is not success ful but a diagnosis is strongly suspected, exploratory laparotomy with intraoperative ultrasound may be undertaken. In gastrinoma patients who have

underlying MEN 1, tumors are generally small and multiple; the role of routine surgery in this setting remains more controversial but generally is still recommended in patients with larger tumors mea suring ≥1.5–2 cm in diameter. ■ ■INSULINOMA Patients with insulinoma generally present with symptoms of hypogly cemia, which may include confusion, headache, disorientation, visual difficulties, irrational behavior, and even coma. In some cases, the diag nosis of insulinoma may not be immediately evident, and patients with insulinoma may initially be diagnosed with psychiatric illnesses that in retrospect were hypoglycemic symptoms. The diagnosis of insulinoma is generally confirmed with elevated fasting insulin levels in conjunc tion with elevated proinsulin and C-peptide. Fasting hypoglycemia can also be caused by severe liver disease, alcoholism, and poor nutrition. Postprandial hypoglycemia may also occur after gastric bypass surgery. Surreptitious use of insulin or hypoglycemic agents may be difficult to distinguish from an insulinoma. Evaluation of proinsulin and C-pep tide levels, both of which should be normal in patients using exogenous insulin, and measurement of sulfonylurea levels in serum or plasma are helpful in such cases. The hypoglycemia associated with insulinomas can be severe and challenging to manage. While somatostatin analogues are usually effec tive in treating symptoms of hormone hypersecretion associated with other types of NETs, they should be used with caution in patients with insulinoma. Somatostatin analogues may suppress counterregulatory hormones, such as growth hormone (GH), glucagon, and catechol amines, and precipitously worsen hypoglycemia. Diazoxide has histori cally been used in the initial management of patients with insulinoma and results in inhibition of insulin release, though it can also be associ ated with side effects including sodium retention and nausea. Evero limus, in addition to its antitumor effect (see below), is effective in improving glycemic control in patients with insulinoma. The benefits of everolimus in this setting may be related both to induction of insulin resistance and a direct antitumor effect. The use of anti-insulin recep tor monoclonal antibodies may be highly effective in treating the hypo glycemia associated with insulinoma, although currently their use for this indication remains investigational Insulinomas may be difficult to localize, as they are less consistently avid on somatostatin scintigraphy than other pancreatic NETs. Insulinomas are also generally small, with the majority measuring <2 cm in diameter. Because of their generally small size, insulinomas are best localized with endoscopic ultrasound (EUS). In the absence of metastatic disease, surgical resection is usu ally recommended. The primary treatment for exophytic or peripheral insulinomas is enucleation. If enucleation is not possible because of invasion or the location of the tumor within the pancreas, then pan creatoduodenectomy for tumors in the head of the pancreas or distal pancreatectomy with preservation of the spleen for smaller tumors not involving splenic vessels may be considered. ■ ■GLUCAGONOMA Patients with glucagonoma most commonly present with a charac teristic dermatitis, called necrolytic migratory erythema (Fig. 89-2). The rash usually involves intertriginous sites, especially in the groin or buttock, and can wax and wane. Other common presenting symptoms of glucagonoma include glucose intolerance and weight loss. The diag nosis of glucagonoma can be confirmed by demonstrating an increased plasma glucagon level, generally in excess of 1000 pg/mL. Somatostatin analogues are usually highly effective as an initial treatment to alleviate the symptoms and rash associated with glucagon hypersecretion. The majority of glucagonomas are large in size at presentation and arise in

FIGURE 89-2 Glucagonoma syndrome. Patients with glucagonoma may present with a classic skin rash, necrolytic migratory erythema (shown). Other presenting symptoms include glucose intolerance and weight loss. the tail of the pancreas. For patients with localized disease, distal pan

createctomy and splenectomy are recommended. A hypercoagulable state has been reported in up to 33% of patients with glucagonoma, and perioperative anticoagulation should generally be employed. ■ ■SOMATOSTATINOMA Patients with somatostatinoma typically present with diabetes mellitus, gallbladder disease, diarrhea, and steatorrhea. Somatostatinomas occur primarily in the pancreas or duodenum, are usually large, and are com monly metastatic at presentation. They are only rarely associated with MEN 1. The diagnosis of somatostatinoma is based on the demonstra tion of elevated plasma somatostatin levels, and as such, the potential benefits of using somatostatin analogues as a treatment for patients with somatostatinoma are questionable. Surgery is recommended for patients with localized disease. ■ ■VIPOMA VIPomas are associated with a distinct syndrome that has been variously called Verner-Morrison syndrome, pancreatic cholera, and WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria). VIP is a 28-amino-acid peptide that mimics the effects of the cholera toxin by stimulating chloride secretion in the small intestine and increasing smooth-muscle contractility, resulting in profound diarrhea. Treatment of dehydration, hypokalemia, and electrolyte losses with fluid and electrolyte replacement is the most critical initial treatment for patients with VIPoma. VIPomas are usually solitary and arise in the pancreatic tail. Elevated plasma levels of VIP are typical but should not be the only basis of the diagnosis of VIPomas because they can occur with some diarrheal states including inflammatory bowel disease, in the setting of small-bowel resection, and radiation enteritis. Chronic surreptitious use of laxatives/diuretics can be particularly difficult to detect clinically. Somatostatin analogues are usually highly effective in controlling the diarrhea; surgical resection is recommended for patients with localized disease. ■ ■OTHER SECRETORY PANCREATIC NETS Pancreatic NETs secreting GH-releasing factor (GRF), calcitonin, ACTH, and PTH-related protein have also been described; it is also

possible for pancreatic NETs to secrete more than one hormone or for the secretory profiles to evolve over time. Gastrinomas, in particular, may evolve and may be associated with secretion of ACTH, resulting in ectopic Cushing’s syndrome. Tumors secreting these hormones may not be as responsive to treatment with somatostatin analogues as the more common pancreatic NETs and the associated hormonal symptoms may cause significant morbidity. As with other pancreatic NETs, patients with localized disease are generally treated with surgi cal resection. In patients with ACTH-secreting tumors, the associated symptoms of Cushing’s syndrome can be alleviated with the use of metyrapone, an agent that directly inhibits cortisol synthesis. Adrenal ectomy may also be considered if resection of the primary tumor is not possible or in the setting of metastatic disease.

