Gastrointestinal Neuroendocrine Tumors Treatment (PDQ®)–Health Professional Version

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General Information About Gastrointestinal Neuroendocrine (Carcinoid) Tumors

Epidemiology

The age-adjusted incidence of neuroendocrine (carcinoid) tumors worldwide is approximately 2 per 100,000 people.[1,2] The average age at diagnosis is 61.4 years.[3] Neuroendocrine tumors (also called NETs) represent about 0.5% of all newly diagnosed malignancies.[2,3]

Anatomy

Neuroendocrine tumors are rare, slow-growing tumors that originate in cells of the diffuse neuroendocrine system. They occur most frequently in tissues derived from the embryonic gut. Foregut tumors, which account for up to 25% of cases, arise in the lung, thymus, stomach, or proximal duodenum. Midgut tumors, which account for up to 50% of cases, arise in the small intestine, appendix, or proximal colon. Hindgut tumors, which account for approximately 15% of cases, arise in the distal colon or rectum.[4] Other sites of origin include the gallbladder, kidney, liver, pancreas, ovary, and testis.[3-5]

Gastrointestinal neuroendocrine tumors, especially tumors of the small intestine, are often associated with other cancers. Synchronous or metachronous cancers occur in approximately 29% of patients with small intestinal neuroendocrine tumors.[3] However, it is possible that the association may be due in part to the serendipitous discovery of slow-growing neuroendocrine tumors, which are found while staging or investigating symptoms from other tumors.

Histology

The term carcinoid may be used for well-differentiated neuroendocrine tumors or carcinomas of the gastrointestinal tract only. The term should not be used to describe pancreatic neuroendocrine tumors or islet cell tumors.[6] Data regarding carcinoids and other neuroendocrine tumors, such as poorly differentiated neuroendocrine carcinomas, may be combined in some epidemiological and clinical studies, rendering separate consideration difficult. Occurring nonrandomly throughout the gastrointestinal tract are more than 14 cell types, which produce different hormones.[7] Although the cellular origin of neuroendocrine tumors of the gastrointestinal tract is uncertain, consistent expression of cytokeratins in neuroendocrine tumors and the expression of the caudal-related homeodomain protein 2 (Cd2 protein), an intestinal transcription factor in endocrine tumors of the small intestine, suggests an origin from an epithelial precursor cell.[8] For more information, see Pancreatic Neuroendocrine Tumors (Islet Cell Tumors) Treatment and the Cellular and Pathological Classification of Gastrointestinal Neuroendocrine Tumors section.

Most neuroendocrine tumors of the small and large intestines occur sporadically, while others may occur within the background of an inherited neoplasia syndrome such as multiple endocrine neoplasia type 1 (MEN1) or neurofibromatosis type 1 (NF1) (e.g., gastrin-producing G-cell tumors and somatostatin-producing D-cell tumors of the duodenum, respectively).[9] Tumor multifocality is the rule within the background of neuroendocrine cell hyperplasia, but multifocality is found in approximately one-third of patients with small enterochromaffin cell tumors in the absence of proliferative or genetic factors. Clonality studies suggest that most of these neoplasms are separate primary lesions.[10,11] Gastric neuroendocrine tumors may be associated with chronic atrophic gastritis.[7]

Histopathology

Individual carcinoid tumors have specific histological and immunohistochemical features based on their anatomical location and endocrine cell type. However, all carcinoids share common pathological features that characterize them as well-differentiated neuroendocrine tumors.[5] In the gastric or intestinal wall, carcinoids may occur as firm white, yellow, or gray nodules and may be intramural masses or may protrude into the lumen as polypoid nodules. The overlying gastric or intestinal mucosa may be intact or have focal ulceration.

Neuroendocrine cells have uniform nuclei and abundant granular or faintly staining (clear) cytoplasm. They are present as solid or small trabecular clusters or are dispersed among other cells, which may make them difficult to recognize in sections stained with hematoxylin and eosin; immunostaining enables their exact identification.[12] At the ultrastructural level, neuroendocrine cells contain cytoplasmic membrane-bound dense-cored secretory granules (diameter >80 NM) and may also contain small clear vesicles (diameter 40–80 NM) that correspond to the synaptic vesicles of neurons.

Molecular genetics

Occasionally, gastrointestinal carcinoids occur in association with inherited syndromes, such as MEN1 and NF1.[13-15]

MEN1 is caused by alterations of the *MEN1* gene located at chromosomal region 11q13. Most carcinoids associated with MEN1 appear to be of foregut origin.[13] NF1 is an autosomal dominant genetic disorder caused by alteration of the *NF1* gene at chromosome 17q11.[16] Carcinoids in patients with NF1 appear to arise primarily in the periampullary region.[5,17,18] For more information, see Genetics of Endocrine and Neuroendocrine Neoplasias.

In sporadic gastrointestinal carcinoids, numerous chromosomal imbalances have been found by comparative genome hybridization analysis. Gains involving chromosomes 5, 14, 17 (especially 17q), and 19 and losses involving chromosomes 11 (especially 11q) and 18 appear to be the most common. [19,20]

The most common pathogenic variant in gastrointestinal carcinoids is *CTNNB1*. In one study, *CTNNB1* exon 3 variants were found in 27 of 72 cases (37.5%).[21]

However, no consistent genetic markers for gastrointestinal carcinoid prognosis have yet been identified.[9] For more information, see the Cellular and Pathological Classification of Gastrointestinal Neuroendocrine Tumors section.

Carcinoid syndrome

Carcinoid syndrome, which occurs in fewer than 20% of patients with neuroendocrine tumors, is caused by the release of metabolically undergraded vasoactive amines into the systemic circulation. It is associated with flushing, abdominal pain and diarrhea, bronchoconstriction, and carcinoid heart disease.[22,23] Because vasoactive amines are efficiently metabolized by the liver, carcinoid syndrome rarely occurs in the absence of hepatic metastases. Exceptions include circumstances in which venous blood draining from a tumor enters directly into the systemic circulation (e.g., primary pulmonary or ovarian carcinoids, pelvic or retroperitoneal involvement by metastatic or locally invasive small bowel carcinoids, or extensive bone metastases).

Carcinoid heart disease develops in more than one-third of patients with carcinoid syndrome. Pathologically, the cardiac valves become thickened because of fibrosis, and the tricuspid and pulmonic valves are affected to a greater extent than the mitral and aortic valves. Symptoms include: [22]

- Tricuspid and pulmonic regurgitation.
- Pulmonary stenosis.
- Mitral and aortic insufficiency.
- Cardiac dysrhythmias.

Severe carcinoid heart disease is associated with reduced survival. For more information, see the Prognostic Factors section.

Site–Specific Clinical Features

The clinical features of gastrointestinal neuroendocrine tumors vary according to anatomical location and cell type.[5,12,24] Most neuroendocrine tumors in the gastrointestinal tract are located within 3 feet (~90 cm) of the ileocecal valve, with 50% found in the appendix.[25] They are often detected fortuitously during surgery for another gastrointestinal disorder or during emergency surgery for appendicitis, gastrointestinal bleeding, or perforation.[26]

Gastric neuroendocrine tumors

Most gastric neuroendocrine tumors are enterochromaffin-like (ECL)-cell neuroendocrine tumors; rarely, other types may occur in the stomach. For more information, see Table 1.

Type I ECL-cell gastric neuroendocrine tumors, the most common type, typically do not have clinical symptoms. They are often discovered during endoscopy for reflux, anemia, or other reasons. They are typically multifocal. Occurring most commonly in women (female-to-male ratio, 2.5:1) at a mean age of 63 years, achlorhydria may be present, and hypergastrinemia or evidence of antral G-cell hyperplasia is usually found.[5,24,27] These tumors are gastrin-driven and arise in a background of chronic atrophic gastritis of the corpus, usually because of autoimmune pernicious anemia but sometimes caused by *Helicobacter pylori* infection.[9]

Type II ECL-cell neuroendocrine tumors, the least common type of gastric neuroendocrine tumor, occur at a mean age of 50 years with no sex predilection. The hypergastrinemia associated with MEN1-

Zollinger-Ellison syndrome (ZES) is thought to promote the ECL-cell hyperplasia that leads to type II tumors.[27,28]

Type I and type II ECL-cell gastric neuroendocrine tumors have been reported to metastasize in fewer than 10% of cases.[27,29] Type III gastric ECL-cell neuroendocrine tumors, the second most common type of gastric neuroendocrine tumor, occur mostly in men (male-to-female ratio, 2.8:1) at a mean age of 55 years.[27] There are no neuroendocrine manifestations, and patients typically present with signs and symptoms related to an aggressive tumor.[5,30]

Duodenal neuroendocrine tumors

Duodenal neuroendocrine tumors comprise only 2% to 3% of gastrointestinal neuroendocrine tumors. They are discovered incidentally or because of symptoms from hormonal or peptide production. These tumors may also arise in the periampullary region, obstruct the ampulla of Vater, and produce jaundice.[3,5,31] The age at presentation varies widely (range, 19–90 years; mean age, 53 years). [15,32]

The most common duodenal neuroendocrine tumors are gastrin-producing G-cell tumors (~two-thirds), followed by somatostatin-producing D-cell tumors (~one-fifth), which rarely produce systemic manifestations of somatostatin excess.[5,31,33]

Gastrin production from G-cell neuroendocrine tumors (also called gastrinomas if serum gastrin levels are elevated) results in ZES in approximately one-third of the cases of duodenal G-cell tumors.[24] Although duodenal G-cell neuroendocrine tumors may occur sporadically, 90% of patients with MEN1 develop them.[5] The clinical manifestations of serum gastrin elevation include:

- Nausea.
- Vomiting.
- Abdominal pain.
- Hemorrhage from multiple and recurrent peptic ulcers.
- Gastroesophageal reflux caused by excess acid production.
- Diarrhea from hypergastrinemia.

