Gastrointestinal neuroendocrine tumors in 2020

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Abstract

Gastrointestinal neuroendocrine tumors are rare slow-growing tumors with distinct histological, biological, and clinical characteristics that have increased in incidence and prevalence within the last few decades. They contain chromogranin A, synaptophysin and neuron-specific enolase which are necessary for making a diagnosis of neuroendocrine tumor. Ki-67 index and mitotic index correlate with cellular proliferation. Serum chromogranin A is the most commonly used biomarker to assess the bulk of disease and monitor treatment and is raised in both functioning and non-functioning neuroendocrine tumors. Most of the gastrointestinal neuroendocrine tumors are non-functional. World Health Organization updated the classification of neuroendocrine tumors in 2017 and renamed mixed adenoneuroendocrine carcinoma into mixed neuroendocrine neoplasm. Gastric neuroendocrine tumors arise from enterochromaffin like cells. They are classified into 4 types. Only type I and type II are gastrin dependent. Small intestinal neuroendocrine tumor is the most common small bowel malignancy. More than two-third of them occur in the terminal ileum within 60 cm of ileocecal valve. Patients with small intestinal neuroendocrine tumors frequently show clinical symptoms and develop distant metastases more often than those with neuroendocrine tumors of other organs. Duodenal and jejun-ileal neuroendocrine tumors are distinct biologically and clinically. Carcinoid syndrome generally occurs when jejuno-ileal neuroendocrine tumors metastasize to the liver. Appendiceal neuroendocrine tumors are generally detected after appendectomy. Colonic neuroendocrine tumors generally present as a large tumor with local or distant metastasis at the time of diagnosis. Rectal neuroendocrine tumors are increasingly being diagnosed since the implementation of screening colonoscopy in 2000. Gastrointestinal neuroendocrine tumors are diagnosed and staged by endoscopy with biopsy, endoscopic ultrasound, serology of biomarkers, imaging studies and functional somatostatin scans. Various treatment options are available for curative and palliative treatment of gastrointestinal neuroendocrine tumors.
INTRODUCTION

Neuroendocrine tumors (NETs) arise from the diffuse system of neuroendocrine cells i.e. cells with features of both nerve cells (which can receive message from the nervous system) and endocrine cells (which have the ability to synthesize and secrete monoamines, peptides and hormones)[1]. Neuroendocrine cells do not have any axons or nerve terminals. The electrical signals from the nervous system can be converted into hormonal signals with production of hormones, peptides and amines. As neuroendocrine cells are ubiquitous in our body, NETs can form in different organs including the gastrointestinal tract (GI), pancreas, lungs, gallbladder, thymus, thyroid gland, testes, ovaries and skin. Most of the NETs are in the GI (55%) or in the bronchopulmonary system (25%). NETs can develop throughout the GI (GI-NETs) in the following areas: The small intestine (45%), rectum (20%), appendix (16%), colon (11%), and stomach (7%) [2]. The diagnosis of rectal NETs has surpassed the diagnosis of small intestinal NETs (SI-NETs) since the year 2000 (except year 2001) when screening colonoscopy was implemented[3]. NETs are a heterogenous group of benign or malignant tumors with various morphologies and functions. The incidence and prevalence of NETs have been increasing over the last few decades[4]. About 40% NETs are hormone secreting[5]. Most NETs are slow growing with a small percentage of NETs being rapidly growing[6]. About 20% of NETs are associated with hereditary genetic syndromes like multiple endocrine neoplasia type 1 (MEN1) and neurofibromatosis type 1 (NF-1)[7]. We will review the epidemiology, classification, biology, clinical aspects, and management of GI-NETs in this article.

EPIDEMIOLOGY

NETs constitute only 0.5% of all malignant conditions and 2% of all malignant tumors of the GI[8]. In the United States, the incidence and prevalence of NETs have been increasing over the last few decades possibly due to early-stage detection, increased awareness, and widespread use of endoscopy and imaging studies for various gastrointestinal diseases. There was a 6.4-fold increase in annual age-adjusted incidence of NETs from 1973 (1.09 per 100000 persons) to 2012 (6.98 per 100000 persons). This increased incidence was found in all organs. 2000-2012 Surveillance, Epidemiology, and End Results (SEER) 18 registry showed the highest incidence of GI-NET to be 3.56 per 100000 population[9]. The prevalence also increased from 0.006% in 1993 to 0.048% in 2012. NETs are more prevalent in females than in males with a ratio of 2.5:1[10]. Bronchopulmonary NETs are more common in Caucasians[11] whereas GI-NETs are more common in African Americans[12].
CLASSIFICATION OF GASTROINTESTINAL NET

In 2017, the World Health Organization (WHO) updated the classification of NET. The histologic grading is based on mitotic index and Ki-67 index which are recorded in hot spots of the tumor. During cell division, Ki-67 protein is found in the cell nucleus. The proportion of Ki-67 – positive tumor cells (Ki-67 index) correlates with cellular proliferation, clinical course and its prognosis. Higher grade is considered if there is any discrepancy between mitotic index and Ki-67 index. The mixed adenoneuroendocrine carcinoma was renamed as MiNEN (mixed neuroendocrine neoplasm) considering that the mixed neoplasms may contain non-endocrine component other than adenocarcinoma, for example acinar cell carcinoma or squamous cell carcinoma. Each component must be at least 30% to fall into the category of MiNEN[13]. The 2017 WHO Classification of GI-NETs is outlined in the Table 1[14].

BIOLOGY OF NET

NETs are slowly growing tumors. As mentioned before, neuroendocrine cells have both neural and endocrine characteristics. They have cytoplasmic dense core granules which contain chromogranin A (CgA), synaptophysin and Neuron-specific enolase (NSE) and can synthesize and secrete various physiologically active monoamines, peptides and hormones. CgA and synaptophysin are necessary for diagnostic confirmation but proliferative index of Ki-67 and mitotic index are necessary for prognostic information. CgA is released from the cytoplasmic chromaffin granules into the blood, and as a result, serum CgA is raised in both non-functioning and functioning NETs. Serum CgA is the most commonly used biomarker to assess the disease burden and monitor treatment response[15]. The type of hormone secreted by functioning NETs varies with different organs. While GI-NETs synthesize and secrete serotonin and other vasoactive amines, Pancreatic-NETs (P-NETs) produce and secrete glucagon, insulin, gastric and somatostatin. Recently, there has been tremendous progress in the understanding of tumor microenvironment (TME) of NETs. TME consists of stromal cells, extracellular matrix (ECM), endothelial cells and inflammatory cells. NET cells activate and proliferate stromal cells i.e., fibroblasts by secreting various soluble factors which include serotonin, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β). Fibroblast activation leads to local and distant fibrosis. Some peculiar changes are seen in the ECM of NETs. In SI-NET, focal desmoplasia is common[16] and this is due to the presence of plenty of myofibroblasts/stellate cells producing collagen III fibers, desmin and vimentin[17]. Somatostatin receptors and their downstream pathways have been found to be primary regulators of neuroendocrine cell proliferation, protein synthesis and hormone secretion[18]. Various proangiogenic factors are secreted by NET cells. These include vascular endothelial growth factor, FGF, PDGF, semaphorins and angiopoietins. These lead to endothelial cell recruitment, proliferation, and neovascularization making the tumor highly vascular (density of microvessels becomes 10 times higher than that in epithelial tumors)[19]. Different immune cells (T cell, B cells, macrophages, dendritic cells, NK cells and mast cells) infiltrate the NETs making the TME immunosuppressed; this is more pronounced in P-NETs than SI-NETs probably due to a higher mutation rate in P-NETs[20]. CD+FoxP3+ T regulatory (Treg) and tumor-associated macrophage infiltration have been associated with high-grade NET[21,22] and poor prognosis. Soluble inhibitory factors secreted by NETs impair the maturation and function of dendritic cells, and as a result, antigen presentation to dendritic cells becomes impaired. NK cells also show impaired cytolytic activity in patients with GI-NETs. Tumor-infiltrating neutrophils, mast cells and macrophages can cause complex inflammatory and angiogenic responses. It is not known whether tumor-infiltrating lymphocytes have anti-tumor activity in the TME that can lead to an indolent course of NETs. Checkpoint proteins are heterogeneously expressed in GI/G2 NETs. NEC and 3% of P-NETs express enough checkpoint proteins to become appropriate candidates for immunotherapy[23]. Thus, TME not only controls the behavior, growth, invasive and metastatic capabilities, and local and systemic immune suppressive effects of NETs but also response to treatment.
Table 1 World Health Organization classification of gastrointestinal neuroendocrine tumors