■ ■PANCREATIC NETS ARISING IN THE SETTING OF MEN 1 Pancreatic NETs occurring in patients with MEN 1 are typically multiple and often pursue a relatively indolent course. Because of the high probability of multiple tumors, surgical resection of confirmed pancreatic NETs in patients with MEN 1 is usually undertaken with caution given the likelihood of tumors arising in the remaining pan creas if partial pancreatectomy is undertaken as well as the significant morbidities associated with total pancreatectomy. However, for symp tomatic tumors or for growing tumors >2 cm in size, surgical resection may still be considered. CHAPTER 89 ■ ■NONFUNCTIONING PANCREATIC NETS As noted above, the majority of pancreatic NETs are not associated with symptoms of hormone hypersecretion and are considered “non functional.” As a result, they often remain clinically silent and either are diagnosed incidentally or are not diagnosed until widespread, metastatic disease is present resulting in anatomic symptoms. If they are localized at diagnosis, the general treatment recommendation is surgical resection; however, the management of small, asymptomatic

pancreatic NETs is debated. Assuming tumors are low grade, patients with incidentally discovered, low-grade tumors measuring <1 cm in size can generally be safely followed. However, some studies have sug gested that at least some tumors measuring <2 cm in size can pursue a more aggressive course and that surgical resection may be warranted in some cases. Management of small, incidentally discovered, asymptom atic, low-grade pancreatic NETs is therefore based on clinical judge ment, taking into account surgical risk and patient comorbidities. For tumors measuring >2 cm in diameter, metastases pose a significant risk and surgical resection is generally recommended in patients for whom surgery is not contraindicated. Gastrointestinal Neuroendocrine Tumors CLINICAL PRESENTATION AND MANAGEMENT OF LOCALIZED EXTRAPANCREATIC GASTROINTESTINAL NEUROENDOCRINE TUMORS Extrapancreatic GI NETs, historically called carcinoid tumors, may arise virtually anywhere in the GI tract and differ significantly in their clinical characteristics depending on their location. The most common locations for extrapancreatic NETs are the stomach, distal small intes tine, appendix, and rectum. ■ ■GASTRIC NETS Gastric NETs can be categorized into three groups: type 1 (associated with chronic atrophic gastritis); type 2 (associated with gastrinomas and ZES), and type 3 (sporadic, gastric NETs). Type 1 gastric NETs are the most common of the three types. In type 1 gastric NETs, chronic atrophic gastritis results in loss of acid secretion with consequent loss of the negative feedback loop on gastrin-producing cells in the antrum of the stomach. Pernicious anemia is also commonly associated with this condition; classic laboratory findings are a markedly elevated gastrin level and low levels of vitamin B12. Unchecked gastrin secretion in these patients results in hyperplasia of the endocrine cells in the gastric fundus. A typical finding on endoscopy is diffuse endocrine cell hyperplasia with multiple gastric carcinoid tumors (Fig. 89-3). These

PART 4 Oncology and Hematology FIGURE 89-3 Multifocal gastric neuroendocrine tumor. (Courtesy of Christopher Huang, MD, Boston Medical Center.) tumors generally pursue a benign course and can be monitored with serial endoscopy. In cases where tumors continue to grow or become symptomatic, antrectomy to remove the source of gastrin production can result in tumor regression. Type 2 tumors are rare and usually occur in the setting of gastrinoma; as with type 1 gastric NETs, elevated gastrin levels result in diffuse gastric neuroendocrine hyperplasia and multifocal gastric NETs. Resection of the gastrinoma, removing the source of gastrin production, is the treatment of choice. In contrast to type 1 and type 2 gastric NETs, type 3 gastric NETs are generally solitary, arise in the setting of normal gastrin levels, and may pursue a far more aggressive course. For early-stage, smaller tumors, endoscopic or wedge resection may be performed. For larger tumors, partial gastrectomy with lymphadenectomy is recommended. ■ ■NETS OF THE SMALL INTESTINE Small-bowel NETs occur most commonly in the terminal ileum and are notoriously difficult to diagnose at an early stage. One reason for this is that they arise within the muscularis, and their submucosal location makes them difficult to see during routine colonoscopy (Fig. 89-4A). Small-bowel NETs are also often multifocal; multifocal tumors appear to arise independently throughout the small intestine, although the mechanisms underlying this phenomenon remain uncertain. A B FIGURE 89-4 Small intestine neuroendocrine tumor. A. Small intestine neuroendocrine tumors arising in submucosal location. The submucosal location of small intestine neuroendocrine tumors, together with their location beyond the ileocecal valve in the terminal ileum, can make endoscopic detection challenging. B. Classic “spoke and wheel” appearance of calcified mesenteric mass associated with small intestine primary neuroendocrine tumor. Mesenteric fibrosis commonly leads to intermittent obstructive symptoms and can also lead to ischemia when the mesenteric vasculature is involved. (Fig. B: Courtesy of Christina LeBedis,

MD, Boston Medical Center.)

Small-bowel NETs are often associated with desmoplasia and mes enteric fibrosis, likely as a result of fibroblast proliferation stimulated by tumor serotonin secretion. Mesenteric fibrosis frequently results in intermittent small-bowel obstruction and, in some cases, bowel ischemia due to involvement of the mesenteric vessels. Patients may experience symptoms of intermittent abdominal pain and associated diarrhea, sometimes for months or years before diagnosis, that because of the difficulty in diagnosis are often attributed to irritable bowel syn drome. One classic finding that can aid in diagnosis is that the lymph node metastases associated with small intestine NETs are usually larger than the primary tumor and may be calcified, which, together with the tethering of the small intestine caused by the associated fibrosis, results in a classic “spoke and wheel” appearance on CT (Fig. 89-4B). Surgical resection of the primary tumor and associated metastases is recommended when feasible and is performed with curative intent when distant metastatic disease is not already present. Resection should also be considered in patients with metastatic disease experi encing intermittent obstruction or abdominal discomfort thought to be related to the primary tumor or associated mesenteric disease. Some have also advocated the routine resection of asymptomatic small-bowel primary tumors in patients with distant metastatic disease, with the rationale that this may be a way to prevent the future development of fibrosis and obstruction and preempt the development of unresectable disease due to tumor involvement of the mesenteric vessels. However, the available data on the benefits of resecting an asymptomatic primary tumor in this context are conflicting. Some studies have suggested that this practice results in an overall survival benefit, but the retrospective nature of these studies makes the data difficult to interpret given the high potential for selection bias in patients taken to surgery compared with those who were not. Other studies have suggested that prophy lactic primary tumor resection confers no survival benefit and that surgery can be safely delayed until it is indicated based on the develop ment of symptoms. ■ ■NETS OF THE APPENDIX NETs are one of the most common tumors arising in the appendix. They are typically discovered incidentally in younger individuals undergoing appendectomy for acute appendicitis and not uncom monly are identified only at the time of pathology review. While the unexpected diagnosis of an appendiceal NET in such situations can cause considerable anxiety, in the majority of cases, the prognosis is excellent. Indeed, the clinical behavior of appendiceal NETs has been inferred from multiple large retrospective surgical series that suggest that the risk of lymph node or distant metastases from appendiceal NETs with well-differentiated histology and a tumor diameter measur ing <2 cm is extremely low. In such cases, appendectomy alone is felt to be a sufficient surgical procedure. In contrast, the risk of metastases for tumors measuring 2–3 cm is ~20–30% and is even greater for tumors measuring >3 cm. For patients with larger tumors, more formal staging studies with either