The most common symptom is abdominal pain; both abdominal pain and diarrhea are present in approximately 50% of patients. In contrast to sporadic gastrinomas, which are usually solitary lesions, gastrinomas in patients with MEN1-ZES are usually multiple and smaller than 5 mm.[5]

Somatostatin-producing D-cell tumors occur exclusively in and around the ampulla of Vater, and as many as 50% of patients with D-cell neuroendocrine tumors have NF1.[34] Most patients with this type of tumor and NF1 are Black women, and their tumors are exclusively located in the periampullary region.[15,32] As a result of their location, these tumors may cause local obstructive symptoms and signs such as jaundice, pancreatitis, or hemorrhage. Although D-cell tumors produce somatostatin, systemic manifestations of excess somatostatin such as steatorrhea, diarrhea, diabetes mellitus, hypochlorhydria and achlorhydria, anemia, and cholelithiasis are rare.[31]

Jejunal and ileal neuroendocrine tumors

Most jejunal and ileal neuroendocrine tumors are argentaffin-positive, substance P–containing, and serotonin-producing EC-cell tumors that generate carcinoid syndrome when hepatic or retroperitoneal nodal metastases are present. L-cell, glucagon-like polypeptide-producing, and pancreatic polypeptide- and polypeptide YY-producing tumors occur less frequently.[24] Ileal neuroendocrine tumors develop preferentially in the terminal ileum.[12] Jejunal and ileal neuroendocrine tumors occur equally in men and women at a mean age of 65.4 years.[3] Similar to all neuroendocrine tumors, jejunal and ileal neuroendocrine tumors vary in their biological behavior and ability to metastasize. Typically, EC-cell neuroendocrine tumors of the small intestine metastasize to lymph nodes and the liver.[5] Patients with these lesions may be asymptomatic. The primary tumor may cause small intestinal obstruction, ischemia, or bleeding, and some patients may complain of a long history of intermittent crampy abdominal pain, weight loss, fatigue, abdominal distention, diarrhea, or nausea and vomiting.[5,23,35]

At the time of diagnosis, ileal neuroendocrine tumors (i.e., carcinoids plus poorly differentiated neuroendocrine carcinomas) are commonly larger than 2 cm and have metastasized to regional lymph nodes; in as many as 40% of cases, the tumors are multifocal.[12] Immunocytochemically, the cells contain serotonin, substance P, kallikrein, and catecholamine. Approximately 20% of patients with ileal neuroendocrine tumors have regional lymph node and liver metastases. Most gastrointestinal neuroendocrine tumors secrete their bioactive peptides and amines into the portal circulation, and the effects of these biochemical mediators are diminished or negated by hepatic detoxification; accordingly, carcinoid syndrome (e.g., flush, diarrhea, and endocardial fibrosis) occurs only in patients with liver metastases because hepatic detoxification of serotonin is bypassed.

Appendiceal neuroendocrine tumors

Most appendiceal neuroendocrine tumors are serotonin-producing EC-cell tumors similar to neuroendocrine tumors that occur in the jejunum and ileum. Less commonly, appendiceal neuroendocrine tumors are L-cell tumors similar to those in the colon.[16] The biological behavior of both cell types is strikingly different in the appendix compared with tumors of the ileum and nonappendiceal colon. Most appendiceal neuroendocrine tumors have a benign clinical course and do not metastasize, perhaps because growth in the appendix produces obstruction, appendicitis, and subsequent surgical removal.[5,36] Although appendiceal neuroendocrine tumors occur at all ages, patients with these tumors tend to be much younger than patients diagnosed with other appendiceal neoplasms or carcinoids at other sites. Appendiceal neuroendocrine tumors are reportedly more common in women.[3,5] However, age and sex patterns may be spurious, reflecting the younger age range of patients who typically undergo appendectomy for inflammatory appendicitis, and the larger number of incidental appendectomies performed in women during pelvic operations. For more information, see Pediatric Gastrointestinal Neuroendocrine Tumors Treatment.

Colorectal neuroendocrine tumors

Most colorectal neuroendocrine tumors occur in the rectum; fewer arise in the cecum.[5] In the cecum, argentaffin-like EC-cell neuroendocrine tumors are most common, become increasingly less common in the more distal colon, and are uncommon in the rectum.[31] Rectal neuroendocrine tumors account for approximately one-fourth of gastrointestinal neuroendocrine tumors and fewer than 1% of all rectal cancers.[3,31] Most rectal neuroendocrine tumors have L-cell differentiation. The mean age of patients at diagnosis for colonic neuroendocrine tumors is 66 years and for rectal neuroendocrine tumors, 56.2 years. Colorectal neuroendocrine tumors have no sex predilection, and

rectal neuroendocrine tumors are more common in the Black population.[3,37] Abdominal pain and weight loss are typical symptoms of colonic neuroendocrine tumors, but more than 50% of patients with rectal neuroendocrine tumors are asymptomatic, and the tumors are discovered at routine rectal examination or screening endoscopy.[24] Symptoms of rectal neuroendocrine tumors include bleeding, pain, and constipation. Metastatic disease from colonic neuroendocrine tumors may produce carcinoid syndrome, whereas metastatic disease from rectal neuroendocrine tumors is not associated with carcinoid syndrome.[5,38]

Diagnostics: Biochemical Markers, Imaging, and Approach

Biochemical markers

Biochemical investigations in the diagnosis of gastrointestinal neuroendocrine tumors include the use of 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) collection, which has a specificity of approximately 88%, although the sensitivity is reported to be as low as 35%.[39-41] A time-consuming test, 5-HIAA requires dietary avoidance of serotonin-rich foods, such as bananas, tomatoes, and eggplant.[42] Measurement of plasma chromogranin A (CgA), first described in a study of adrenal gland secretions in 1967 as one of the soluble protein fractions (also including CgB and CgC) of chromaffin granules, is also useful.[43] Although plasma levels of CgA are very sensitive markers of gastrointestinal neuroendocrine tumors, they are nonspecific because they are also elevated in other types of neuroendocrine tumors, such as pancreatic and small cell lung carcinomas.[44-46] Plasma CgA appears to be a better biochemical marker of neuroendocrine tumors than urinary 5-HIAA.[47] Numerous investigations have revealed an association between plasma CgA levels and disease severity.[26] However, false-positive plasma levels of CgA may occur in patients on proton pump inhibitors, reported to occur even with short-term, low-dose treatment.[48,49] Many other biochemical markers are associated with neuroendocrine tumors—including substance P, neurotensin, bradykinin, human chorionic gonadotropin, neuropeptide L, and pancreatic polypeptide —but none match the specificity or predictive value of 5-HIAA or CgA.[44]

Imaging

Imaging modalities for gastrointestinal neuroendocrine tumors include the use of somatostatin scintigraphy with indium In 111 (111In)-octreotide; bone scintigraphy with technetium Tc 99m-methylene diphosphonate (99mTc-MDP); iodine I 123-metaiodobenzylguanidine (123I-MIBG) scintigraphy; computed tomography (CT); capsule endoscopy; enteroscopy; and angiography.[26]

Somatostatin receptor scintigraphy

There are five different somatostatin receptor (SSTR) subtypes. More than 70% of neuroendocrine tumors of both the gastrointestinal tract and pancreas express multiple subtypes, with a predominance of receptor subtype 2 [sst(2)] and receptor subtype 5 [sst(5)].[50,51] The synthetic radiolabeled SSTR analogue 111In-DTP-d-Phe10-{octreotide} affords an important method, somatostatin receptor scintigraphy (SRS), to localize carcinoid tumors, especially sst(2)-positive and sst(5)-positive tumors; imaging is accomplished in one session, and small primary tumors and metastases are diagnosed more readily than with conventional imaging or imaging techniques requiring multiple sessions.[26,52,53] Overall sensitivity of the octreotide scan is reported to be as high as 90%; however, failed detection may result from various technical issues, small tumor size, or inadequate expression of SSTRs.[26,54]

Bone scintigraphy

Bone scintigraphy with 99mTc-MDP is the primary imaging modality for identifying bone involvement in neuroendocrine tumors, with detection rates reported to be 90% or higher.[26] 123I-MIBG is concentrated by neuroendocrine tumors in as many as 70% of cases, using the same mechanism as norepinephrine, and is used successfully to visualize neuroendocrine tumors. However, 123I-MIBG appears to be about half as sensitive as 111In-octreotide scintigraphy in detecting tumors.[26,55]