| Well-differentiated neuroendocrine neoplasms (NENs) | Ki-67 index (%) | Mitotic index/10 HPF |
|----------------------------------------------------|-----------------|---------------------|
| NET grade 1 (G1)                                   | < 3             | < 2                 |
| NET grade 2 (G2)                                   | 3-20            | 2-20                |
| NET grade 3 (G3)                                   | > 20            | > 20                |
| Poorly differentiated neuroendocrine neoplasms (NENs) |                 |                     |
| NEC grade 3                                         |                 |                     |
| - Small cell type                                   | > 20            | > 20                |
| - Large cell type                                   |                 |                     |
| Mixed neuroendocrine neoplasms (MiNEN)             |                 |                     |

Source: Adapted from WHO Classification of Tumors of Endocrine Organs, Fourth edition (2017) [14]

CLINICAL ASPECTS OF GI-NETS

Gastric NETs

Most of them develop from enterochromaffin-like cells (ECL cells) while a small proportion develop from non-ECL cells of gastric mucosa. G-NETs constitute 7% to 8% of all NETs. The incidence of gastric NETs (G-NETs) has been increasing (more than 10-fold over the last 30 years) [24]. As per the SEER 9 registry, the incidence of G-NETs increased from 0.31 per 1000000 persons in 1975 to 4.85 per 1000000 persons in 2014 [25]. The increased incidence is probably due to multiple factors including the extensive use of upper endoscopies, evaluation of subepithelial lesions by endoscopic ultrasonographies (EUS), improved immunohistochemical staining, imaging modalities, tumor biomarkers, molecular markers and increased awareness of the diagnosis. There are rare reported cases of well-differentiated NENs (gastric carcinoids) developing after long-term use of proton pump inhibitors [26,27]. G-NETs are classically categorized into 4 types [28] as described below and summarized in Table 2.

Type I: It is the most common type of G-NETs accounting for 70%-80% of all G-NETs. It occurs in response to hypergastrinemia in the setting of achlorhydria (gastric pH > 7) typically seen in autoimmune chronic atrophic gastritis (CAG) where gastric parietal cells in the gastric body and fundus are destroyed by an autoimmune process. About 5% of autoimmune CAG may develop type I G-NET. It can also occur in Helicobacter pylori-induced CAG with hypergastrinemia [30]. Hypergastrinemia leads to ECL cells hyperplasia and promotes the formation of G-NETs in patients with CAG [31]. Most of the time, G-NETs are diagnosed incidentally in the investigation of patients with anemia or dyspepsia or other gastrointestinal symptoms. Endoscopically, they generally appear as smooth, rounded, subcentimeter, subepithelial multiple polypoid lesions with or without central depression in the gastric fundus or gastric body [32]. EUS may show a hypoechoic or isoechoic lesion with regular margins in the lamina propria (2nd echo layer) or submucosa (3rd echo layer) [33]. EUS is also helpful in finding out local metastasis to lymph nodes which generally occurs in 5% of cases. Computerized tomography (CT) or magnetic resonance imaging (MRI) should be done to rule out any distant metastasis which can happen in 2% of cases. Histologically, most G-NETs are positive for CgA, NSE, and vesicular monoamine transporter 2 (characteristic of histamine producing cells). A multi-disciplinary team should be involved to individualize treatment. Endoscopic resection either by polypectomy, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is the treatment of choice if the lesions are not extensive [34]. But if the lesions are large (> 1 cm), extensive (involving the muscularis propria on EUS), multifocal (> 5) and recurrent on a previous endoscopic resection site, wedge resection of the stomach or even gastric antrectomy should be considered to eliminate the source of gastrin [35]. But all NEC should be treated by radical gastrectomy [36]. Patients should have surveillance.
endoscopy every 6 mo following endoscopic resection or surgery. The prognosis of type I G-NETs is excellent with a 5-year survival of almost 100% (90%-95%)[30]. One study suggested that Netazepide (a gastrin/cholecystokinin 2 receptor antagonist) could be a potential medical treatment of type I G-NETs as it decreased the number and size of type I G-NETs as well as serum CgA[31].

Type II: It is the least common type of G-NETs accounting for 5%-6% of all G-NETs. It occurs in response to hypergastrinemia in the setting of hyperchlorhydria (gastric pH ≤ 2) typically associated with MEN1-Zollinger-Ellison syndrome (ZES) and rarely sporadic ZES[32]. In patients with normal gastric mucosa, hypergastrinemia causes gastric mucosal hypertrophy, ECL hyperplasia and dysplasia. However, a defect in the suppressor protein menin due to mutation of MEN1 gene located on chromosome 11q13 leads to transformation of G-NETs[33]. As a result, G-NETs occur in < 1% of sporadic ZES and 13%-43% of MEN1-ZES[34]. Endoscopically, they appear as multiple, small (1-2 cm) polyoid lesions in the stomach. Histologically, they are generally well differentiated NENs limited to muocsa and/or submucosa. Metastasis can occur in 10% to 13% of cases. Treatment includes surgical resection of gastrinoma and aggressive gastrectomy. There are some case series showing somatostatin analogue octreotide could regress the type II G-NETs and serum gastrin levels[35]. The prognosis of type II G-NETs is good with a 5-year survival of 70%-90%.

Type III: These are sporadic G-NETs accounting for 15%-20% of all G-NETs. They occur most commonly in men over the age 50 years in the presence of normogastrinemia and normal gastric mucosa. They develop from ECL cells in most cases in the absence of ECL hyperplasia and are not dependent on gastrin. Patients are often asymptomatic or may present with abdominal pain, weight loss and iron deficiency anemia (IDA)[36]. Hepatic metastasis can be the initial presentation. Endoscopically, they appear as a large (> 2 cm), solitary, polyoid tumor arising from the gastric body, fundus or gastric antrum. Histologically, they are aggressive grade 3 NECs with high potential for local and distant metastasis (> 50%) regardless of their size. Treatment of non-metastatic type III G-NET is surgical resection (partial or total gastrectomy) and regional lymphadenectomy[37]. Treatment options for metastatic lesions include octreotide (for carcinoid syndrome) systemic chemotherapy (streptozocin, 5-fluorouracil with leucovorin, cyclophosphamide, doxorubicin, oxaplatin, dacarbazine), molecular targeted agents (bevacizumab, sunitinib, sorafenib, everolimus), targeted radionucleotide therapies (indium-DTPA-octreotide, Lutetium-DOTATyr3-octreotide, Yttrium-DOTATyr3-octreotide), transarterial chemoembolization (TACE) and radiofrequency ablation (for symptomatic hepatic metastasis)[38]. Type III G-NET carries a worse prognosis with a 5-year survival rate of less than 35%.