cross-sectional imaging or somatostatin scintigraphy are generally recommended to assess for distant metastases, and a subsequent right colectomy to remove regional lymph nodes is performed if no distant metastases are observed. Whether right colectomy should be per formed for tumors measuring <2 cm with features such as mesoappen diceal invasion or tumor origin at the appendiceal base, which in some series have suggested a poorer prognosis, remains uncertain. Addi tionally, tumors may arise in which neuroendocrine cells are admixed with mucin-producing cells or cells exhibiting features of frank adeno carcinoma. In such mixed neuroendocrine-adenocarcinoma tumors, sometimes termed “adenocarcinoids,” treatment recommendations are generally dictated by the more aggressive component of the tumor and align with typical

recommendations for colorectal adenocarcinoma. ■ ■RECTAL NETS With the increased use of screening colonoscopy, the diagnosis of rectal NET has also become more common. For unclear reasons, the incidence of rectal carcinoid tumors shows geographic variation. In European studies, they compose up to 14% of all NETs, while in some Asian series (Japan, China, Korea), they compose up to 90% of all NETs. The majority of rectal NETs are small, measuring <1 cm in diameter, and have well-differentiated histology. These tumors rarely metastasize and can usually be safely removed endoscopically with subsequent endoscopic monitoring. In contrast, up to one-third of rectal NETs between 1 and 2 cm are associated with metastases, and those >2 cm, though uncommon, metastasize in >70% of patients. When identified early, these tumors generally require a surgical resec tion. In contrast to NETs of the appendix and small intestine, hormone secretion from rectal NETs, even when metastatic, is exceedingly rare. CLINICAL PRESENTATION, DIAGNOSIS, AND EVALUATION OF PATIENTS WITH METASTATIC NEUROENDOCRINE TUMORS While patients who undergo resection of localized NETs may be at risk of developing tumor recurrence or metastatic disease, postoperative treatment has not yet been shown to alter the risk of recurrence, and systemic adjuvant therapy is not recommended following resection of well-differentiated NETs, as it is for some other cancers. Whether adju vant systemic therapy may be of benefit following resection of highgrade NETs is uncertain, and an approach utilizing platinum-based chemotherapy with or without external-beam radiation, analogous to that used in small-cell carcinoma, is sometimes considered. The evaluation of patients with known or suspected metastatic disease generally includes both standard cross-sectional imaging such as CT or MRI and somatostatin scintigraphy. Somatostatin scintig raphy in this setting is based on the fact that >90% of NETs express somatostatin receptors. Gallium-68 (68GA) dotatate, as well as 68GA DOTATOC and copper-64 dotatate, are all radioligands bound to a somatostatin analogue and can be used as a nuclear medicine tracer to perform positron emission tomography (PET) scanning that is highly sensitive in detecting both primary NETs and metastases (Fig. 89-5). Because of the sensitivity of these approaches, false-positive results can occur due to somatostatin receptor expression in other tissues. Physi ologic uptake in the pancreatic uncinated process is common; uptake can also occur in the setting of sarcoidosis, in meningiomas, and in thyroid goiter or thyroiditis. Standard fluorodeoxyglucose (FDG) PET scans are often negative in well-differentiated NET due to their low metabolic activity but can show uptake in higher-grade tumors; conversely, rates of somatostatin expression tend to be lower in highergrade tumors, and 68GA dotatate scans may be negative in this setting. The utility of blood-based tumor markers in NETs is controversial. The circulating tumor marker chromogranin A is commonly used as a screen for the presence of NETs and also to monitor for both recur rence and progression of disease in patients with known metastases. While chromogranin A is elevated in patients with metastatic NETs, it is neither particularly sensitive nor specific. A broad range of different assays for chromogranin A have also posed challenges in interpreting results in a standardized fashion. Chromogranin A is often elevated in a number of nonmalignant conditions, including in patients with

CHAPTER 89 FIGURE 89-5 Gallium-68 dotatate positron emission tomography (PET) scan demonstrating a small-bowel neuroendocrine tumor and associated mesenteric mass. (Courtesy of Sara Meibom, MD, Boston Medical Center.) Gastrointestinal Neuroendocrine Tumors impaired renal function and in patients who are taking PPIs. Elevated values of chromogranin A should be interpreted with caution in patients in whom a NET is being considered but in whom a diagnosis has not been established. The overall survival durations for patients with metastatic NETs vary significantly, depending on both the primary location of the tumor and the histologic grade. Median

survival durations for patients with well-differentiated NETs have markedly increased in recent years, likely reflecting both earlier diagnoses and improved treatments. For example, in early analyses of the SEER database, the median survival for patients with advanced pancreatic NETs was ~2 years; this had increased to 4 years in a more recent analysis. Similar increases were observed in patients with advanced small intestine NETs, where the median survival for patients with well-differentiated small intestine NETs exceeds 5 years. The sometimes prolonged survival of patients with NETs can make it challenging to determine at what point to initiate treatment. In patients with symptoms of hormone secretion, decisions to initiate therapy are straightforward. In asymptomatic patients, on the other hand, observation off treatment can sometimes be appropriate. Nevertheless, the natural course of NETs is ultimately to progress, and if treatment is not initiated, close monitoring is essen tial to ensure patients maximize access to available treatment options over the course of their disease. MANAGEMENT OF SYMPTOMS OF HORMONE HYPERSECRETION AND THE CARCINOID SYNDROME Patients with advanced NETs may in some cases experience more symptoms from hormone hypersecretion than from tumor bulk. The management of hormonal symptoms associated with pancreatic NETs depends on the hormone being secreted (see above). Patients with GI NETs, particularly those with small intestine or appendiceal primaries, may develop the carcinoid syndrome. Flushing and diarrhea are the two most common symptoms associated with carcinoid syndrome. The characteristic flush is of sudden onset; it is a deep red or violaceous erythema of the upper body, especially the neck and face, often associ ated with a feeling of warmth. Flushes may be precipitated by stress, alcohol, exercise, and certain foods such as cheese. Flushing episodes initially are brief, lasting 2–5 min, though later in the disease course, they may last hours. The diarrhea associated with carcinoid syndrome