CT/MRI

CT and magnetic resonance imaging (MRI) are important modalities used in the initial localization of primary neuroendocrine tumors and/or metastases. The median detection rate and sensitivity of CT and/or MRI have been estimated at 80%. Detection rates by CT alone range between 76% and 100%, while MRI detection rates are between 67% and 100%.[26] CT and MRI may be used for initial localization of the tumor only because both imaging techniques may miss lesions otherwise detected by 111In-octreotide scintigraphy. One study has shown that lesions in 50% of patients were missed, especially in lymph nodes and extrahepatic locations.[26,56]

PET

A promising approach for positron emission tomography (PET) as an imaging modality to visualize gastrointestinal neuroendocrine tumors appears to be the use of the radioactive-labeled serotonin precursor carbon C 11-5-hydroxytryptophan (11C-5-HTP). With 11C-5-HTP, tumor detection rates have been reported to be as high as 100%, and some investigators have concluded that 11C-5-HTP PET should be used as a universal method for detecting neuroendocrine tumors.[57-59] In one study of neuroendocrine tumors, including 18 patients with gastrointestinal carcinoids, 11C-5-HTP PET detected tumor lesions in 95% of patients. In 58% of cases, 11C-5-HTP PET detected more lesions than SRS and CT, compared with the 7% that 11C-5-HTP PET did not detect.[59] Other imaging approaches have been investigated using technetium-labeled isotopes, combining CT/MRI with fluorine F 18-fluorodopa PET, combining iodine I 131-MIBG with 111In-octreotide, and coupling the isotopes gallium Ga 68 and copper Cu 64 to octreotide.[26]

EUS

Endoscopic ultrasonography (EUS) may be a sensitive method for the detection of gastric and duodenal neuroendocrine tumors and may be superior to conventional ultrasonography, particularly in the detection of small tumors (2–3 mm) that are localized in the bowel lumen.[60,61] In one study, EUS was reported to have an accuracy of 90% for the localization and staging of colorectal neuroendocrine tumors.[62]

Capsule endoscopy

Capsule endoscopy may prove useful in the detection of small bowel carcinoids.[63]

Enteroscopy

Double-balloon enteroscopy is a time-consuming procedure that is being studied in the diagnosis of small bowel tumors, including neuroendocrine tumors.[64,65] It is usually performed under general anesthesia, although it can be done under conscious sedation.

Angiography

MRI angiography has replaced angiography to a large extent. However, selective and supraselective angiography may be useful to:

- Demonstrate the degree of tumor vascularity.
- Identify the sources of vascular supply.
- Delineate the relationship of the tumor to adjacent major vascular structures.
- Provide information regarding vascular invasion.

Angiography may be useful as an adjunct to surgery, particularly in the case of large invasive lesions in proximity to the portal vein and superior mesenteric artery. Overall, this imaging technique provides a more precise topographic delineation of the tumor or tumor-related vessels and facilitates resection. [26]

General diagnostic approaches

As might be expected, diagnostic approaches to gastrointestinal neuroendocrine tumors vary according to anatomical location. In 2004, a consensus statement regarding the diagnosis and treatment of gastrointestinal neuroendocrine tumors was published on behalf of the European Neuroendocrine Tumor Society,[66] which details site-specific approaches to diagnosis.

Prognostic Factors

Factors that determine the clinical course and outcome of patients with gastrointestinal neuroendocrine tumors are complex and multifaceted and include:[67]

- The site of origin.
- The size of the primary tumor.
- The anatomical extent of disease.

Elevated expression of the proliferation antigen Ki-67 and the tumor suppressor protein p53 have been associated with poorer prognosis; however, some investigators suggest that the Ki-67 index may be helpful in establishing prognosis of gastric lesions only and maintain that no consistent genetic markers of prognosis have yet been discovered.[9] Adverse clinical prognostic indicators include:

- Carcinoid syndrome.
- Carcinoid heart disease.
- High concentrations of the tumor markers urinary 5-HIAA and plasma chromogranin A.

Follow-Up and Survivorship

In general, patients with neuroendocrine tumors of the appendix and rectum experience longer survival than patients with tumors of the stomach, small intestine, and colon. Neuroendocrine tumors in the small intestine, even small ones, are more likely to metastasize than those in the appendix, colon, and rectum.[67] Appendiceal and rectal neuroendocrine tumors are usually small at initial detection and have rarely metastasized. The presence of metastases has been associated with a reduction in 5-year survival ranging from 39% to 60% in several case series and reviews.[3,68-71] Some patients with metastatic neuroendocrine tumors have an indolent clinical course with survival of

several years, whereas others experience an aggressively malignant course with short survival. Although metastases are associated with a shorter survival in large patient samples, the presence of metastases alone does not sufficiently predict the clinical course of the individual patient.

Approximately 35% of neuroendocrine tumors of the small intestine are associated with carcinoid syndrome. The relatively common neuroendocrine tumors of the appendix and rectum rarely produce this syndrome, and neuroendocrine tumors from other sites have intermediate risks.[71,72] Investigations using echocardiographic criteria for carcinoid heart disease found prevalences ranging from 35% to 77% among patients with carcinoid syndrome.[73-77] The tricuspid valve is affected more frequently and severely than the pulmonic valve, and the presence and severity of carcinoid heart disease, particularly tricuspid valve dysfunction, is associated with shortened survival.[74,76-78] One study involving 64 patients with midgut carcinoid syndrome found 5-year survival rates of 30% for those with severe carcinoid heart disease versus 75% for those with no cardiac disease.[76]

In another study, statistically significantly reduced survival was observed for patients with midgut neuroendocrine tumors who had urinary 5-HIAA concentrations greater than 300 μmol/24 hours compared with patients who had lower concentrations of urinary 5-HIAA.[79] Correspondingly, a study of patients with midgut carcinoid syndrome showed that urinary 5-HIAA levels greater than 500 μmol/24 hours were associated with shorter survival.[76] The degree of elevation of urinary 5-HIAA is also associated with the severity of carcinoid symptoms, with the highest levels being observed in patients with carcinoid heart failure.[76,80] In one study, vascular endothelial growth factor (VEGF) expression by low-grade tumors and surrounding stromal cells was associated with progression-free survival (PFS); median durations of PFS in patients with strong and weak VEGF expression were 29 months and 81 months, respectively.[81]

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Cellular and Pathological Classification of Gastrointestinal Neuroendocrine Tumors

A variety of neuroendocrine cells normally populate the gastrointestinal mucosa and submucosa. The type, location, and secretory products of gastrointestinal neuroendocrine cells are well defined and are summarized in Table 1. As previously noted, individual neuroendocrine (carcinoid) tumors have specific histological and immunohistochemical features based on their anatomical location and neuroendocrine cell type. However, all carcinoids share common pathological features that characterize them as well-differentiated neuroendocrine tumors.[1]

Table 1. Gastrointestinal Neuroendocrine Cells[a]

Cell Type	Location	Secretory Product
G cell	Gastric antrum and duodenum	Gastrin
ECL cell	Gastric fundus and body	Histamine
D cell	Stomach, duodenum, jejunum, colon, and rectum	Somatostatin
EC cell	Stomach, duodenum, jejunum, ileum, colon, and rectum	Serotonin, motilin, and substance P
CCK cell	Duodenum and jejunum	Cholecystokinin
GIP cell	Duodenum and jejunum	Gastric inhibitory polypeptide
M cell	Duodenum and jejunum	Motilin
S cell	Duodenum and jejunum	Secretin
PP cell	Duodenum	Pancreatic polypeptide
L cell	Jejunum, ileum, colon, and rectum	Polypeptide YY
N cell	Jejunum and ileum	Neurotensin

CCK = cholecystokinin; D = somatostatin–producing; EC = enterochromaffin; ECL = enterochromaffin–like; G = Gastrin cell; GIP = gastric inhibitory polypeptide; L = enteroendocrine; M = motilin; N = neurotensin; PP = pancreatic polypeptide; S = secretin.

[a]*Adapted from* [1-3]

Updated in 2000, the World Health Organization (WHO) classification is clinically and prognostically useful for patients with newly diagnosed neuroendocrine tumors of the gastrointestinal tract because it accounts for specific biological behavior according to location and tumor differentiation.[4,5]

This classification distinguishes between the following:

- Well-differentiated, mostly benign tumors with an excellent prognosis.
- Well-differentiated carcinomas with a low malignant potential and a favorable prognosis.
- Poorly differentiated carcinomas (small cell and fewer large cell), which are highly malignant and carry a poor prognosis.

In this classification, the term carcinoid (or typical carcinoid) is used only for well-differentiated neuroendocrine tumors of the gastrointestinal tract, excluding the pancreas, and the term malignant carcinoid (or atypical carcinoid) is used for the corresponding well-differentiated neuroendocrine tumors at the same gastrointestinal tract locations.[6,7] Despite some uncertainty surrounding the role of cell proliferation indices in the prognosis of neuroendocrine tumors, it is clear that poorly differentiated carcinomas are highly aggressive and require a special therapeutic approach.[7-9] In a second step, the WHO classification subdivides gastrointestinal neuroendocrine tumors on the basis of localization and biology to achieve a prognostically relevant classification of the tumors.[5-7,9] In this subclassification, gastrointestinal anatomical locations include:

- Stomach (four different types).
- Duodenum (and proximal jejunum) (five different types).
- Ileum (including the distal jejunum).
- Appendix.
- Colon-rectum.