Type IV: They are the most rare of all G-NETs. They occur more commonly in males above the age of 60 (mean age 63-70 years). They are of non-ECL cell origin and gastrin-independent. Hypergastrinemia is seen in one third of cases and CAG is frequently (82% of cases) present[39]. Patients may present with dyspepsia,
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Endoscopically, the tumor appears as a large (usually > 4 cm) polypoid tumor anywhere in the stomach. At the time of diagnosis, type IV G-NETs may have already metastasized to the lymph nodes and liver. Histologically, they are aggressive NECs grade 3 almost identical to gastric adenocarcinoma except for the presence of endocrine cells in the tumor matrix. Angioinvasion, lymphoinvasion and deep wall invasion are also present. Immunohistochemically, CgA may be absent but NSE and synaptophysin are strongly expressed. Treatment of localized type IV G-NET includes partial or total gastrectomy with regional lymphadenectomy followed by adjuvant chemotherapy. Cisplatin-based chemotherapy (etoposide plus platolin) is offered as the first line treatment for metastatic type IV G-NET. FOLFOX (folinic acid, fluorouracil and oxaliplatin) and FOLFIRI (folinic acid, fluorouracil and irinotecan) are considered as second-line treatment options when Cisplatin-based therapy fails. The prognosis is extremely poor with a mean survival of 6.5-14.9 mo.

**SI-NETs**

Their incidence has surpassed that of small bowel adenocarcinomas. Currently the most common primary small bowel malignancy accounting for 25% of all GI-NETs. SI-NETs arise from enterochromaffin cells located at the base of the intestinal crypts in the submucosa. The incidence of SI-NET has increased probably due to increased diagnostic modalities. As per SEER registry, the age-adjusted annual incidence of jejunal and ileal NETs is 0.67 per 100000 population in the United States. SI-NETs are indolent, often multifocal and have a distal predilection. More than two thirds of SI-NETs are in the terminal ileum within 60 cm of ileocecal valve. The approximate distribution of SI-NET is duodenum—2%, jejunum-7% and ileum-89%. Patients with SI-NETs frequently experience clinical symptoms. SI-NETs metastasize to distant locations more often than other types of NETs. Duodenal and jejuno-ileal NETs are biologically and clinically distinct.

**Duodenal NETs**

They are becoming more prevalent. They represent 2% to 3% of all GI-NETs. More commonly seen in males, the mean age of diagnosis is 6th decade of life. Most of the duodenal NETs (d-NETs) are solitary, small lesions limited to the duodenal mucosa and submucosa. The majority remain silent and are diagnosed incidentally during routine investigations. At the time of diagnosis, 40% to 60% of d-NETs are already metastatic to regional lymph nodes and 10% to the liver. Tissue diagnosis is generally done by endoscopic biopsy or EUS with fine needle aspiration (FNA). All patients with d-NETs should be checked for fasting serum gastrin, serum CgA and screen for MEN1 syndrome. 5-types of d-NETs are found. These are described as follows and summarized in Table 3.

**Gastrinomas:** They are subcentimeter multiple tumors originating from G-cells in the submucosal layer of proximal duodenum (D1-57%, D2-31%, D3-6% and D4-3%) and secrete excessive gastrin. They account for about 10% of all d-NETs. They are the most common functional d-NETs followed by somatostatinoma > 80% of gastrinomas arise in the gastrinoma triangle (arbitrarily defined - superiorly confluence of cystic duct and common bile duct, inferiorly 2nd and 3rd portion of duodenum, and medially body and neck of pancreas). Duodenal wall gastrinoma is seen in 40%-50% of all gastrinoma. They are the most common cause of ZES. They could be sporadic (75%) or part of MEN1-ZES. Clinically they present with chronic, recurrent and refractory peptic ulcer disease (PUD), chronic diarrhea, and gastroesophageal reflux disease (GERD). 54% of duodenal gastrinomas can be malignant. Gastrinomas are generally diagnosed biochemically by the presence of high fasting serum gastrin level, basal acid output (BAO)/maximal acid output (MAO) > 0.6 and positive Secretin suppression test. Duodenal gastrinomas can be localized by various investigations which include EUS, somatostatin receptor scintigraphy (SRS), CT, MRI, selective angiography, Indium 111-labeled diethyleneriamine penta-acetic acid (DTPA) octreotide and (68)Ga-DOTATE PET/CT scan. Recent studies suggest that (68)Ga-DOTATE PET/CT scan is more sensitive and specific than 111In-DTPA-Octreotide scan in detecting primary and metastatic NETs. Intraoperative endoscopic transillumination of duodenal wall (transillumination from the serosal side by the surgeon while examining the mucosal side by the endoscopist) is also very helpful in detecting duodenal wall gastrinomas. The treatment of nonmetastatic duodenal gastrinoma is surgical resection or enucleation of the tumor without pancreaticoduodenectomy. In patients with duodenal gastrinoma with hepatic metastases, surgical resection offers the best chance for cure. The 5-year survival rate for patients with non-metastatic gastrinoma is approximately 70%-80%.
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| Type                  | Location                              | Presenting symptoms                                      | Diagnosis                                                                 | Treatment                                                                                                                                 |
|-----------------------|---------------------------------------|----------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Gastrinomas           | Proximal duodenum. > 80% gastrinoma triangle | Chronic diarrhea, recurrent and refractory peptic ulcer disease, gastroesophageal reflux disease | BAO/MAO > 0.6, positive Secretin suppression test, EUS, somatostatin receptor scintigraphy (SRS), CT, MRI, selective angiography, Indium 111-labeled diethylenetriamine penta-acetic acid (DTPA) octreotide and (68)Ga-DOTATE PET/CT scan | Surgical resection or enucleation of the tumor without pancreaticoduodenectomy for nonmetastatic duodenal gastrinoma. In patients with duodenal gastrinoma with hepatic metastasis treatment options include hormonal therapy with octreotide, chemotherapy (streptozocin, doxorubicin, 5-fluorouracil), radiotherapy with yttrium 90-DOTA-lanreotide, hepatic embolization alone or with chemoembolization, cytoreductive surgery and liver transplantation. |
| Somatostatinoma       | Ampullary or peri-ampullary region     | Nausea, abdominal pain, weight loss, obstructive jaundice or very rarely somatostatinoma syndrome | CT, MRI, endoscopy, EUS-FNA                                                | Endoscopic resection should be adequate if the NET is less than 1 cm. Transduodenal excision should be done for 1-2 cm tumor. But Whipple’s surgery with local lymph node resection should be considered for more than 2 cm tumor. |
| Gangliocytic paraganglioma | Peri-ampullary region                  | Asymptomatic, gastrointestinal bleeding, anemia, abdominal pain | Endoscopy, EUS-FNA, CT                                                      | Endoscopic resection or radical excision including pancreaticoduodenectomy depending on the size, depth of invasion and lymph node metastasis. |
| Non-functioning d-NETs | Proximal duodenum                      | Asymptomatic, nausea, vomiting                           | Transduodenal resection is indicated for d-NETs invading the muscularis propria. Radial surgery is advocated for d-NETs > 2 cm in diameter, d-NETs with lymph nodes involvement and all peri-ampullary d-NETs | Endoscopic resection or radical surgery or chemotherapy. |
| Duodenal NECs         | Peri-ampullary region                  | Asymptomatic, nausea, vomiting                           | Endoscopy, EUS-FNA                                                         | Endoscopic resection or radical excision including pancreaticoduodenectomy depending on the size, depth of invasion and lymph node metastasis. |

BAO: Basal acid output; MAO: Maximal acid output; (68)Ga-DOTATE PET/CT scan: Gallium-68 DOTATE positron emission tomography/computed tomography scan; d-NETs: Duodenal neuroendocrine tumors; CT: Computerized tomography; MRI: Magnetic resonance imaging; EUS: Endoscopic ultrasonography; FNA: Fine needle aspiration.