Carcinoid tumor Tryptophan Telotristat ethyl Tryptophan hydroxylase Hydroxytryptophan (5-HTP) Aromatic L-amino acid decarboxylase Serotonin (5-HT) 5-HT stored in secretory granules Secretion 5-HT in blood Monoamine oxidase Aldehyde dehydrogenase 5-Hydroxyindolacetic acid (5-HIAA) PART 4 Oncology and Hematology 5-HIAA filtered by kidney Excretion 5-HIAA in urine FIGURE 89-6 Serotonin synthesis and secretion in neuroendocrine tumors. Tryptophan is converted to hydroxytryptophan by tryptophan hydroxylase within the tumor cell and, subsequently, to serotonin (5-HT). Serotonin is subsequently converted to 5-hydroxyindole acetic acid (5-HIAA), which can be measured in a 24-h urine collection and can facilitate the diagnosis of carcinoid syndrome. Telotristat ethyl inhibits tryptophan hydroxylase and can be used as a treatment for carcinoid syndrome. may or may not be associated with flushing and is described as watery in nature. Diarrhea can be profound, sometimes occurring in excess of 10 times daily and is one of the symptoms that most significantly interferes with activities of daily living. Less common manifestations of the carcinoid syndrome include wheezing or asthma-like symptoms. Impaired cognitive function has also been described in particularly advanced cases. The main secretory product implicated in the carcinoid syndrome is serotonin (5-HT). Serotonin is synthesized from tryptophan by the enzyme tryptophan hydroxylase (Fig. 89-6). Up to 50% of dietary tryp tophan can be used in this synthetic pathway by tumor cells, resulting in inadequate supplies for conversion to niacin; hence, some patients develop symptoms of niacin deficiency and pellagra-like lesions. Serotonin has numerous biologic effects, including the stimulation of intestinal secretion, increasing intestinal motility, and the stimulation of fibroblast growth. Other secreted products contributing to carcinoid syndrome symptoms are thought to include histamines and tachyki nins, including substance P. ■ ■DIAGNOSIS AND TREATMENT OF THE CARCINOID SYNDROME While the carcinoid syndrome can develop in patients with NETs from almost any site, it is most commonly

associated with appendiceal or small intestine NETs. In these patients, the syndrome usually develops only after the development of hepatic metastases or retroperitoneal lesions, allowing entry of serotonin and other vasoactive substances into the systemic circulation. While serotonin levels can be measured in plasma, such measurements are frequently highly variable. Evi dence of excess serotonin secretion can be more reliably confirmed by

measuring levels of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA), either in plasma or using a 24-h urine collection. Urine collections can be challenging, and false-positive elevations may occur if the patient is eating serotonin-rich foods (e.g., salmon, eggs). As a result, elevated levels of 5-HIAA are suggestive but not diagnostic of the carcinoid syndrome. Patients with NETs may also experience symptoms of carcinoid syndrome related to other secreted products, including histamine, absent evidence of serotonin secretion. Con versely, patients without NETs may also describe symptoms analogous to carcinoid syndrome but due to other causes. The symptoms associ ated with systemic mastocytosis, in particular, can be easily confused with carcinoid syndrome. The symptoms of carcinoid syndrome, including diarrhea, are generally refractory to standard antidiarrheals or other traditional medications but can often be well controlled with somatostatin analogues (Fig. 89-7). Somatostatin is a 14-amino-acid peptide that inhibits the secretion of a broad range of hormones. Due to its short half-life, administration of somatostatin itself is not therapeutically practical. Longer-acting somatostatin analogues, including octreotide and lanreotide, share an 8-amino-acid binding domain with naturally occurring somatostatin and bind primarily to somatostatin receptor subtypes 2 and 5. Both have been shown to be effective in the treatment of carcinoid syndrome. The presence of somatostatin receptors on NETs is predictive of response to somatostatin analogues and can be easily confirmed with uptake on somatostatin scintigraphy such as 68GA dotatate PET scan. Somatostatin analogue side effects are generally mild. Mild nausea, abdominal discomfort, bloating, and loose stools occur in up to onethird of patients during the first month or two of treatment but usually subsequently subside. Patients with persistent symptoms of bloating or loose stools may be experiencing pancreatic insufficiency associ ated with use of somatostatin analogues; use of pancreatic enzyme supplements can ameliorate these symptoms. Mild glucose intoler ance may also occur due to inhibition of insulin secretion. One of the more significant side effects associated with somatostatin analogues is impaired gallbladder contractility, resulting in delayed gallbladder emptying, and long-term administration of somatostatin analogues has been associated with an increased risk of cholelithiasis. For this reason, patients with advanced NETs in whom surgery is planned and for whom somatostatin analogue therapy is being considered should generally also undergo prophylactic cholecystectomy. Over time, for reasons that remain uncertain, patients receiving somatostatin analogues for symptoms of hormone secretion may become refractory to treatment. Not uncommonly, such patients experience symptom exacerbation toward the final week of each treat ment cycle. Such patients may benefit from an increased frequency of administration (i.e., every 3 weeks) or use of additional short-acting octreotide for breakthrough symptoms. The association between high levels of circulating serotonin and symptoms of the carcinoid syndrome has also led to efforts aiming to directly inhibit serotonin synthesis (Fig. 89-6). This approach was first undertaken in the late 1960s with the drug para-chlorophenylalanine, which was reported to reduce symptoms of carcinoid syndrome but also caused significant central nervous system (CNS) side effects. Telotristat ethyl, a tryptophan hydroxylase inhibitor with minimal CNS penetra tion, was evaluated in a randomized trial that enrolled 135 patients with persistent carcinoid syndrome–related diarrhea while receiving somatostatin analogues. Treatment with telotristat ethyl

was associated with a reduction in bowel movement frequency as well as significant decreases in urinary 5-HIAA compared to placebo, consistent with its mechanism of directly inhibiting serotonin synthesis. Thus, telotristat is a treatment option for patients with carcinoid syndrome who have persistent diarrhea despite treatment with somatostatin analogues. ■ ■CARCINOID CRISIS Carcinoid crisis has been described in the setting of tumor manipula tion during surgery and, less commonly, after other interventions such as hepatic artery embolization or radionuclide therapy. It may also occur as a result of exogenous administration of epinephrine or during