For more information about a clinicopathological correlation of cell types and anatomical location, see the Site-Specific Clinical Features section.

In addition, in the WHO classification scheme, gastrointestinal neuroendocrine tumors have been grouped with pancreatic neuroendocrine tumors (islet cell tumors) and labeled as gastroenteropancreatic neuroendocrine tumors (GEP-NETS). However, because of differences in chromosomal alteration patterns and molecular genetics between gastrointestinal neuroendocrine tumors and pancreatic neuroendocrine tumors, some investigators have suggested that this gastroenteropancreatic neuroendocrine tumors grouping requires reassessment.[7,9,10]

Because there were no proven molecular and genetic alterations with clinical and prognostic relevance, only traditional morphological and histopathological criteria were used in the classification. In addition to the level of differentiation, these criteria include:

- Size of the tumor.
- Presence or absence of angioinvasion.
- Proliferative activity (as measured by a Ki-67 index).[5,6]

Traditional cytological and histopathological assessment of growth patterns and cellular features of well-differentiated neuroendocrine tumors seldom help predict their functional behavior and degree of malignancy. In general, typical neuroendocrine tumors in the stomach, appendix, or rectum have an excellent prognosis.[6] In contrast, poorly differentiated neuroendocrine tumors that are composed of cells displaying severe nuclear atypia, a high mitotic index, and few secretory granules are invariably high-grade malignancies.[7]

Diagnostic markers that help to identify gastrointestinal neuroendocrine tumors include:

- Cytosolic and cell-membrane markers such as neuron-specific enolase, protein gene product 9.5, histidine carboxylase, vesicular monoamine transporter 2 (VMAT2), and neural-cell adhesion molecule CD56 (high sensitivity and low specificity).

- Small vesicle-associated markers such as synaptophysin and synaptic vesicle protein 2 (high sensitivity and high specificity).
- Large secretory granule-associated markers such as chromogranins A, B, and C and CD57 (low sensitivity and high specificity).
- Somatostatin receptors.
- Specific peptide hormone markers such as serotonin, somatostatin, and gastrin.[7,8]

Hormones that are highly specific for certain gastrointestinal neuroendocrine tumors are serotonin and substance P for ileal and appendiceal NETS, and VMAT2 for *ECLomas*.[7]

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Stage Information for Gastrointestinal Neuroendocrine Tumors

American Joint Committee on Cancer (AJCC) Stage Groupings and TNM Definitions

The AJCC has designated staging by TNM (tumor, node, metastasis) classification to define neuroendocrine tumors.[1-6]

Gastric neuroendocrine tumors

Table 2. Definitions of TNM Stage I Neuroendocrine Tumors of the Stomach[a]

Stage	TNM	Description
I	T1, N0, M0	T1 = Invades the lamina propria or submucosa and ≤1 cm in size.[b]
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.
T = primary tumor; N = regional lymph nodes; M = distant metastasis.
[a]Reprinted with permission from AJCC: Neuroendocrine Tumors: Stomach. In: Amin MB, Edge SB, Greene FL, et al., eds.: *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer, 2017, pp. 351–9.
[b]The explanation for superscript b is at the end of Table 5.

Table 3. Definitions of TNM Stage II Neuroendocrine Tumors of the Stomach[a]

Stage	TNM	Description
II	T2 or T3, N0, M0	T2 = Invades the muscularis propria or >1 cm in size.[b]
		T3 = Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.
T = primary tumor; N = regional lymph nodes; M = distant metastasis.
[a]Reprinted with permission from AJCC: Neuroendocrine Tumors: Stomach. In: Amin MB, Edge SB, Greene FL, et al., eds.: *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer, 2017, pp. 351–9.
[b]The explanation for superscript b is at the end of Table 5.

Table 4. Definitions of TNM Stage III Neuroendocrine Tumors of the Stomach[a]

Stage	TNM	Description
III	T1, T2, T3, or T4; N1; M0	T1, T2, T3, or T4 = See Stage IV Neuroendocrine Tumors of the Stomach below in Table 5.
		N1 = Regional lymph node metastasis.
		M0 = No distant metastasis.
	T4, N0, M0	T4 = Invades visceral peritoneum (serosal) or other organs or adjacent structures.[b]
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors: Stomach. In: Amin MB, Edge SB, Greene FL, et al., eds.: *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer, 2017, pp. 351–9.

[b]The explanation for superscript b is at the end of Table 5.

Table 5. Definitions of TNM Stage IV Neuroendocrine Tumors of the Stomach[a]

Stage	TNM	Description
IV	TX, T0, T1, T2, T3, or T4; NX, N0, N1; M1	TX = Primary tumor cannot be assessed.
		T0 = No evidence of primary tumor.
		T1 = Invades the lamina propria or submucosa and ≤1 cm in size.[b]
		T2 = Invades the muscularis propria or >1 cm in size.[b]

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors: Stomach. In: Amin MB, Edge SB, Greene FL, et al., eds.: *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer, 2017, pp. 351–9.

[b]For any T, add (m) for multiple tumors [TX(#), where X = 1-4 and # = number of primary tumors identified]; for multiple tumors with different Ts, use the highest.

Stage	TNM	Description
		T3 = Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa.
		T4 = Invades visceral peritoneum (serosal) or other organs or adjacent structures.[b]
		NX = Regional lymph nodes cannot be assessed.
		N0 = No regional lymph node metastasis.
		N1 = Regional lymph node metastasis.
		M1 = Distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors: Stomach. In: Amin MB, Edge SB, Greene FL, et al., eds.: *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer, 2017, pp. 351–9.

[b]For any T, add (m) for multiple tumors [TX(#), where X = 1-4 and # = number of primary tumors identified]; for multiple tumors with different Ts, use the highest.

Duodenal neuroendocrine tumors

Table 6. Definitions of TNM Stage I Neuroendocrine Tumors of the Duodenum and Ampulla of Vater[a]

Stage	TNM	Description
I	T1, N0, M0	T1 = Tumor invades the mucosa or submucosa only and is ≤1 cm (duodenal tumors); tumor ≤1 cm and confined within the sphincter of Oddi (ampullary tumors).
		N0 = No regional lymph node involvement.
		M0 = No distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Duodenum and Ampulla of Vater. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 361–73.

Table 7. Definitions of TNM Stage II Neuroendocrine Tumors of the Duodenum and Ampulla of Vater[a]

Stage	TNM	Description
II	T2 or T3; N0, M0	T2 = Tumor invades the muscularis propria or is >1 cm (duodenal); tumor invades through sphincter into duodenal submucosa or muscularis propria, or is >1 cm (ampullary).
		T3 = Tumor invades the pancreas or peripancreatic adipose tissue.
		N0 = No regional lymph node involvement.
		M0 = No distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Duodenum and Ampulla of Vater. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 361–73.

Table 8. Definitions of TNM Stage III Neuroendocrine Tumors of the Duodenum and Ampulla of Vater[a]

Stage	TNM	Description
III	T4, N0, M0	T4 = Tumor invades the visceral peritoneum (serosa) or other organs.
		N0 = No regional lymph node involvement.
		M0 = No distant metastasis.
	Any T, N1, M0	Any T = See Stage IV Neuroendocrine Tumors of the Duodenum and Ampulla of Vater below in Table 9.
		N1 = Regional lymph node involvement.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

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Stage	TNM	Description
		M0 = No distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

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Table 9. Definitions of TNM Stage IV Neuroendocrine Tumors of the Duodenum and Ampulla of Vater[a]

Stage	TNM	Description
IV	Any T, Any N, M1	TX = Primary tumor cannot be assessed.
		T1 = Tumor invades the mucosa or submucosa only and is ≤1 cm (duodenal tumors); tumor ≤1 cm and confined within the sphincter of Oddi (ampullary tumors).
		T2 = Tumor invades the muscularis propria or is >1 cm (duodenal); tumor invades through sphincter into duodenal submucosa or muscularis propria, or is >1 cm (ampullary).
		T3 = Tumor invades the pancreas or peripancreatic adipose tissue.
		T4 = Tumor invades the visceral peritoneum (serosa) or other organs.
		NX = Regional lymph nodes cannot be assessed.
		N0 = No regional lymph node involvement.
		N1 = Regional lymph node involvement.
		M1 = Distant metastases.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

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Jejunal and ileal neuroendocrine tumors

Table 10. Definitions of TNM Stage I Neuroendocrine Tumors of the Jejunum and Ileum[a]

Stage	T[b]NM	Description
I	T1, N0, M0	T1 = Invades lamina propria or submucosa and ≤1 cm in size.
		N0 = No regional lymph node metastasis has occurred.
		M0 = No distant metastasis.
T = primary tumor; N = regional lymph nodes; M = distant metastasis.		
[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Jejunum and Ileum. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 375–87.		
[b]The explanation for superscript b is at the end of Table 13.		

Table 11. Definitions of TNM Stage II Neuroendocrine Tumors of the Jejunum and Ileum[a]

Stage	T[b]NM	Description
II	T2 or T3; N0, M0	T2 = Invades muscularis propria or >1 cm in size.
		T3 = Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa.
		N0 = No regional lymph node metastasis has occurred.
		M0 = No distant metastasis.
T = primary tumor; N = regional lymph nodes; M = distant metastasis.		
[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Jejunum and Ileum. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 375–87.		
[b]The explanation for superscript b is at the end of Table 13.		