Somatostatinomas: They originate from D-cells in the ampullary or periampullary region of the duodenum and secrete excessive amount of somatostatin. They can be sporadic or part of MEN1 syndrome or associated with NF-1. They occur in up to 10% of patients with NF-1. Somatostatinomas are generally solitary, large, malignant tumors and have metastasized to lymph nodes or the liver at the time of diagnosis. Clinically, duodenal somatostatinomas may present with non-specific or mechanical symptoms like nausea, abdominal pain, weight loss, obstructive jaundice or very rarely somatostatinoma syndrome which consists of the triad of diabetes mellitus, cholelithiasis and steatorrhea. Most of the time, duodenal somatostatinomas are detected incidentally during imaging studies like CT or MRI or endoscopy. They can be further evaluated by EUS with FNA or FNA biopsy (FNAB). Histologically, psammoma bodies are present inside the tumor cells in 68% cases of duodenal somatostatinoma. Endoscopic resection should be adequate if the NET is less than 1 cm. Transduodenal excision should be done for 1-2 cm tumor. But Whipple’s surgery...
with local lymph node resection should be considered for tumors that exceed 2 cm.

**Gangliocytic paraganglioma:** They are rare duodenal NETs with a predilection for the second part of duodenum near the ampulla. The tumor mostly exhibits a benign nature except regional lymph node metastasis in 5% to 7% of cases. The tumor size varies from 0.5 cm to 10 cm (average 2.5 cm). They can remain asymptomatic or present with gastrointestinal bleeding and anemia due to mucosal ulceration or abdominal pain due to mass effect. They are generally detected during imaging studies done for other indications. Endoscopically, they look like subepithelial tumors, deeming mucosal biopsy nondiagnostic. The tumors are isoechoic on EUS. CT can identify them as soft tissue masses. Histologically, they consist of spindle, epitheloid and ganglion cells and the diagnosis is confirmed by immunohistochemical staining. Treatment includes endoscopic resection or radical excision including pancreaticoduodenectomy depending on the size, depth of invasion and lymph node metastasis.

**Non-functioning d-NETs:** The majority (90%) of d-NETs are non-functional and are detected during routine endoscopy done for other reasons. Patients may remain asymptomatic or present with obstructive symptoms like nausea, vomiting or jaundice. EMR should be considered for d-NETs < 2 cm confined to submucosa. Transduodenal resection is indicated for d-NETs invading the muscularis propria. Radial surgery is advocated for d-NETs > 2 cm in diameter, d-NETs with lymph nodes involvement and all peri-ampullary d-NETs.

**Duodenal NECs:** They are extremely rare aggressive tumors proximal to the ampullary region. Patients may present with abdominal pain, nausea, vomiting and gastrointestinal bleeding. Upper endoscopy may show a polyoid mass near the ampulla and this is further evaluated by EUS-FNA/FNAB. Histologically solid “sheetlike” proliferation of tumor cells with high mitotic index is found. In comparison to well-differentiated NENs, duodenal NECs are more invasive in terms of lymphovascular invasion, duodenal wall invasion beyond submucosa, local lymph node metastasis and distant metastasis. Its course of deterioration is rapidly progressive despite radical surgery or chemotherapy.

**Jejuno-ileal NETs**

They account for 23% to 28% of all GI-NETs. Most of the Jejuno-ileal NETs (JI-NETs) are nonfunctioning. The mean age of diagnosis is 6th or 7th decade of life with no sex predilection. The JI-NETs are generally > 2 cm in size, and consist of multiple tumors in up to 40% of cases. At the time of diagnosis, 70% of them have invaded the muscularis propria with metastasis to the regional lymph nodes, and 50% of patients may have hepatic metastasis regardless of tumor size. The hallmark of JI-NETs is desmoplastic reaction leading to mesenteric fibrosis which may manifest in about 50% of cases. Fibrosis around the metastatic lymph nodes causes mesenteric contraction which can kink the small bowel resulting in intestinal obstruction. Mesenteric fibrosis can also impinge on the mesenteric blood vessels giving rise to mesenteric ischemia in about 10% of affected patients. Desmoplastic reaction can also involve the retoperitoneum leading to retroperitoneal fibrosis, obstructive uropathy and hydronephrosis. Clinically, patients may be completely asymptomatic or may present with abdominal pain, intestinal obstruction, gastrointestinal bleeding and decreased urination. Radiologically, mesenteric fibrosis appears as a mesenteric mass with linear soft tissue opacities and possible calcification radiating outwards in a “wheel spoke” pattern. Mesenteric fibrosis does not depend on the NET size or Ki-67 proliferative index. It is associated with not only various comorbidities but also distant metastasis and poor prognosis. Diagnostic modalities include: (1) Biomarkers: Serum CgA, serum NSE and urinary 5-hydroxy indole acetic acid (as a marker of carcinoid syndrome); (2) Diagnostic endoscopy: Capsule endoscopy and balloon-assisted or spiral endoscopy; and (3) Diagnostic imaging: SRS (OctreoScan), (68)Ga-DOTATE PET/CT or 111In-DTPA-Octreotide scan.

Treatment of JI-NET includes surgical resection of primary NET with regional lymphadenectomy even in the presence of hepatic metastasis. There is no role of chemotherapy in well- differentiated JI-NEN. Combination chemotherapy - capcitabine and temozolomide for metastatic poorly differentiated JI-NEN, and combination of cisplatin or carboplatin and etoposide for JI-NEC have been found to be helpful. Hepatic metastasis can be treated by octreotide therapy, transarterial embolization with microparticles (bland embolization), TACE, radiotherapy (peptide receptor radionucleotide therapy) with yttrium 90-DOTA-lanreotide or 177-lutetium-
loperamide and cholestyramine are good adjunctive therapies to control diarrhea.

carcinoid syndrome refractory to (peptide receptor radioligand therapy): Can improve diarrhea in patients with carcinoid syndrome refractory to octreotide in combination with octreotide can improve flushing and diarrhea in patients with tremendous side effects; (3) Everolimus - a mammalian target of rapamycin inhibitor cell cycle arrest and inhibit angiogenesis. But Interferon is rarely used because of its therapy (flushing, diarrhea) in 40% to 50% of cases refractory to somatostatin analog can control diarrhea in patients with carcinoid syndrome not responding to somatostatin analog therapy; (2) Interferon-alpha: 3 to 5 million units to 3 to 5 times per week can improve the symptoms of carcinoid syndrome (flushing, diarrhea) in 40% to 50% of cases refractory to somatostatin analog therapy. Interferon has multiple antitumor effects as it can stimulate T cells, induce cell cycle arrest and inhibit angiogenesis. But Interferon is rarely used because of its tremendous side effects; (3) Everolimus - a mammalian target of rapamycin inhibitor in combination with octreotide can improve flushing and diarrhea in patients with carcinoid syndrome refractory to octreotide therapy; (4) 177-Lutetium dotate (peptide receptor radioligand therapy): Can improve diarrhea in patients with carcinoid syndrome refractory to octreotide; and (5) Anti-diarrheal agents – lomotil, loperamide and cholestyramine are good adjunctive therapies to control diarrhea.