Gly Cys Ala

s s Cys Thr Phe Ser

Native somatostatin-14 D-Phe Cys Phe D-BNAL Cys D-Trp s s s s Lys Cys Thr Thr Cys Thr Octreotide Lanreotide FIGURE 89-7 Somatostatin analogues. Commonly used somatostatin analogues include octreotide and lanreotide, which mirror the molecular structure of human somatostatin and bind to somatostatin receptors on neuroendocrine tumors. Somatostatin analogues inhibit tumoral hormone secretion and also have an antiproliferative effect. Radiolabeled somatostatin analogues such as 177Lu-DOTA-octreotate, shown in the figure, share a similar molecular structure and are used therapeutically. induction of anesthesia. It is most common in patients who already have significant symptoms of carcinoid syndrome and is thought to be caused by a sudden release of biologically active compounds from the tumor. Carcinoid crisis can be life-threatening and can manifest as either profound hypotension or hypertension. Prospective studies on the prevention and management of carcinoid crisis are limited; how ever, somatostatin analogues should be readily available during surgical procedures, and in some cases, continuous prophylactic intravenous administration of somatostatin analogues has been utilized as a way to mitigate risk. ■ ■CARCINOID HEART DISEASE Carcinoid heart disease occurs in approximately two-thirds of patients with the carcinoid syndrome. Carcinoid heart lesions are characterized by plaque-like, fibrous endocardial thickening that classically involves the right side of the heart and often causes retraction and fixation of the leaflets of the tricuspid and pulmonary valves (Fig. 89-8). The fibrosis in carcinoid heart disease is thought to be directly related to exposure of heart valve fibroblasts to high circulating levels of serotonin. Lesions FIGURE 89-8 Carcinoid heart disease. Fibrosis secondary to elevated levels of circulating serotonin classically involves the tricuspid valve, resulting in valve retraction and tricuspid regurgitation.

Asn Phe Lys Phe Trp

Lys

Thr D-Phe Cys Tyr HN HOOC Tyr O D-Trp N N s D-Trp 177Lu s Lys N N Lys Thr Cys Thr Val HOOC COOH 177Lu-DOTA-Tyr3-Octreotate CHAPTER 89 similar to those observed in carcinoid heart disease were observed in patients receiving fenfluramine, a drug also known to increase serotonin signaling, as well as in patients receiving ergot-containing dopamine receptor agonists for Parkinson’s disease. Metabolites of fenfluramine, as well as the dopamine receptor agonists, have high affinity for serotonin receptor subtype 5-HT2B receptors, whose activa tion is known to cause fibroblast mitogenesis and which are normally expressed in heart valve fibroblasts. These observations support the hypothesis that serotonin overproduction in patients with carcinoid

syndrome mediates the valvular changes by activating 5-HT2B receptors in the endocardium. Gastrointestinal Neuroendocrine Tumors Tricuspid regurgitation is a nearly universal feature of carcinoid heart disease; tricuspid stenosis, pulmonary regurgitation, and pulmo nary stenosis may also occur. Left-sided heart disease occurs in <10% of patients and has been associated with the presence of a patent fora men ovale. The preponderance of lesions in the right heart is related directly to the fact that serotonin is secreted by liver metastases or retroperitoneal tumor deposits into the venous circulation and subse quently into the right atrium and right ventricle. The lower incidence of heart disease in the left heart is postulated to be due to the fact that serotonin is metabolized in the pulmonary vasculature before entering the left atrium and ventricle. Among patients with carcinoid syndrome, patients with heart disease exhibit higher levels of serum serotonin and urinary 5-HIAA excretion than patients without heart disease. Treat ment with somatostatin analogues resulting in decreased serotonin secretion does not result in regression of cardiac lesions. Reduction of serotonin levels as a result of treatment with somatostatin analogues or with the tryptophan hydroxylase inhibitor telotristat ethyl seems likely to slow progression of carcinoid heart disease but has not been formally evaluated in clinical trials. Right-sided heart failure in patients with carcinoid heart disease may lead to significant morbidity and mortality. The development of mul tiple new treatments to improve overall disease control in patients with advanced NETs has led to increased interest in valvular replacement, which may result in significant clinical benefit in appropriately selected patients with carcinoid heart disease. The appropriate timing of valve replace ment in such patients can be challenging given the competing desires to perform surgery before the onset of severe right-sided heart failure, which can increase surgical morbidity, and the need to achieve adequate overall tumor control. However, advanced and less invasive techniques, includ ing catheter-based valve replacement, have made valve replacement an increasingly attractive option for patients with this condition.

HEPATIC-DIRECTED THERAPY FOR METASTATIC NETS The liver is one of the most common sites for metastases in patients with NETs and, in some cases, is the only site of metastatic disease. Hepatic-directed therapies can often be effective as a means of control ling, if not eliminating, metastases, particularly in patients who have more indolent tumors with well-differentiated histology. Common approaches for such patients include surgical resection, ablation or embolization, and orthotopic liver transplantation.

For patients with limited hepatic disease whose tumors have welldifferentiated histology, surgical resection is generally considered the preferable option. While data are limited to retrospective series with the consequent risk of selection bias, long-term survival durations and symptomatic improvements reported in select populations of patients undergoing hepatic resection of neuroendocrine liver metastases compare favorably with outcomes associated with other management approaches, and 5-year survival rates approach 90% in some series. In patients in whom anatomy precludes resection or in whom a greater number of lesions are present, radiofrequency ablation or cryoabla tion can also be used, either as a primary treatment modality or as an adjunct to surgical resection. While ablation is considered to be less morbid than hepatic resection, it is generally utilized only in smaller tumors so that zones of ablation are limited. PART 4 Oncology and Hematology In most cases, however, liver metastases are large, multiple, and involve both lobes of the liver. In such cases, the benefit of surgical resection and ablation is limited. Hepatic arterial embolization can be considered in these cases, assuming that extrahepatic disease remains relatively limited and that clinical benefit can be achieved by reduc ing hepatic