Table 12. Definitions of TNM Stage III Neuroendocrine Tumors of the Jejunum and Ileum[a]

Stage	T[b]NM	Description
III	T1, T2, T3, or T4; N1, N2; M0	T1, T2, T3, or T4 = See Stage IV Neuroendocrine Tumors of the Jejunum and Ileum below in Table 13.
		N1 = Regional lymph node metastasis <12 nodes.
		N2 = Large mesenteric masses (>2 cm) and/or extensive nodal deposits (≥12), especially those that encase the superior mesenteric vessels.
		M0 = No distant metastasis.
	T4, N0, M0	T4 = Invades visceral peritoneum (serosal) or other organs or adjacent structures.
		N0 = No regional lymph node metastasis has occurred.
		M0 = No distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

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[b]The explanation for superscript b is at the end of Table 13.

Table 13. Definitions of TNM Stage IV Neuroendocrine Tumors of the Jejunum and Ileum[a]

Stage	T[b]NM	Description
IV	TX, T0, T1, T2, T3, or T4; NX, N0, N1, N2; M1	TX = Primary tumor cannot be assessed.
		T0 = No evidence of primary tumor.
		T1 = Invades lamina propria or submucosa and ≤1 cm in size.
		T2 = Invades muscularis propria or >1 cm in size.
		T3 = Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa.
		T4 = Invades visceral peritoneum (serosal) or other organs or adjacent structures.
		NX = Regional lymph nodes cannot be assessed.
		N0 = No regional lymph node metastasis has occurred.
		N1 = Regional lymph node metastasis <12 nodes.
		N2 = Large mesenteric masses (>2 cm) and/or extensive nodal deposits (≥12), especially those that encase the superior mesenteric vessels.
		M1 = Distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Jejunum and Ileum. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 375–87.

[b]For any T, add (m) for multiple tumors [TX(#) or TX(m), where X = 1-4, and # = number of primary tumors identified[c]]; for multiple tumors with different T, use the highest.

[c]Example: If there are two primary tumors, only one of which invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal), we define the primary tumor as either T3(2) or T3(m).

Appendiceal neuroendocrine tumors

Table 14. Definitions of TNM Stage I Neuroendocrine Tumors of the Appendix[a]

Stage	TNM	Description
I	T1, N0 M0	T1 = Tumor ≤2 cm in greatest dimension.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.
T = primary tumor; N = regional lymph nodes; M = distant metastasis.		
[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Appendix. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 389–94.		

Table 15. Definitions of TNM Stage II Neuroendocrine Tumors of the Appendix[a]

Stage	TNM	Description
II	T2 or T3; N0, M0	T2 = Tumor >2 cm but ≤4 cm.
		T3 = Tumor >4 cm or with subserosal invasion or involvement of the mesoappendix.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.
T = primary tumor; N = regional lymph nodes; M = distant metastasis.		
[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Appendix. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 389–94.		

Table 16. Definitions of TNM Stage III Neuroendocrine Tumors of the Appendix[a]

Stage	TNM	Description
III	T1, T2, T3, or	T1, T2, T3, or T4 = See Stage IV Neuroendocrine Tumors of the Appendix below in Table 17.
T = primary tumor; N = regional lymph nodes; M = distant metastasis.		
[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Appendix. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 389–94.		

Stage	TNM	Description
	T4; N1; M0	N1 = Regional lymph node metastasis.
		M0 = No distant metastasis.
	T4, N0, M0	T4 = Tumor perforates the peritoneum or directly invades other adjacent organs or structures (excluding direct mural extension to adjacent subserosa of adjacent bowel), e.g., abdominal wall and skeletal muscle.
		N0 = No regional lymph node metastasis.
		M0 = No distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Appendix. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 389–94.

Table 17. Definitions of TNM Stage IV Neuroendocrine Tumors of the Appendix[a]

Stage	TNM	Description
IV	TX, T0, T1, T2, T3, or T4; NX, N0, N1; M1	TX = Primary tumor cannot be assessed.
		T0 = No evidence of primary tumor.
		T1 = Tumor ≤2 cm in greatest dimension.
		T2 = Tumor >2 cm but ≤4 cm.
		T3 = Tumor >4 cm or with subserosal invasion or involvement of the mesoappendix.
		T4 = Tumor perforates the peritoneum or directly invades other adjacent organs or structures (excluding direct mural extension to adjacent subserosa of adjacent bowel), e.g., abdominal wall and skeletal muscle.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Appendix. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 389–94.

Stage	TNM	Description
		NX = Regional lymph nodes cannot be assessed.
		N0 = No regional lymph node metastasis.
		N1 = Regional lymph node metastasis.
		M1 = Distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Appendix. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 389–94.

Colonic and rectal neuroendocrine tumors

Table 18. Definitions of TNM Stage I Neuroendocrine Tumors of the Colon and Rectum[a]

Stage	T[b]NM	Description
I	T1, N0, M0	T1 = Tumor invades the lamina propria or submucosa and is ≤2 cm.
		N0 = No regional lymph node metastasis has occurred.
		M0 = No distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Colon and Rectum. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 395–406.

[b]The explanation for superscript b is at the end of Table 21.

Table 19. Definitions of TNM Stages IIA and IIB Neuroendocrine Tumors of the Colon and Rectum[a]

Stage	T[b]NM	Description
IIA	T2, N0, M0	T2 = Tumor invades the muscularis propria or is >2 cm with invasion of the lamina propria or submucosa.
		N0 = No regional lymph node metastasis has occurred.
		M0 = No distant metastasis.
IIB	T3, N0, M0	T3 = Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa.
		N0 = No regional lymph node metastasis has occurred.
		M0 = No distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Colon and Rectum. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 395–406.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[b]The explanation for superscript b is at the end of Table 21.

Table 20. Definitions of TNM Stage IIIA and IIIB Neuroendocrine Tumors of the Colon and Rectum[a]

Stage	T[b]NM	Description
IIIA	T4, N0, M0	T4 = Tumor invades the visceral peritoneum (serosa) or other organs or adjacent structures.
		N0 = No regional lymph node metastasis has occurred.
		M0 = No distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Colon and Rectum. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 395–406.

[b]The explanation for superscript b is at the end of Table 21.

Stage	T[b]NM	Description
IIIB	T1, T2, T3, or T4; N1; M0	T1 = Tumor invades the lamina propria or submucosa and is ≤2 cm.
		T2 = Tumor invades the muscularis propria or is >2 cm with invasion of the lamina propria or submucosa.
		T3 = Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa.
		T4 = Tumor invades the visceral peritoneum (serosa) or other organs or adjacent structures.
		N1 = Regional lymph node metastasis.
		M0 = No distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Colon and Rectum. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 395–406.

[b]The explanation for superscript b is at the end of Table 21.

Table 21. Definitions of TNM Stage IV Neuroendocrine Tumors of the Colon and Rectum[a]

Stage	T[b]NM	Description
IV	TX, T0, T1, T2, T3, or T4	TX = Primary tumor cannot be assessed.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Colon and Rectum. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 395–406.

[b]For any T, add (m) for multiple tumors [TX(#) or TX(m), where X = 1-4 and # = number of primary tumors identified[c]]; for multiple tumors with different T, use the highest.

[c]Example: If there are two primary tumors, only one of which invades through the muscularis propria into the subserosal tissue without penetration of the overlying serosa, we define the primary tumor as either T3(2) or T3(m).

Stage	T[b]NM	Description
	Any N; M1	T0 = No evidence of primary tumor.
		T1 = Tumor invades the lamina propria or submucosa and is ≤2 cm.
		T2 = Tumor invades the muscularis propria or is >2 cm with invasion of the lamina propria or submucosa.
		T3 = Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa.
		T4 = Tumor invades the visceral peritoneum (serosa) or other organs or adjacent structures.
		NX = Regional lymph nodes cannot be assessed.
		N0 = No regional lymph node metastasis has occurred.
		N1 = Regional lymph node metastasis.
		M1 = Distant metastasis.

T = primary tumor; N = regional lymph nodes; M = distant metastasis.

[a]Reprinted with permission from AJCC: Neuroendocrine Tumors of the Colon and Rectum. In: Amin MB, Edge SB, Greene FL, et al., eds.: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, pp. 395–406.

[b]For any T, add (m) for multiple tumors [TX(#) or TX(m), where X = 1-4 and # = number of primary tumors identified[c]]; for multiple tumors with different T, use the highest.

[c]Example: If there are two primary tumors, only one of which invades through the muscularis propria into the subserosal tissue without penetration of the overlying serosa, we define the primary tumor as either T3(2) or T3(m).