Carcinoid syndrome

It is the combination of symptoms which occur in about 20%-30% of cases of JI-NETs when they metastatize to the liver. The syndrome occurs when bioactive amines and peptides (about 40 different types) produced by the NETs enter the systemic circulation. 90% of carcinoid syndrome have metastatic NETs to the liver except bronchopulmonary NETs, ovarian NETs and GI-NETs with extensive retroperitoneal lymph node metastasis as they can release their bioactive amines directly into the systemic circulation and do not need to be metastatic to the liver to produce carcinoid syndrome. Clinically, the syndrome is characterized by chronic flushing (occurring in 94% of patients), and/or diarrhea (occurring in 80% of patients). Other manifestations include wheezing (occurring in 10%-20% of patients) due to bronchospasm, pellagra due to niacin deficiency and carcinoid heart disease (occurring in 40%-50% of patients). Flushing is due to excessive release of tachykinins (substance P, neurokinin A, neuropeptide K) and histamine. Diarrhea is mainly due to excessive secretion of serotonin which increases gastrointestinal motility and secretion. Bronchospasm is histamine-induced but carcinoid wheezing should not be confused with bronchial asthma as administration of beta-2 agonist may cause severe and prolonged vasodilatation. As most of the dietary tryptophan (70% instead of only 1% normally) is converted to serotonin by the NETs leading to deficiency of tryptophan necessary for niacin synthesis, niacin deficiency occurs. Carcinoid heart disease is due to histamine-induced plaque-like deposit of fibrous tissue on the endocardium and valves of right heart leading to restrictive cardiomyopathy, and tricuspid and pulmonary regurgitation with or without coexistent stenosis and ultimately right heart failure. Diagnosis of carcinoid syndrome is supported by elevated 24 h urinary 5 hydroxyindoleacetic acid (5-HIAA) which has a sensitivity and specificity of > 90% and elevated serum CgA which is released from well-differentiated NETs. The level of 5-HIAA reflects tumor burden and decreases with treatment response. There are various food and medications that can affect 5-HIAA level. Tryptophan rich food (like banana, plum, pineapple, kiwi, eggplant, avocado, peanut, walnut, pecan, oats, beans, lentils, seeds, tofu, cheese, eggs, fish, chicken, turkey and red meat) can yield a false positive result. Acetaminophen, nicotine, caffeine, guaifenesin, phenobarbital and methamphetamine can increase 5-HIAA levels. Alcohol, aspirin, imipramine, methyldopa, levodopa, monoamine oxidase inhibitors, corticotropin and INH can decrease 5-HIAA level. Patients should be advised to stop taking these medications 24 h before and during urine collection.

Treatment options for carcinoid syndrome: (1) Long-acting somatostatin analog: Octreotide LAR 20 mg to 30 mg or lanreotide 60 mg to 120 mg intramuscularly every 4 wk. Flushing and diarrhea are improved in 80% of patients by this therapy. If the symptoms are not adequately controlled, Octreotide LAR or lanreotide can be given every 3 wk instead of every 4 wk; (2) Hepatic resection: considered in neuroendocrine liver metastasis when 90% or more of the disease bulk can be resected keeping every 3 wk instead of every 4 wk; (2) Hepatic resection: considered in neuroendocrine symptoms are not adequately controlled, Octreotide LAR or lanreotide can be given 4 Octreotide LAR 20 mg to 30 mg h before and during urine collection. Before testing, patients should be advised to stop taking these medications 24 h before and during urine collection. Before testing, patients should be advised to stop taking these medications 24 h before and during urine collection.
Ahmed M. Gastrointestinal neuroendocrine tumors

Carcinoid crisis
Carcinoid crisis is a critical complication of carcinoid syndrome characterized by wide fluctuation of blood pressure (hemodynamic instability) with a predominance of hypotension, severe flushing, dyspnea and confusion due to release of huge amount of bioactive amines from the NET into the systemic circulation\(^{[10]}\). The crisis is triggered by either exposure to anesthetic agents or manipulation of the tumor during biopsy or surgery or embolization. Treatment is administration of mega dose of octreotide (500 μg to 1000 μg intravenous bolus followed by infusion of octreotide 50 μg to 200 μg per hour\(^{[9]}\). Administration of intravenous fluid alone may not be effective. Calcium and adrenergic agents should be avoided to improve blood pressure as paradoxical effect can occur in these patients as they can increase release of bioamines from the NETs. Prophylactically, octreotide 300 μg to 400 μg is given intravenously or subcutaneously prior to biopsy, surgery and embolization of NETs to reduce the occurrence of carcinoid crisis\(^{[10]}\).

Carcinoid heart disease
Patients with carcinoid syndrome generally present with symptoms and signs of right heart failure with systolic murmur along the left sternal edge. Diagnosis is established by doing 24 h urinary 5-HIAA and transthoracic echocardiography\(^{[10]}\). N-terminal pro-brain natriuretic peptide (NT-proBNP) > 260 ng/mL is also useful as a biomarker of the presence of carcinoid heart disease\(^{[10]}\). Management includes administration of somatostatin analogs and other measures to control carcinoid syndrome as well as treatment of right heart failure with salt and water restriction, loop diuretics and digoxin. Tricuspid and pulmonary valve should be replaced in case of symptomatic valve disease and progressive ventricular dysfunction\(^{[10]}\). Annual clinical evaluation with serum NT-proBNP should be done for early detection of carcinoid heart disease. Carcinoid heart disease should be managed by a multidisciplinary team which includes gastroenterologists, oncologists, NET experts, endocrinologists, cardiologists and cardiothoracic surgeons.

Appendiceal NET
Appendiceal NET represents the 3rd most common NET in the GI. Most of the patients are asymptomatic and diagnosed incidentally with 0.3% to 0.9% cases undergoing appendectomy. The average age of diagnosis is 42 years and it occurs more commonly in females than in males\(^{[10]}\). They are generally submucosal and have a predilection to be located at the tip of the appendix\(^{[10]}\) but in about 10% of cases, they can develop at the base of the appendix leading to obstruction and appendicitis\(^{[10]}\). Histologically, appendiceal NETs are EC-cell (serotonin-producing) NETSs, L-cell-type NETs and MiNENs (goblet cell cancer and adenocarcinoid). The local and distant metastatic potential depends on the size and histology of the NET. NET size > 2 cm, NEC and MiNEN have higher incidence of metastasis\(^{[10,10]}\). Consensus guideline (Table 4) suggests that simple appendectomy should be enough if the NET size is < 1 cm. If the NET size is 1 cm to 2 cm, appendectomy and periodic post-operative follow up is recommended for 5 years. Right hemicolectomy should be considered in this category if any of the following criteria is present: involvement of the base of the appendix, cecal infiltration, invasion into the mesoappendix or serosa, involvement of tumor margin, positive lymph nodes, lymphovascular invasion, presence of goblet cells or poorly differentiated cells, Ki67 index > 2%, MiNEN\(^{[10]}\). If the NET is > 2 cm, treatment is right hemicolectomy within 3 mo from the time of appendectomy but staging work up is required. The National Comprehensive Cancer Network recommends multiphasic CT or MRI of abdomen and pelvis. SRS-based scan (Octreoscan) or (68)Ga-DOTATE PET/CT, serum CgA, 24 h 5-HIAA should also be considered\(^{[10]}\). Colonoscopy is also indicated to evaluate for synchronous colorectal cancer\(^{[10]}\).