tumor bulk. Hepatic artery embolization is based on the principle that tumors in the liver derive most of their blood supply from the hepatic artery, whereas healthy hepatocytes derive most of their blood supply from the portal vein. Multiple different emboliza tion techniques have been explored, ranging from the simple infusion of gel foam powder into the hepatic artery (bland embolization) to the administration of chemotherapy or chemotherapy-eluting beads into the hepatic artery (chemoembolization) or the intra-arterial admin istration of radioisotope-tagged microspheres (radioembolization). Limited data suggest an optimal approach to embolization, and few studies have compared these approaches directly. Tumor response rates with all of these approaches generally exceed 50%. Specific approaches are therefore often tailored to the patient, taking into account tumor location, overall tumor burden, and comorbidities. Bland emboliza tion, for example, may be associated with less morbidity, whereas che moembolization or radioembolization may result in longer durations of response. The role of orthotopic liver transplantation for the treatment of NETs remains uncertain. Data from available institutional series sug gest that a small number of highly selected patients may achieve longterm survival. However, 5-year overall median survival durations in most series are ~50%, and the majority of patients undergoing hepatic transplantation develop tumor recurrence. Additionally, the wide spread utility of hepatic transplantation is limited by organ availability. Decisions regarding proceeding with transplantation in patients with advanced NETs are therefore highly individualized. SYSTEMIC TREATMENT TO CONTROL TUMOR GROWTH While hepatic-directed therapies can be effective in the management of patients with liver-predominant disease, a majority of patients will either present with or ultimately develop more widespread metastases. A number of systemic treatment options have been developed and can be effective in treating such patients. These options include treatment with traditional somatostatin analogues, peptide receptor radioligand therapy, traditional cytotoxic chemotherapy, and an increasing array of molecularly targeted therapies targeting the mTOR or vascular endo thelial growth factor (VEGF) pathways (Table 89-3). The choice and sequence of therapy depend in part on the type of tumor, the extent of disease, and patient symptoms and comorbidities.

TABLE 89-3 Selected Randomized Trials of Therapeutic Agents for the Treatment of Advanced Neuroendocrine Tumors (NETs) NUMBER OF PATIENTS PROGRESSION-FREE SURVIVAL TUMOR TYPE Pancreatic and Extrapancreatic NETs Lanreotide vs placebo (CLARINET)

65% vs 33% at 2 years

(p <.001) 177-Lutetium dotatate vs octreotide (NETTER 2) 226 (limited to histologic grade 2 and 3 tumors) 22.8 vs 8.5 months (p <.0001) Cabozantinib vs placebo (CABINET) 298 (203 extrapancreatic NETs [epNET] and 95 pancreatic NETs [pNET]) 8.5 vs 4 months (epNET);

13.8 vs 4.5 months (pNET)

(p <.0001 for both cohorts) Pancreatic NET Everolimus vs placebo (RADIANT 3)

11 vs 4.6 months (p <.001) Sunitinib vs placebo

11.4 vs 5.5 months (p <.001) Surufatinib vs placebo

10.9 vs 3.7 months (p = .001) Temozolomide/ capecitabine vs temozolomide

22.7 vs 14.4 months (p = .021) Extrapancreatic NET Octreotide vs placebo (PROMID)

14.3 vs 6 monthsa Everolimus + octreotide vs octreotide (RADIANT 2)

16.4 vs 11.3 months Everolimus vs placebo (RADIANT 4)

11 vs 3.9 months Surufatinib vs placebo

9.2 vs 3.8 months (p <.0001) Pazopanib vs placebo

11.6 vs 8.5 months (p <.0005) 177-Lutetium dotatate vs octreotide (NETTER 1)

65.2 vs 10.8% at 20 months (p <.001) aTime to tumor progression. ■ ■SOMATOSTATIN ANALOGUES Somatostatin analogues were originally developed as a treatment to reduce hormone secretion in NETs but are also effective in slowing tumor growth. The biologic mechanisms underlying this effect remain uncertain, but clinical studies have been definitive. The first of these studies, the PROMID study, randomized patients with metastatic small-intestinal NET to receive either octreotide LAR at a dose of 30 mg monthly or placebo. The median time to tumor progression in patients receiving octreotide was 14 months compared to only 6 months for patients receiving placebo. Because the study was limited to patients with small-intestinal NET, the generalizability of these results to patients with NETs of other origins, including pancreatic NET, was initially uncertain. This question was ultimately addressed by the phase 3 CLARINET trial, which compared lanreotide, a soma tostatin analogue that is similar to octreotide in its somatostatin receptor–binding affinities, to placebo in 204 patients with a range of advanced well- or moderately differentiated gastroenteropancreatic NETs. Progression-free survival duration at 2 years was 65% in patients receiving lanreotide and 33% in patients receiving placebo, a difference that was statistically significant. One unusual aspect of the PROMID and CLARINET studies is the difference in progression-free survival durations in the placebo arms of the studies, which has been attributed to differences in patient selection. Either octreotide or lanreotide is currently considered an acceptable option for control of tumor growth in patients with advanced NETs. The timing of initiation of somatostatin analogues in patients with advanced NETs remains uncertain. The variable clinical course of NETs means that tumors can remain indolent for years even without treatment. For patients with asymptomatic, small-volume disease, observation alone may be an appropriate initial option. However, for

patients with a larger disease burden, evidence of disease progression, or symptomatic disease, somatostatin analogues are generally used as an initial systemic treatment due to their ease of use and tolerability. ■ ■PEPTIDE RECEPTOR RADIOLIGAND THERAPY Peptide receptor radioligand therapy employs the systemic administra tion of radiolabeled somatostatin analogues and is a treatment option for patients who require more aggressive treatment due to progression on traditional somatostatin analogues or other therapies (Fig. 89-7). Peptide receptor radioligand therapy may also be considered as an initial treatment in patients with significant symptoms or tumor bur den. With this approach, a radioligand is coupled to a somatostatin analogue, using the somatostatin analogue to target the tumor. When bound to the tumor cell, the radioligand is then internalized, resulting in cell death. Due to its mechanism of action, peptide receptor radioli gand therapy is only considered in patients whose tumors demonstrate uptake on somatostatin