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Treatment Option Overview for Gastrointestinal Neuroendocrine Tumors

Treatment options for patients with gastrointestinal neuroendocrine (carcinoid) tumors include:

- Surgery.
- Somatostatin analogues.
- Interferons.
- Treatment of hepatic metastases.
- Radionuclides.
- Management of neuroendocrine tumor–related fibrosis.
- Symptomatic therapy.
- Molecular-targeted therapies (under clinical evaluation).
- Therapies for symptomatic relief.
- Antifibrotic therapies (under clinical evaluation).[1]

Surgery

The only potentially curative therapy for gastrointestinal neuroendocrine tumors, which may be possible in as many as 20% of patients, is resection of the primary tumor and local lymph nodes.[2-4] Endoscopic surgery may be suitable for some tumors depending on the location, number, size, and degree of malignancy.[4] Resection of nonhepatic tumor primaries is associated with increased median survival ranging from 69 to 139 months.[5,6] However, the extent of resection depends on the site of origin of a given tumor, the involvement of surrounding structures, and the extent of metastases.[1]

Somatostatin Analogues

The development of long-acting and depot formulations of somatostatin analogues has been important in the amelioration of symptoms of carcinoid syndrome. The result has been a substantial improvement in quality of life with relatively mild adverse effects.[1,7] The inhibitory effects of somatostatin on neurotransmission, motor and cognitive functions, smooth muscle contractility, glandular and exocrine secretions, intestinal motility, and absorption of nutrients and ions are mediated by cyclic adenosine monophosphate inhibition.[8,9] Experimentally, somatostatin has been shown to have a cytostatic effect on tumor cells. This effect involves hyperphosphorylation of the

retinoblastoma gene product and G1 cell cycle arrest, in addition to somatostatin receptor (SSTR) subtype 3 [sst(3)]-mediated (and to a lesser extent, SSTR subtype [sst(2)]-mediated) apoptosis.[10-12] Somatostatin also appears to have some antiangiogenic properties.[1] However, only a small number of patients treated with somatostatin analogue therapy experience partial tumor regression.[1,4]

Available somatostatin analogues display high affinity for sst(2) and SSTR subtype 5, low affinity for SSTR subtype 1 and SSTR subtype 4, and medium affinity for sst(3). For more information, see the Somatostatin receptor scintigraphy section. Octreotide, a short-acting somatostatin analogue and the first biotherapeutic agent used in the management of neuroendocrine tumors, exhibits beneficial effects that are limited to symptom relief, with about 70% of patients experiencing resolution of diarrhea or flushing. [1,4]

In the treatment of neuroendocrine tumors, lanreotide, a long-acting somatostatin analogue administered every 10 to 14 days, has an efficacy similar to that of octreotide and an agreeable formulation for patient use.[13] The effects of lanreotide on symptom relief are comparable to those of octreotide, with 75% to 80% of patients reporting decreased diarrhea and flushing; however, there appears to be little improvement in tumor responses over shorter-acting octreotide.[1] Depot formulations include long-acting repeatable (LAR) octreotide and a slow-release depot preparation of lanreotide. One study comparing subcutaneous short-acting octreotide with monthly LAR octreotide reported an increased median survival from the time of metastatic disease diagnosis (143 months vs. 229 months in favor of the LAR form), representing a 66% lower risk of death among patients treated with the LAR formulation.[14] A randomized controlled study in patients with metastatic midgut neuroendocrine tumors showed improved time to tumor progression with monthly LAR octreotide compared with placebo. For more information, see the Treatment of Jejunal and Ileal Neuroendocrine Tumors section.

The typical duration of treatment with somatostatin analogues is approximately 12 months because of the development of tachyphylaxis (reported less frequently with long-acting formulations) and/or disease progression.[15-17] In the management of carcinoid crises, intravenous somatostatin analogues are effective; crises are usually precipitated by anesthesia, surgical interventions, or radiologic interventions.[18] Adverse effects of somatostatin analogue administration include:[19,20]

- Nausea.
- Cramping.
- Loose stools.
- Steatorrhea.
- Cardiac conduction abnormalities and arrhythmias.
- Endocrine disturbances (e.g., hypothyroidism, hypoglycemia, or, more commonly, hyperglycemia).
- Gastric atony (rarely).

Biliary sludge and cholelithiasis occur in as many as 50% of the patients, but few patients (1%–3%) develop acute symptoms requiring cholecystectomy.[21]

Interferons

The most researched interferon in the treatment of neuroendocrine tumors is interferon alfa (IFN alfa). Comparable to somatostatin analogues, the most pronounced effects of IFN alfa are inhibition of disease progression and symptom relief, with approximately 75% of patients reporting the resolution of diarrhea or flushing.[1] IFN alfa, like other IFNs studied in the treatment of neuroendocrine tumors (e.g., IFN gamma and human leukocyte interferon), has substantial adverse effects, including alopecia, anorexia, fatigue, weight loss, fever, a flu-like syndrome, and myelosuppression. However, IFN alfa may show greater antitumor activity than somatostatin analogues.[13] Both single-agent and multiagent chemotherapeutics appear to have little role in the management of these essentially chemoresistant tumors; no protocol has shown objective tumor response rates greater than 15%.[1]

Treatment of Hepatic Metastases

The management of hepatic metastases may include surgical resection; hepatic artery embolization; cryoablation and radiofrequency ablation (RFA); and orthotopic liver transplant.[1] In one large review of 120 patients with neuroendocrine tumors, a biochemical response rate of 96% and a 5-year survival rate of 61% were reported for patients whose hepatic metastases were resected surgically.[22] The 5-year survival rate without surgical therapy was approximately 30%.[4] For hepatic artery embolization, the most frequently used single agent is gelatin powder. In more than 60 patients with neuroendocrine tumors, the use of gelatin powder resulted in 34% and 42% of patients achieving biochemical and tumor-diminution responses, respectively.[23-25] Trials using transcatheter arterial occlusion with chemoembolization have also been performed, with the most thoroughly researched combination involving hepatic artery ligation with gelatin foam and doxorubicin (4 trials and 66 patients), resulting in biochemical responses in 71% of patients and tumor regression in approximately 50% of patients.[1] However, the duration of response can be short lived after embolization, and embolization may be associated with adverse effects that range from transient symptoms (e.g., pain, nausea, fever, and fatigue), which occur in 30% to 70% of patients, to liver enzyme abnormalities, which occur in as many as 100% of patients (i.e., transaminitis and postembolization syndrome), to florid and potentially lethal carcinoid crisis with massive release of vasoactive substances.[4]

In one prospective trial, 80 RFA sessions were performed in 63 patients with neuroendocrine hepatic metastases (including 36 carcinoids), and 92% of the patients reported at least partial symptom relief. In the same 63 patients, 70% had significant or complete relief at 1 week postoperatively, with a perioperative morbidity of 5%; duration of symptom control was 11 ± 2.3 months, and median survival time was 3.9 years after the first RFA.[26] There are few trials of cryoablation of hepatic metastases, and the results of liver transplant for metastatic disease are disappointing, reflecting the typically advanced disease states of transplant recipients.[1]

Information about ongoing clinical trials is available from the NCI website.

Radionuclides

The four radionuclide conjugates most commonly used in the treatment of neuroendocrine tumors are iodine I 131-metaiodobenzylguanidine (131I-MIBG), indium In 111 (111In), yttrium Y 90, and lutetium Lu 177 (177Lu), with the latter three bound to a variety of somatostatin analogues. However, the median tumor response rate for the patients treated with 131I-MIBG is less than 5%, although the modality appears somewhat more effective in achieving biochemical stability (~50%) or tumor stability (~70%).[1] Although 111In-labeled somatostatin analogues are the most commonly studied

radiopeptides to date, largely reflecting their availability, and with therapeutic benefits similar to 131I-MIBG, the most promising advance in radiopeptide therapeutics has been the development of 177Lu-octreotate, which emits both beta and gamma radiation.[1] In the largest patient series treated to date with lutetium-labeled somatostatin analogues (n = 131; 65 with gastrointestinal neuroendocrine tumors), remission rates were correlated positively with high pretherapy octreotide scintigraphy uptake and limited hepatic tumor load.[27] In patients with extensive liver involvement, median time to progression was shorter (26 months) compared with patients who had either stable disease or tumor regression (>36 months).

Management of Neuroendocrine Tumor–Related Fibrosis

Bowel obstruction secondary to peritoneal fibrosis is the most common presenting symptom of small intestinal neuroendocrine tumors. Heart failure secondary to right-sided valvular fibrosis represents a serious extraintestinal manifestation of neuroendocrine tumor–related fibrosis. It occurs in 20% to 70% of patients with metastatic disease and it accounts for as much as 50% of neuroendocrine tumor mortality.[28,29] There is no effective pharmacological therapy for either clinical problem. In the instance of bowel obstruction, surgical lysis of the adhesions often is technically demanding because of the cocoon-like effects of extensive fibrosis stimulated by the various tumor-derived growth factors.[30] Valvular replacement usually is required to manage carcinoid heart disease.[1]

Symptomatic Therapy

In addition to the use of long-acting depot formulations of somatostatin analogues to ameliorate neuroendocrine tumor symptoms, supportive care of patients includes:

- Advising them to avoid factors that induce flushing or bronchospastic episodes, including:
  - Ingestion of alcohol, certain cheeses, capsaicin-containing foods, and nuts.
  - Stressful situations.
  - Some kinds of physical activity.