Colonic NETs
The second most prevalent advanced gastrointestinal cancer after colorectal cancer. As per SEER registry, the incidence of colonic NETs increased from 0.02 per 100000 in 1973 to 0.2 per 100000 in 2004\(^{[10]}\). The mean age of presentation of colonic NETs is 7th decade of life and female to male ratio is about 2:1\(^{[10]}\). Colonic NETs arises from Kulchitsky cells or enterochromaffin cells located within the crypts of Lieberkuhn of colon. Nearly 70% of colonic NETs are in the right colon, particularly in the cecum\(^{[10]}\). The patients remain asymptomatic until the NET size becomes large because of increased diameter of right colon than left colon. At the time of diagnosis, the average size of the NETs is about 5 cm and most have local or distant metastasis. Patients
Table 4 Appendiceal neuroendocrine tumor: Size and surgery

| Appendiceal NET size | Surgery |
|----------------------|---------|
| < 1 cm               | Simple appendectomy |
| 1 cm to 2 cm         | Appendectomy and periodic post-operative follow up is recommended for 5 yr. Right hemicolectomy should be considered in the presence of involvement of base of the appendix, cecal infiltration, invasion into the mesoappendix or serosa, involvement of tumor margin, positive lymph nodes, lymphovascular invasion, presence of goblet cells or poorly differentiated cells, Ki67 index > 2% or MiNEN |
| > 2 cm               | Right hemicolectomy within 3 mo from the time of appendectomy but staging work up is required. This includes multiphasic computerized tomography or magnetic resonance imaging of abdomen and pelvis. SRS-based scan (Octreoscan) or (68)Ga-DOTATE PET/CT, serum CgA, 24 h 5-HIAA and colonoscopy to evaluate for synchronous colorectal cancer |

NET: Neuroendocrine tumors; (68)Ga-DOTATE PET/CT scan: Gallium-68 DOTATE positron emission tomography/computed tomography scan; CgA: Chromogranin A; 5-HIAA: 5 hydroxylindoleacetic acid; MiNEN: Mixed neuroendocrine neoplasm.

generally present with abdominal pain due to mass effect or tumor-induced desmoplastic reaction, gastrointestinal bleeding and weight loss. Sometimes, colonic NETs are detected as a mass lesion during screening colonoscopy. Treatment is segmental colectomy with wide regional lymphadenectomy. The overall 5-year survival is 33% to 42%. Imaging studies should be done to stage colonic NETs.

**Rectal NETs**

There is 10-fold increased incidence of rectal NETs over the last 30 years. The incidence of rectal NETs is approximately 1 per 100000 populations per year\(^1\). The mean age of diagnosis of rectal NETs is about 56 years and they are slightly more common in males than in females\(^1\). They also have higher incidence and prevalence in both Asian Americans and African Americans as compared to Caucasians. Most of the rectal NETs remain asymptomatic and are diagnosed incidentally during screening colonoscopy or when lower endoscopy is done for another reason\(^4\). Symptomatic patients may present with rectal bleeding, rectal discomfort, pruritis ani and change in bowel habit. Endoscopically, rectal NETs appear as smooth, round, sessile, polypoid lesions with overlying normal appearing or yellow-discolored mucosa, usually located within 5 to 10 cm of the anal verge. But as the diameter of the NET exceeds 5 mm, atypical endoscopic findings are noted and these include semipedunculated appearance, hyperemia, central depression, erosion and ulceration\(^4\). Most of the rectal NETs (80% to 90%) are < 1 cm in size, confined to the submucosa and well-differentiated NENs at the time of diagnosis. EUS and MRI of the pelvis play an important role in the evaluation of depth of rectal NETs and regional lymph node involvement. MRI is more sensitive in detecting nodal disease, and EUS in differentiating submucosal from muscularis propria involvement. Conventional polypectomy is ineffective as most of the rectal NETs are submucosal. In one study, complete resection rate by conventional polypectomy was 30.9%\(^6\). Piecemeal biopsy removal of rectal NETs should be discouraged as histological assessment of lateral and deep margins cannot be done. Traditional EMR (submucosal injection to lift the lesion followed by snare polypectomy) is effective for lesions < 0.5 cm. Curative resection of rectal NETs ≤ 1 cm in size can be done by device-assisted EMR (cap-assisted EMR or ligation-assisted EMR) or ESD as long as EUS examination does not show muscularis propria invasion and pararectal lymph node metastasis\(^7,8\). If the rectal NET is 1 cm to 2 cm in size and there is no muscularis propria invasion and pararectal lymph node metastasis, ESD or wide surgical excision is recommended. As the metastatic potential is high with rectal NET > 2 cm in size, low anterior resection or abdominoperineal resection is advocated in those cases. SRS-based scan (Octreoscan) or (68)Ga-DOTATE PET/CT should be done to detect any distant metastasis. Treatment options for metastatic rectal NETs include systemic therapies, liver directed therapies and palliative surgery. As per European Neuroendocrine Tumor Society, patients should have surveillance following complete resection of rectal NETs as follows: (1) Rectal NET < 1 cm (grade 1 or 2): No surveillance needed; (2) Rectal NET < 1 cm (grade 3): Annual colonoscopy for 5 years; (3) Rectal NET 1 cm to 2 cm (irrespective of grade): Colonoscopy, EUS and MRI at 12 mo, then colonoscopy every 5 years; (4) Rectal NET > 2 cm (grade 1 or 2): Annual colonoscopy, EUS and MRI for 5 years; and (5) Rectal NET > 2 cm (grade 3): Colonoscopy, EUS and MRI every 4 mo to 6 mo during the first year, then annually for 5 years.
Serum CgA can give additional information during surveillance if elevated at time diagnosis and normalized after resection of the NET so that increase in CgA level may indicate recurrence of the NET. Rectal NETs have the best prognosis among all the GI-NETs with a 5-year survival rate of 74% to 88% as per SEER database and Norwegian Register of Cancer for the period 1993–2004 [12].

**CONCLUSION**

The GI-NETs are rare but their incidence and prevalence have been increasing. They have characteristic biology, histopathology and clinical behavior. Most of the time, they are slow growing tumors but can be rapidly growing at times depending on the site, size and grade of the tumor. Majority of the GI-NETs are non-functioning except a few which can secrete bioactive amines and hormones and produce hormonal syndrome. Patients tend to be asymptomatic but can sometimes present with symptoms from mechanical causes as the tumor enlarges or causes fibrosis along with GI bleeding. GI-NETs are generally diagnosed and staged by endoscopy with biopsy, serology of biomarkers, EUS, imaging studies and functional somatostatin scans. Histologically, diagnosis is confirmed by positive immunohistochemical staining of CgA and synaptophysin. Treatment and prognosis depend on the grade and stage of the tumor. Current treatment modalities include endoscopic resection, surgery, somatostatin analog therapy, Peptide receptor radioligand therapy, chemotherapy, liver targeted therapy (radiofrequency ablation, bland embolization and chemoembolization) and symptomatic treatment. Immunotherapy will serve as a future treatment modality. Patients should be kept under surveillance program following treatment of GI-NETs.

**REFERENCES**

1. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. *Gastroenterology* 2005; 128: 1717-1751 [PMID: 15887161 DOI: 10.1053/j.gastro.2005.03.038]

2. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg* 2004; 240: 117-122 [PMID: 15213627 DOI: 10.1097/01.sla.0000129342.67174.67]

3. Taghavi S, Jayarajan SN, Powers BD, Davey A, Willis AI. Examining rectal carcinoids in the era of screening colonoscopy: a surveillance, epidemiology, and end results analysis. *Dis Colon Rectum* 2013; 56: 952-959 [PMID: 23838863 DOI: 10.1097/DCR.0b013e318291f12]

4. Taal BG, Visser O. Epidemiology of neuroendocrine tumours. *Neuroendocrinology* 2004; 80 Suppl 1: 3-7 [PMID: 15477707 DOI: 10.1159/000080731]

5. Cancer. Net. Neuroendocrine Tumor of the Gastrointestinal Tract: Introduction. 2018 Aug. Available from: https://www.cancer.net/cancer-types/neuroendocrine-tumor-gastrointestinal-tract/introduction

6. Cancer. Net. View All Pages Neuroendocrine Tumors. Introduction. 2019 Apr. Available from: https://www.cancer.net/cancer-types/neuroendocrine-tumor/view-all

7. Wang R, Zheng-Pywell R, Chen HA, Bibb JA, Chen H, Rose JB. Management of Gastrointestinal Neuroendocrine Tumors. *Clin Med Insights Endocrinol Diabetes* 2019; 12: 1179551419884058 [PMID: 31695546 DOI: 10.1177/1179551419884058]