scintigraphy. Several different radioligands have been evaluated, the most suc cessful of which have been yttrium (90Y) and lutetium (177Lu). These two ligands differ from one another in terms of their particle energy and tissue penetration; of the two, 90Y-DOTA-TOC emits higherenergy β particles and has deeper tissue penetration. 90Y-DOTA-TOC has been evaluated in numerous series with overall tumor responses reported in approximately one-third of patients. Enthusiasm for this approach, however, has been tempered due to concerns about side effects including both renal and hematologic toxicity. 177Lu-DOTA-octreotate emits both β particles and lower-energy γ particles and, in most studies, has been associated with less toxicity than 90Y-DOTA-TOC. Initial single-center studies with 177Lu-DOTAoctreotate showed promising antitumor activity, and based on these studies, a randomized trial of 177Lu-dotatate in midgut GI NETs was undertaken. In this study (NETTER-1), 229 patients with inoper able, somatostatin receptor–positive midgut NETs were randomly assigned to receive either four doses of 177Lu-dotatate administered intravenously every 8 weeks or treatment with high-dose octreotide LAR (60 mg) every 4 weeks. Treatment with 177Lu-dotatate was associ ated with objective tumor responses in 18% of patients and also was associated with a significant improvement in progression-free survival: progression-free survival at month 20 was 10.8% for octreotide LAR alone and 65.2% in the 177Lu-dotatate group. Subsequent analyses have also suggested improved overall survival associated with 177Lu-dotatate treatment, as well as improvements in quality of life across a number of parameters, including global health status, overall physical functioning, fatigue, pain, and diarrhea. One limitation of the NETTER-1 study was its restriction to patients with advanced small intestine NETs with low-grade histology. A subse quent study, NETTER-2, randomized 226 patients with a broader range of gastroenteropancreatic neuroendocrine tumors that were higher grade (grade 2 or 3) to receive treatment with 177Lu-dotatate or octreo tide alone. This study confirmed the activity of 177Lu-dotatate in this patient population; median progression-free survival was 22.8 months for patients receiving 177Lu-dotatate and 8.5 months for patients receiv ing octreotide alone. The renal clearance of radiopeptides, including 177Lu-DOTA-octreo tate, poses a risk of renal toxicity; this risk can be mitigated with the coadministration of intravenous amino acids during treatment. Longerterm safety data are available from large institutional series that include

> 1000 patients. Reported toxicities from these series have included rare cases of acute leukemia and myelodysplastic syndrome, presumably associated with radiation exposure. Nevertheless, these studies generally support both the efficacy and safety of 177Lu-dotatate as a treatment for patients with a range of somatostatin receptor–positive NETs. ■ ■ALKYLATING AGENTS While the efficacy of traditional cytotoxic chemotherapy appears to be minimal in most extrapancreatic GI NETs, alkylating agents have a clear role in the treatment of advanced pancreatic NETs. Streptozocinbased combination therapy was historically used as treatment standard in such patients but has largely fallen out of favor due to both toxicity

concerns and a cumbersome administration schedule. Temozolomide is an orally administered alkylating agent that has largely replaced streptozocin as a backbone in combination regimens used for the treat ment of pancreatic NETs.

Initial studies evaluating temozolomide in combination with a range of different agents showed that temozolomide-based combination ther apy was associated with tumor responses in 24–70% of patients. One of the most active combination regimens appeared to be temozolomide and capecitabine. This combination was subsequently compared to temozolomide alone in a prospective randomized study undertaken by the Eastern Cooperative Oncology Group (ECOG) that enrolled 144 patients with advanced pancreatic NETs. The overall response rates in the two arms were relatively similar; 33% of patients who received the combination of temozolomide and capecitabine experienced objective tumor responses as compared to 28% of the patients who received temozolomide as a single agent. However, progression-free survival was significantly longer in the combination arm (22.7 vs 14.4 months). Based on these results, the combination of temozolomide and capecitabine is now the preferred chemotherapy combination for advanced pancreatic NETs. The reason that some pancreatic NETs respond to alkylating agents while others do not is uncertain. In patients with glioblastoma, methyl ation of the promoter region for methylguanine DNA methyltransfer ase (MGMT) is associated with decreased MGMT protein expression and is highly associated with temozolomide responsiveness. MGMT is an enzyme that is responsible for repairing DNA damage induced by alkylating agents. Reduced levels of MGMT presumably impair the ability of tumor cells to repair their DNA in response to treatment and enhance the cytotoxicity of temozolomide. Several retrospective stud ies, as well as data from the prospective ECOG study, have suggested that lack of MGMT expression in pancreatic NET may be associated with responsiveness to temozolomide-based therapy, although findings have not been definitive. CHAPTER 89 Gastrointestinal Neuroendocrine Tumors SMALL-MOLECULE TYROSINE KINASE INHIBITORS The highly vascular nature of NETs combined with observations in preclinical models that disruption of signaling pathways associated with VEGF inhibits neuroendocrine cell growth prompted a number of clinical trials evaluating therapeutic agents that inhibit the VEGF pathway in both pancreatic and extrapancreatic NETs. The VEGF pathway is activated through the binding of VEGF to its cell surface receptor, which initiates an intracellular signaling cascade that pro motes angiogenesis as well as cell growth, proliferation, and survival. Clinical trials of VEGF pathway inhibitors in NETs have included a number of small-molecule tyrosine kinase inhibitors that, while they differ to some extent in specificity, all have in common the property targeting VEGFR2, the receptor isoform most strongly implicated in promoting angiogenesis. Sunitinib, a multitargeted tyrosine kinase inhibitor that inhibits a range of growth factor receptors including VEGFR2, was one of the first agents in this class found to have activity in pancreatic NETs. In an initial phase 2 trial, sunitinib was administered to 109 patients with either pancreatic or extrapancreatic NET. Of 61 patients with pancre atic NET enrolled in the study, 11 had evidence of an objective tumor response. Based on these observations, sunitinib was evaluated in an international, randomized trial in which continuous administration of sunitinib (37.5 mg daily) was compared with placebo in 171 patients with advanced, progressive pancreatic NET. The median progressionfree survival was significantly longer in patients treated with sunitinib compared with patients treated with placebo (11.4 vs 5.5 months). Common side effects associated with sunitinib included hypertension, proteinuria, and fatigue. A second VEGFR-targeted tyrosine kinase inhibitor, surufatinib, was evaluated in a randomized trial in which 264 patients with advanced pancreatic NETs from 21 centers in China were randomized to receive either surufatinib, administered at a dose of 300 mg daily, or placebo. Patients receiving surufatinib experienced a median progressionfree survival duration of 10.9 months, as compared to 3.7 months in

patients receiving placebo, closely mirroring the results of the earlier sunitinib study. Cabozantinib, a tyrosine kinase inhibitor with activ ity against not only VEGFR but also c-MET and related growth factor receptors, was evaluated against placebo in a randomized trial led by the ALLIANCE cooperative group that included both pancreatic and extrapancreatic NETs. Among the 95 pancreatic NET patients in the study, median progression-free survival was 13.8 months for those receiving cabozantinib and 4.5 months for those receiving placebo. Other small-molecule tyrosine kinase inhibitors that have been evalu ated in smaller, single-arm studies and have shown activity in pancre atic NETs, include sorafenib, pazopanib, and axitinib.