- Diarrhea may be treated with conventional antidiarrheal agents such as loperamide or diphenoxylate; more pronounced diarrhea may be treated with the 5-HT receptor subtype 2 antagonist cyproheptadine, which is effective in as many as 50% of patients and may also help alleviate anorexia or cachexia in patients with a malignant carcinoid syndrome.[1]

- Histamine 1 receptor blockade with fexofenadine, loratadine, terfenadine, or diphenhydramine may help treat skin rashes, particularly in histamine-secreting gastric neuroendocrine tumors.

- Bronchospasm can be managed with theophylline or beta-2 adrenergic receptor agonists such as albuterol.[1]

Carcinoid crisis is manifested by profound flushing, extreme blood pressure fluctuations, bronchoconstriction, dysrhythmias, and confusion or stupor lasting hours or days and may be provoked by induction of anesthesia or an invasive radiologic procedure.[18,31] This potentially fatal condition can occur after manipulation of tumor masses (including bedside palpation), administration of chemotherapy, or hepatic arterial embolization.[32] In contrast with the treatment of other causes of acute hypotension, the use of calcium and catecholamines should be avoided in carcinoid crisis because these agents provoke the release of bioactive tumor mediators that may perpetuate or worsen the situation. Plasma infusion and octreotide are used for hemodynamic support. For the

most part, the use of somatostatin analogues has replaced other pharmacological maneuvers in the treatment of crises, and their use has been associated with increased survival rates. Prophylactic use of subcutaneous octreotide or the administration of a depot somatostatin analogue in a timely fashion before any procedures are undertaken is mandatory to prevent the development of a crisis.[1]

Molecular-Targeted Therapies

Various therapies targeting vascular endothelial growth factor (VEGF), platelet-derived growth factor receptor, and mammalian target of rapamycin (mTOR) are in development.[1,33] Therapeutic agents under investigation include the VEGF monoclonal antibody, bevacizumab and VEGF tyrosine kinase inhibitors, sunitinib, vatalanib, and sorafenib.

General Therapeutic Approaches

As might be expected, therapeutic approaches to gastrointestinal neuroendocrine tumors vary according to anatomical location. In 2004, a consensus statement regarding the diagnosis and treatment of gastrointestinal neuroendocrine tumors was published on behalf of the European Neuroendocrine Tumor Society,[4] which details site-specific approaches to treatment.

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Treatment of Gastric Neuroendocrine Tumors

Type I gastric neuroendocrine (carcinoid) tumors smaller than 1 cm are indolent with minimal risk for invasion and can be removed with endoscopic mucosal resection.[1-3] Local surgical excision may be performed for rare larger or invasive tumors, but exceptional cases with large multifocal lesions may require gastric resection. Follow-up with yearly endoscopic surveillance and repeated gastroscopy with multiple gastric biopsies is required, and treatment with somatostatin analogues may prevent recurrence.[4]

For type II neuroendocrine tumors, surgery is focused on removing the source of hypergastrinemia, typically by excision of duodenal gastrinomas in patients with multiple endocrine neoplasia type I via duodenotomy with resection of lymph node metastases.[5-7] Because of their generally benign course similar to type I tumors, type II tumors can usually be managed with endoscopic resection (particularly for tumors <1 cm), followed by close endoscopic surveillance.[1,3] Liberal surgical excision or gastric resection with regional lymphadenectomy is performed for larger and multifocal tumors or for those with deep wall invasion or angioinvasion.[3] In patients with multiple tumors, somatostatin analogue treatment may be used to reduce tumor growth, particularly if hypergastrinemia has not been reversed by surgery.[4]

Sporadic type III gastric neuroendocrine tumors, which behave more aggressively than type I and type II tumors, are treated with gastric resection and regional lymphadenectomy.[3] Tumors larger than 2 cm or those with atypical histology or gastric wall invasion are most appropriately dealt with by gastrectomy or radical gastrectomy.[1,8,9] Most of these tumors are metastatic at the time of presentation.[8] The 5-year survival rate may approach 50%, but, in patients with distant metastases, it is only 10%.[10,11]

Subtyping gastric neuroendocrine tumors is helpful in the prediction of malignant potential and long-term survival and as a guide to management.[12] Based on a combined population from 24 Swedish hospitals, one study of 65 patients with gastric neuroendocrine tumors (51 type I, 1 type II, 4 type III,

and 9 poorly differentiated [designated as type IV in the study]), management varied according to tumor type. Among all of the patients, 3 received no specific treatment, 40 underwent endoscopic or surgical excision (in 10 cases combined with antrectomy), 7 underwent total gastrectomy, and 1 underwent proximal gastric resection. Radical tumor removal could not be performed in 2 of 4 patients with type III tumors and in 7 of 9 patients with poorly differentiated tumors. For more information, see the Cellular and Pathological Classification of Gastrointestinal Neuroendocrine Tumors section. Five- and 10-year crude survival rates were 96.1% and 73.9%, respectively, for type I tumors (not different from the general population) but only 33.3% and 22.2% for poorly differentiated gastric neuroendocrine tumors.[12][Level of evidence C2]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Duodenal Neuroendocrine Tumors

Duodenal neuroendocrine (carcinoid) tumors are rare, and there is no consensus on the optimal extent of surgical treatment.[1] In a retrospective review of 24 patients with a pathological diagnosis of duodenal neuroendocrine tumor, most tumors (89%) measured smaller than 2 cm in diameter, and most (85%) were limited to the mucosa or submucosa. Lymph node metastases were identified in surgical specimens in 7 (54%) of 13 patients in whom lymph nodes were examined, including 2 patients with tumors smaller than 1 cm, which were limited to the submucosa. At a mean follow-up of 46 months, the disease-specific survival rate was 100%, and only 2 patients had recurrences in regional lymph nodes. No patient was reported to have distant metastases or the carcinoid syndrome. [1][Level of evidence C1] The authors concluded that although duodenal neuroendocrine tumors are indolent, the presence of regional lymph node metastases cannot be predicted reliably on the basis of tumor size or depth of invasion, and their impact on survival is unclear.

In general, endoscopic excision of primary duodenal neuroendocrine tumors appears to be most appropriate for tumors smaller than 1 cm.[1] Duodenal neuroendocrine tumors smaller than 2 cm may be excised locally; for tumors between 1 cm and 2 cm, complete resection is ensured by operative full-thickness excision.[1,2] Follow-up endoscopy is indicated. Tumors larger than 1 cm may be difficult to remove completely endoscopically and should be evaluated with endoscopic ultrasonography before endoscopic resection is attempted because of their potential to invade beyond the submucosa.[3]

Appropriate management of tumors larger than 2 cm can be problematic.[2] However, in general, these tumors can be treated with operative full-thickness excision and regional lymphadenectomy. Lymphadenectomy is performed even in the face of negative preoperative imaging because of the high rate of lymph node metastasis for these tumors.[1]

In addition, some authors recommend that for tumors larger than 2 cm, a regional lymphadenectomy includes the lymph nodes in the following locations:

- Posterior to the duodenum and pancreatic head and anterior to the inferior vena cava.
- Posterolateral to the bile duct and portal vein.
- Anterior to the common hepatic artery.[1,4]

Regardless of the size of the primary tumor, abnormal lymph nodes detected on pretreatment imaging studies or at the time of surgery should be resected. Because little is known about the natural history of unresected, grossly evident lymph node metastases, nonoperative management might otherwise be supported. Node-positive patients should undergo continued radiographic surveillance regardless of the size of the primary tumor.[1]

Ampullary and periampullary duodenal neuroendocrine tumors deserve special consideration because they differ clinically, histologically, and immunohistochemically from neuroendocrine tumors

that occur elsewhere in the duodenum.[5] Although their rarity precludes the establishment of any definitive natural history, these tumors appear to behave unpredictably and might be viewed as a distinct category of carcinoid tumor when treatment options are being considered.[2] Compared with tumors in other duodenal sites, even small (<1 cm) ampullary and periampullary neuroendocrine tumors exhibit distinctly different aggressive behavior, and they may metastasize early.[5,6]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Jejunal and Ileal Neuroendocrine Tumors

At the time of diagnosis, 58% to 64% of patients with neuroendocrine (carcinoid) tumors of the small intestine have metastatic disease in the regional lymph nodes or the liver.[1] Early surgical treatment should include removal of the mesentery by wedge resection and resection of lymph node metastases surrounding the mesenteric artery and vein to preserve intestinal vascular supply and to limit the intestinal resection.[2] With grossly radical tumor resections, patients may remain symptom free for extended periods of time; however, because of the tenacity of neuroendocrine tumors, patients should undergo lifelong surveillance.