8. Moertel CG. Karnofsky memorial lecture. An odyssey in the land of small tumors. *J Clin Oncol* 1987; 5: 1502-1522 [PMID: 2443618 DOI: 10.1200/JCO.1987.5.10.1502]

9. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao J.C. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *Ann Surg* 2017; 266: 569-577 [PMID: 28848665 DOI: 10.1096/j.sla.01.11105]

10. Rindi G, Bordi C, Rappel S, La Rosa S, Stolte M, Solcia E. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. *World J Surg* 1996; 20: 168-172 [PMID: 8661813 DOI: 10.1007/s002689900026]

11. Fink G, Krebsbaum T, Yellin A, Bendayan D, Saute M, Glazer M, Kramer MR. Pulmonary carcinoid: presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. *Chest* 2001; 119: 1647-1651 [PMID: 11396866 DOI: 10.1378/chest.119.6.1647]

12. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; 97: 934-959 [PMID: 12569593 DOI: 10.1002/cncr.11105]

13. Choo J, Kim KW, Kim HJ, Kim DW, Kim KP, Hong SM, Ryu JS, Tirumani SH, Krajewski K, Ramaiya N. What Is New in the 2017 World Health Organization Classification and 8th American Joint Committee on Cancer Staging System for Pancreatic Neuroendocrine Neoplasms? *Korean J Radiol* 2019; 20: 5-17 [PMID: 30627018 DOI: 10.3346/kjr.2018.0040]

14. Kim JY, Hong SM, Ro JY. Recent updates on grading and classification of neuroendocrine tumors. *Ann Diagn Pathol* 2017; 29: 11-16 [PMID: 28807335 DOI: 10.1016/j.anndiagpath.2017.04.005]

15. Capdevila J, Meeker A, Garcia-Carbonero R, Pietras K, Astudillo A, Casanovas O, Scarpa A. Molecular biology of neuroendocrine tumors: from pathways to biomarkers and targets. *Cancer Metastasis Rev* 2014; 33: 345-351 [PMID: 24375591 DOI: 10.1007/s10555-013-9468-y]

16. Rickman DS, Beltran H, Demicheli F, Rubin MA. Biology and evolution of poorly differentiated...
neuroendocrine tumors. Nat Med 2017; 23: 1-10 [PMID: 28586335 DOI: 10.1038/nm.4341]

17 Blažević A, Hofland J, Hofland LJ, Feelders RA, de Herder WW. Small intestinal neuroendocrine tumors and fibrosis: an entangled conundrum. Endocr Relat Cancer 2018; 25: R135-R130 [PMID: 29233841 DOI: 10.1530/ERC-17-0380]

18 Kidd M, Modlin I, Shapiro M, Camp R, Mane S, Usinger W, Murren J. CTGF, intestinal stem cells and carcinoid fibrogenesis. World J Gastroenterol 2007; 13: 5208-5216 [PMID: 17876891 DOI: 10.3748/wjg.v13.i39.5208]

19 Cives M, Pelle’ E, Quaresmini D, Rizzo FM, Tucci M, Silvestri F. The Tumor Microenvironment in Neuroendocrine Tumors: Biology and Therapeutic Implications. Neuroendocrinology 2019; 109: 83-99 [PMID: 30699437 DOI: 10.1159/000497355]

20 Cives M, Strosberg JR. Gastroenteropancreatic Neuroendocrine Tumors. CA Cancer J Clin 2018; 68: 471-487 [PMID: 30295930 DOI: 10.3322/caac.21493]

21 da Silva A, Bowden M, Zhang S, Masugi Y, Thorner AR, Herbert ZT, Zhou CW, Brais L, Chan JA, Hodi FS, Rodig S, Ogino S, Kulkhe MH. Characterization of the Neuroendocrine Tumor Immune Microenvironment. Pancreas 2018; 47: 1123-1129 [PMID: 30153220 DOI: 10.1097/MPA.0000000000001130]

22 Kata SC, Donker C, Glasgow K, Pillarissetty VG, Gönen M, Espat NJ, Klimstra DS, D’Angelica MI, Allen PJ, Jarnagin W, Dematteo RP, Brennan MF, Tang LH. T cell infiltrate and outcome following resection of intermediate-grade primary neuroendocrine tumours and liver metastases. HPB (Oxford) 2010; 12: 674-683 [PMID: 21083792 DOI: 10.1111/j.1477-2578.2010.00231.x]

23 Krug S, Abbassi R, Griesmann H, Sipos B, Wiese D, Blank A, Perren A, Haybaeck J, Hüttemaier S, Rinke A, Gress TM, Michl P. Therapeutic targeting of tumor-associated macrophages in pancreatic neuroendocrine tumors. Int J Cancer 2018; 143: 1806-1816 [PMID: 29696624 DOI: 10.1002/ijc.31562]

24 Kidd M, Gustafsson B, Modlin IM. Gastric carcinoids (neuroendocrine neoplasms). Gastroenterol Clin North Am 2013; 42: 381-397 [PMID: 23639647 DOI: 10.1016/j.gcc.2013.01.009]

25 Yang Z, Wang W, Lu J, Pan G, Pan Z, Chen Q, Liu W, Zhao Y. Gastric Neuroendocrine Tumors (G-Nets): Incidence, Progression and Recent Trend Toward Improved Survival. Cell Physiol Biochem 2018; 45: 389-396 [PMID: 29402806 DOI: 10.1159/000486915]

26 Cavalcoli F, Zilli A, Conte D, Ciafardini C, Massironi S. Gastric neuroendocrine neoplasms and proton pump inhibitors: fact or coincidence? Scand J Gastroenterol 2015; 50: 1397-1403 [PMID: 26059834 DOI: 10.3109/03050572.2015.1054426]

27 Jiana CS, Fossmark R, Visitel T, Qvigstad G, Sørdal O, Marvik R, Waldum HL. Gastric carcinoids after long-term use of a proton pump inhibitor. Aliment Pharmacol Ther 2012; 36: 644-649 [DOI: 10.1111/apt.12192]

28 Salyers WJ, Vega KJ, Munoz JC, Trotman BW, Taney SS. Neuroendocrine tumors of the gastrectestinal tract: Case reports and literature review. World J Gastrointest Oncol 2014; 6: 301-310 [PMID: 25132927 DOI: 10.4251/wjgo.v6.i8.301]

29 Sato Y, Iwafuchi M, Ueki J, Yoshimura A, Mochizuki T, Motoyama H, Sugimura K, Homma T, Narisawa R, Ichida T, Asakura H, Van Thiel DH. Gastric carcinoid tumors without autoimmune gastritis in Japan: a relationship with Helicobacter pylori infection. Dig Dis Sci 2002; 47: 579-585 [PMID: 11911346 DOI: 10.1023/a:1017922202479]

30 Dias AR, Azvedo BC, Alban LBV, Yagi OK, Ramos MF, Jacob CE, Cecconello I, Ribeiro U Jr, Zilberstein B. GASTRIC NEUROENDOCRINE TUMOR: REVIEW AND UPDATE. Arq Bras Cir Dig 2017, 30: 150-154 [PMID: 29257854 DOI: 10.1590/0102-67202017000020016]

31 Sato Y. Endoscopic diagnosis and management of type I neuroendocrine tumors. World J Gastrointest Endosc 2015; 7: 346-353 [PMID: 25901213 DOI: 10.4253/wjge.v7.t4.346]

32 Chin JL, O’Ttoole D. Diagnosis and Management of Upper Gastrointestinal Neuroendocrine Tumors. Clin Endosc 2017; 50: 520-529 [PMID: 29207862 DOI: 10.5964/cej.2017.1131]