Small-molecule tyrosine kinase inhibitors targeting the VEGF path way have also been evaluated in patients with advanced nonpancreatic GI NET. In most of these studies, objective tumor response rates are lower than those seen in pancreatic NET, though many of these initial studies also revealed low rates of tumor progression and encouraging progression-free survival durations, suggesting that these agents had antitumor activity. Pazopanib was compared to placebo in a random ized study undertaken by the ALLIANCE cooperative group, which enrolled 171 patients with nonpancreatic NETs. Patients treated with pazopanib in this study had a superior progression-free survival com pared to those who received placebo (11.6 vs 8.5 months), a difference that was statistically significant. Surufatinib was used in a randomized study of 198 patients with extrapancreatic NETs; the median progres sion-free survival was 9.2 months in patients receiving surufatinib and 3.8 months in those receiving placebo. The strongest results to date have come from a randomized study of cabozantinib (see above) that included 205 patients with extrapancreatic GI NET. In this study, median progression-free survival was 8.5 months in the cabozantinib arm as compared with 4 months in the placebo arm. Taken together with the results in the pancreatic NET cohort (above), these results provide a strong rationale for considering cabozantinib as a treatment option for patients with both advanced pancreatic and nonpancreatic GI NET. PART 4 Oncology and Hematology ■ ■mTOR INHIBITORS mTOR is an intracellular protein kinase that has been implicated in the regulation of a number of processes regulating cell growth in both normal and malignant cells. It functions as a downstream component of the PI3-AKT-mTOR pathway. This pathway is negatively regulated by the tuberous sclerosis complex, comprising TSC1 and TSC2. An association between the development of pancreatic NETs and inherited mutations in TSC2 in patients with tuberous sclerosis complex was a contributing factor to initial interest in exploring mTOR inhibition as a therapeutic approach in this setting. Following initial evidence of antitumor activity associated with everolimus (10 mg daily) in an international, multicenter, phase 2 trial of 160 patients, everolimus monotherapy (10 mg daily) was compared with best supportive care alone in the RADIANT-3 trial that enrolled 410 patients with advanced progressing pancreatic NET. While overall objective responses were uncommon, treatment with everolimus was associated with a significant prolongation in median progression-free survival (11.0 vs 4.6 months) compared to placebo, supporting its use as a standard treatment to control tumor growth in patients with advanced pancreatic NET. Common toxicities associated with evero limus are generally mild and can include stomatitis and rash; a more severe but less common side effect is pneumonitis. Everolimus was also associated with promising activity in early phase 2 studies enrolling patients with extrapancreatic NET. The first large, randomized study evaluating everolimus was the RADIANT-2 trial; 429 patients with advanced GI NETs were randomly assigned to receive octreotide LAR (30 mg intramuscularly every 28 days) with or without everolimus (10 mg daily). Treatment with everolimus in this study was associated with an improvement in median progressionfree survival (16.4 vs 11.3 months), but the difference in this study was of only borderline statistical

significance. A second study, the RADIANT-4 study, enrolled 302 patients with advanced NETs of either GI (excluding pancreatic) or lung origin, randomizing them to receive either everolimus or placebo. In this study, treatment with

octreotide was not required. As in the RADIANT-3 study, objective tumor responses were uncommon; however, median progression-free survival in patients who received everolimus was significantly longer than in those who received placebo (11 vs 3.9 months). Based on the results of this study, everolimus is considered a standard treatment for control of tumor growth in extrapancreatic NETs. ■ ■OTHER SYSTEMIC TREATMENTS FOR CONTROL OF TUMOR GROWTH Interferon α has been used as a treatment for advanced NETs for sev eral decades. With the development of newer approaches, its routine use has diminished. The use of interferon α was based primarily on observations in large, retrospective series where low-dose interferon α was reported to both reduce symptoms of hormonal hypersecre tion and slow tumor progression. Interferon can be myelosuppres sive, requiring dose titration, and in some patients can induce both fatigue and depression. Antitumor activity has also been reported with oxaliplatin-based chemotherapy regimens. A combined analysis of two phase 2 trials examining oxaliplatin-fluoropyrimidine chemotherapy plus bevacizumab in advanced NET suggested antitumor activity for these regimens; the benefit appeared to be greatest in patients with intermediate-grade rather than low-grade tumors. Treatment with immune checkpoint inhibitors has been found to be effective across multiple cancer types. The role of immune check point inhibitors for the treatment of neuroendocrine tumors has not yet been clearly established and appears to depend at least in part on tumor grade. Immunohistochemical and transcriptomic profiling in well-differentiated neuroendocrine tumors has revealed only low levels of PD-1 and PD-L1 expression together with high levels of immuno suppressive gene expression in tumor-associated myeloid cells. The KEYNOTE-158 study investigated the efficacy of pembrolizumab, a monoclonal antibody targeting the checkpoint marker PD-1, in mul tiple cancers, including 107 patients with neuroendocrine tumors of various sites. The overall tumor response rate in the neuroendocrine tumor cohort was only 3.7%. Other immunotherapeutic approaches, including use of chimeric antigen receptor T cells for the treatment of neuroendocrine tumors, remain investigational. ■ ■SYSTEMIC THERAPY FOR HIGH-GRADE NEUROENDOCRINE CARCINOMA High-grade NETs are relatively uncommon and tend to pursue an aggressive clinical course. In contrast to well-differentiated neuroen docrine tumors, high-grade neuroendocrine carcinomas may, at least in some cases, be quite responsive to immunotherapeutic approaches. A basket trial evaluating a combination of the anti-CTLA-4 mono clonal antibody ipilimumab together with the anti-PD-1 monoclonal antibody nivolumab enrolled 32 patients with poorly differentiated nonpancreatic neuroendocrine tumors; the overall tumor response rate was 44% in this cohort. Apart from these more recent immune-based approaches, chemotherapy for advanced high-grade neuroendocrine carcinoma has historically followed a paradigm analogous to that used for small-cell carcinoma of the lung, with combinations of either cis platin or carboplatin administered together with etoposide generally considered the preferred first-line approach. One of the most impor tant elements in determining the optimal chemotherapeutic approach is assessing the Ki-67 proliferative index. A large retrospective series that evaluated 252 patients with high-grade neuroendocrine carci noma found that the activity of platinum-based therapy was greatest in patients who had a Ki-67 proliferative index of 55% or higher; in these patients, the overall tumor response rate was 42%. In contrast, the overall response rate in patients in whom the Ki-67 proliferative index was <55% was only 15%. Acknowledgment Dr. Robert Jensen contributed this chapter in previous editions and some material from his chapter is retained here. ■ ■FURTHER READING Caplin ME et al: Lanreotide in metastatic

enteropancreatic neuroen docrine tumors. N Engl J Med 371:224, 2014.

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