Surgical treatment for advanced neuroendocrine tumors involves prophylactic removal of mesenteric metastases early on because later the disease may become impossible to manage surgically.[3] Repeat surgery may be necessary if mesenteric metastases are left during primary surgery or have progressed after primary surgery.[2] These operations are difficult because of fibrosis between regions of the intestine, and surgery may result in fistulation, intestinal devascularization, or creation of a short bowel.[3] The 5-year survival rate is approximately 50% for those with inoperable liver metastases and approximately 40% for those with inoperable liver and mesenteric metastases.[4,5]

The effect of octreotide (long-acting repeatable, 30 mg intramuscularly every 28 days) on time to tumor progression in patients with metastatic midgut neuroendocrine tumors has been tested in a randomized placebo-controlled clinical trial.[6] Although the planned study accrual was 162 patients, because of slow accrual, it was stopped after 85 evaluable patients were enrolled. At an interim analysis, the median time to tumor progression was 14.3 months in the octreotide group versus 6 months in the placebo group (hazard ratio, 0.34; 95% confidence interval, 0.20–0.59; P < .0001). Quality of life was similar in both treatment groups. There was no difference in overall survival, but about three-quarters of the control group received octreotide at disease progression.[6][Level of evidence B1]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Appendiceal Neuroendocrine Tumors

Approximately 90% of appendiceal neuroendocrine (carcinoid) tumors measure smaller than 1 cm and are not located in the appendiceal base. These tumors can be consistently cured by appendectomy.[1]

Appendiceal neuroendocrine tumors larger than 2 cm require right-sided hemicolectomy and ileocecal lymphadenectomy because of the significant risk of metastasis.[1] For tumors measuring 1 to 2 cm, treatment is controversial, but hemicolectomy may be appropriate if there is invasion in the mesoappendix, if there is residual tumor in the resection margins, or in the presence of lymph node metastases. For same-size lesions confined to the appendiceal wall, appendectomy alone may carry a

low risk for metastases. Acceptable indications for hemicolectomy may include operative specimens that show high proliferative activity (high Ki-67 index), high mitotic index, or signs of angioinvasion, but evidence is limited and histological parameters for risk evaluation in appendiceal neuroendocrine tumors measuring 1 cm to 2 cm requires definition.[1-3] Follow-up should be considered in patients for whom elevated serum chromogranin A may indicate the need for extended operation. Although survival is excellent with locoregional tumor, 10-year survival is approximately 30% with distant metastases.[1]

Goblet cell carcinoid or adenocarcinoid is a rare variant of appendiceal neuroendocrine tumor with mixed endocrine and exocrine features.[1] Often presenting with a diffusely inflamed appendix and occurring in patients at a later age (~50 years), these tumors are aggressive, often with peritoneal and ovarian metastases, and occasionally appearing as mucinous adenocarcinoma.[2-4] They do not express somatostatin receptors and cannot be visualized by indium In 111-octreotide scintigraphy. Goblet cell carcinoids are treated with right-sided hemicolectomy and lymphadenectomy in combination with chemotherapy. For disseminated tumors, aggressive surgical reduction including peritonectomy and oophorectomy may be required.[1] Goblet cell carcinoids have a 10-year survival rate of approximately 60%.[2]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Colonic Neuroendocrine Tumors

Colonic neuroendocrine (carcinoid) tumors are often exophytic and large (>5 cm), but they rarely bleed. Only occasional right-sided lesions are positive with indium In 111-octreotide scintigraphy. Many of these tumors are aggressive with a high proliferation rate, and they often present with more liver metastases than regional lymph node metastases.[1] These tumors of the colon are treated similarly to adenocarcinoma of the colon.[2] Attempts to achieve radical resection by hemicolectomy or subtotal colectomy with lymphadenectomy should be made, but frequently only debulking is possible. The overall 5-year survival rate is approximately 40% and is slightly worse than the survival rate for patients with colon adenocarcinoma.[1]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Rectal Neuroendocrine Tumors

In general, rectal neuroendocrine (carcinoid) tumors often present as very small, isolated lesions.[1] The TNM (tumor, node, metastasis) system is used for rectal neuroendocrine tumors, but size appears to be one of the best estimates of recurrence. Rectal neuroendocrine tumors should be evaluated by endoscopic ultrasonography (EUS) or rectal magnetic resonance imaging (MRI). Tumors smaller than 1 cm can be safely removed by endoscopic excision.[2-5] Excised specimens should be examined histologically to exclude muscularis invasion.[2,6-8]. A report about the patients with rectal carcinoid tumors in the Surveillance, Epidemiology, and End Results (SEER) Program database demonstrated that the 5-year survival rate for patients with stage I carcinoid tumors was 97%.[9]

For patients with tumors that are larger than 2 cm or that have invasion of the muscularis as seen by EUS or MRI, surgical resection with abdominoperineal resection (APR) or low anterior resection (LAR) is recommended because of the high rate of nodal metastases and risk of distant metastatic disease. In the report from the SEER database, patients with stage II or III rectal carcinoid tumors had 5-year survival rates of 84% and 20%, respectively.[9] In a report from the National Cancer Database, among 3,287 patients with rectal carcinoid tumors, the 5-year survival rates for patients with stage II or III disease were 87.3% and 35.5%, respectively.[10]

There is considerable debate about whether local excision or rectal resection (i.e., APR or LAR) is needed for tumors that measure 1 cm to 2 cm. Although it may be possible to recognize tumors with particular atypia and high mitotic index before embarking on the more radical surgery, the presence of muscularis invasion or regional metastases generally supports rectal resection. In a multicenter series of 100 patients who underwent anterior resection for rectal carcinoid tumors, the rate of nodal metastases for patients with tumors between 1 cm and 2 cm was 31%.[11] In this series, tumor size larger than 1 cm and lymphovascular invasion were the two strongest predictors of lymph node metastases. In patients with distant metastases, prognosis is generally poor, with an overall 5-year survival rate of approximately 30%.[12]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Metastatic Gastrointestinal Neuroendocrine Tumors

Although the definitive role of surgery in patients with metastatic disease has not been established, conservative resections of the intestine, mesenteric tumors, and fibrotic areas may improve symptoms and quality of life substantially in patients with metastatic hepatic, mesenteric, and peritoneal neuroendocrine (carcinoid) tumors. If the condition of the patient is such that surgery is not

a greater risk than the disease, the primary tumor should be resected to prevent an emergency presentation with obstruction, perforation, or bleeding.[1] Despite common acceptance that resection of at least 90% of the tumor burden is required to achieve palliation, approximately 60% of patients with surgery alone will experience symptom recurrence; the 5-year survival rate is between 35% and 80%, depending on the experience of the surgical center.[2,3] Because treatment with somatostatin analogues can achieve similar rates of symptom relief with fewer adverse effects, in each patient the benefits of surgical treatment of gastrointestinal neuroendocrine tumors should be weighed carefully against the potential risks of an open exploration. Tumor debulking, however, may potentiate pharmacological therapy by decreasing the secretion of bioactive substances.[4]

Management of hepatic metastases may include surgical resection; hepatic artery embolization; cryoablation and radiofrequency ablation; and orthotopic liver transplant. For more information, see the Treatment of Hepatic Metastases section. Cytoreductive surgery for hepatic metastases from gastrointestinal neuroendocrine tumors can be performed safely with minimal morbidity and mortality resulting in regression of symptoms and prolonged survival in most patients.[5] In one large review that included 120 patients with neuroendocrine tumors, a biochemical response rate of 96% and a 5-year survival rate of 61% were reported for patients whose hepatic metastases were resected surgically.[6][Level of evidence C2]

In the case of liver metastases, localization and resection of the primary tumor may be considered, even among patients in whom the primary neoplasm is asymptomatic. In a retrospective study involving 84 patients, 60 of whom had their primary neoplasm resected, the resected group had a greater median progression-free survival (PFS) of 56 months, compared with 25 months of PFS for the primary nonresected group ($P < .001$). Median survival time for the resected group was longer at 159 months when compared with 47 months for the nonresected group ($P < .001$).[7][Level of evidence C2]

Although the response of neuroendocrine tumors to external-beam radiation therapy is very limited, palliative radiation therapy has some efficacy for bone and brain metastases and in the management of spinal cord metastases.[4]

Treatment with single-agent chemotherapy or multiple-agent chemotherapy appears to be of little benefit in the management of gastrointestinal neuroendocrine tumors because no regimen has shown objective tumor response rates greater than 15%.[4]

Treatment with radionuclides such as iodine I 131-metaiodobenzylguanidine and lutetium Lu 177-octreotate may be of benefit. For more information, see the Radionuclides section.

Somatostatin analogues and interferon alfa are the primary agents used in the treatment of carcinoid syndrome. Management of the symptoms of carcinoid syndrome may also include dietary modification and the use of various antidiarrheal agents, antihistaminics for skin rashes, and theophylline or beta-2 adrenergic receptor agonists for bronchospasm. For more information, see the sections on Somatostatin Analogues, Interferons, and Symptomatic Therapy.

Information about ongoing clinical trials is available from the NCI website.

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Recurrent Gastrointestinal Neuroendocrine Tumors

The prognosis for any patient with progressive or recurrent disease is poor. Decisions about further treatment depend on many factors, including previous treatment, site of recurrence, and individual patient considerations. Attempts at re-resecting slow-growing tumors (e.g., repeat or multiple liver resections) are worthy of consideration after extensive evaluation, as further reduction of tumor volume may provide long-term palliation. Recurrence at any single site may also be potentially resectable. Clinical trials are appropriate and should be considered when possible.

Information about ongoing clinical trials is available from the NCI website.

Current Clinical Trials

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This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of adult gastrointestinal neuroendocrine tumors. It is intended as a resource to inform and assist clinicians in the care of their patients. It does not provide formal guidelines or recommendations for making health care decisions.

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The lead reviewers for Gastrointestinal Neuroendocrine Tumors Treatment are:

- Amit Chowdhry, MD, PhD (University of Rochester Medical Center)
- Leon Pappas, MD, PhD (Massachusetts General Hospital)

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