33 Delle Fave G, Capurso G, Ambiale B, Panzuto F. Gastric neuroendocrine tumors. Neuroendocrinology. 2004; 80 Suppl 1: 16-19 [PMID: 15477710 DOI: 10.1159/000080734]

34 Ozao-Choy J, Buch K, Struhaen JA, Warner RR, Divino CM. Larpasoscopic antrectomy for the treatment of type I gastric carcinoid tumors. J Surg Res 2010; 162: 22-25 [PMID: 20421108 DOI: 10.1016/j.jss.2010.01.005]

35 Kim BS, Oh ST, Yook JH, Kim KC, Kim MG, Jeong JW, Kim BS. Typical carcinoids and neuroendocrine carcinomas of the stomach: differing clinical courses and prognoses. Am J Surg 2010; 200: 328-333 [PMID: 20385369 DOI: 10.1016/j.amjsurg.2009.10.029]

36 Crosby DA, Donohoe CL, Fitzgerald L, Muldoon C, Hayes B, O’Ttoole D, Reynolds JV. Gastric neuroendocrine tumours. Dig Surg 2012; 29: 331-348 [PMID: 23075625 DOI: 10.1159/000342988]

37 Boyce M, Moore AR, Sagatun L, Parsons BN, Varro A, Fossmark R, Waldum HL, Pritchard DM. Netazepide, a gastrin/cholecystokinin-2 receptor antagonist, can eradicate gastric neuroendocrine tumours in patients with autoimmune chronic atrophic gastritis. Br J Clin Pharmacol 2017; 83: 466-475 [PMID: 27704617 DOI: 10.1111/bcp.13146]

38 Delle Fave G, Capurso G, Milione M, Panzuto F. Endocrine tumours of the stomach. Best Pract Res Clin Gastroenterol 2005; 19: 659-673 [PMID: 16253852 DOI: 10.1016/j.bpcg.2005.05.002]

39 Scacheri PC, Davis S, Odom DT, Crawford GE, Perren A, Fossmark R, Waldum HL, Pritchard DM. NETazepide, a gastrin/cholecystokinin-2 receptor antagonist, can eradicate gastric neuroendocrine tumours in patients with autoimmune chronic atrophic gastritis. Br J Clin Pharmacol 2017; 83: 466-475 [PMID: 27704617 DOI: 10.1111/bcp.13146]

40 Cadiot G, Lehy T, Ruzniowski P, Bonfils S, Mignon M. Gastric carcinoid cell evolution in patients with Zollinger-Ellison syndrome. Influence of gastrinoma growth and long-term omeprazole treatment. Dig Dis Sci 1993; 38: 1307-1317 [PMID: 8100759 DOI: 10.1007/BF01290683]

41 Tomassetti P, Migliori M, Caletti GC, Fusaroli P, Cornalides R, Gullo L. Treatment of type II gastric carcinoid tumors with somatostatin analogues. N Engl J Med 2000; 343: 551-554 [PMID: 10954763 DOI: 10.1056/NEJM200008243438058]

42 Cancer Research UK. Types and grades of stomach NETs. [published 30 July 2018]. Available from: https://www.cancerresearchuk.org/about-cancer/neuroendocrine-tumours-net/stomach-nets/types-grades
Okubo Y, Wakyama M, Nemoto T, Kitahara K, Nakayama H, Shibuya K, Yokose T, Yamada M, Shimoda K, Sasai D, Ishiwatari T, Tsuchiya M, Hirota N. Literature survey on epidemiology and
Ahmed M. Gastrointestinal neuroendocrine tumors
discussion 897-8 [PMID: 17188135 DOI: 10.1016/j.surg.2006.07.033]
93 Gupta S, Yao JC, Aharak R, Wallace MJ, Morello FA, Maddof DC, Murthy R, Hicks ME, Ajani JA. Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. Cancer 2003; 9: 261-267 [PMID: 12967136 DOI: 10.1002/1097-0340(20030700)9:7<261::AID-CNCR11>3.0.CO;2-8]
94 Kulke MH, Hörsch D, Caplin ME, Anthony LB, Berglind E, Öberg K, Welin S, Warner RR, Lombard-Bohas C, Kunz PL, Grande E, Valle JW, Fleming D, Lapuerta P, Banks P, Jackson S, Szwambierz B, Sands AT, Pavel M. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. J Clin Oncol 2017; 35: 14-23 [PMID: 27918724 DOI: 10.1200/JCO.2016.69.2780]
95 Öberg K, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with mid-gut carcinoid tumors and carcinoid syndrome. N Engl J Med 1983; 309: 129-133 [PMID: 6191217 DOI: 10.1056/NEJM198307273090301]
96 Frank M, Klose KJ, Wied M, Ishaque N, Schade-Brittinger C, Arnold R. Combination therapy with octreotide and alpha-interferon: effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors. Am J Gastroenterol 1999; 94: 1381-1387 [PMID: 10235222 DOI: 10.1111.j.1572-0241.1999.0190.x]
97 Bainbridge HE, Larbi E, Middleton G. Symptomatic Control of Neuroendocrine Tumours with Everolimus. Horm Cancer 2015; 6: 254-259 [PMID: 26245686 DOI: 10.1007/s12672-015-0233-2]
98 Bushnell DL Jr, O’Dorisio TM, O’Dorisio MS, Menda Y, Hicks RJ, Van Cutsem E, Bauiluz JL, Beesoon-Chazot F, Anthony L, Benson AB, Öberg K, Grossman AB, Connolly M, Bouterla H, Li Y, Kacena KA, LaFrance N, Pauwels SA. 90Y-octreotide for metastatic carcinoid refractory to octreotide. J Clin Oncol 2010; 28: 1652-1659 [PMID: 20194865 DOI: 10.1200/JCO.2009.22.8855]
99 Woodsdie JK, Townsend CM Jr, Mark Evers B. Current management of gastrointestinal carcinoid tumors. J Gastrointest Surg 2004; 8: 742-756 [PMID: 1558337 DOI: 10.1016/j.gassur.2004.04.010]
100 Seymour N, Sawh SC. Mega-dose intravenous octreotide for the treatment of carcinoid crisis: a systematic review. Can J Anaesth 2013; 60: 492-499 [PMID: 23328895 DOI: 10.1007/s1232895-013-9780-1]
101 Kinney MA, Warner ME, Nagorney DM, Rubin J, Schroeder DR, Maxson PM, Warner MA. Perianesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumors. Br J Anaesth 2019; 87: 447-452 [PMID: 11517190 DOI: 10.1093/bja/87.3.447]
102 Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. Heart 2004; 90: 1201-1228 [PMID: 15367531 DOI: 10.1136/hrt.2004.030329]
103 Bhattacharyya S, Tounpanakis C, Caplin ME, Davar J. Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease. Am J Cardiol 2008; 102: 938-942 [PMID: 18085126 DOI: 10.1016/j.amjcard.2008.05.047]
104 Connolly HM, Schuff HV, Abel MD, Rubin J, Askew JW, Li Z, Inda JJ, Luis SA, Nishimura RA, Pelikka PA. Early and Late Outcomes of Surgical Treatment in Carcinoid Heart Disease. J Am Coll Cardiol 2015; 66: 2189-2196 [PMID: 26564596 DOI: 10.1016/j.jacc.2015.09.014]
105 Sandor A, Modlin IM. A retrospective analysis of 1570 appendiceal carcinoids. Am J Gastroenterol 1998; 93: 422-428 [PMID: 9517651 DOI: 10.1111.j.1572-0241.1998.00422.x]
106 Roggo A, Wood WC, Ottinger LW. Carcinoid tumors of the appendix. Ann Surg 1993; 217: 385-390 [PMID: 8466309 DOI: 10.1097/00000658-199304000-00101]
107 Moertel CG, Dockerty MB, Judd ES. Carcinoid tumors of the vermiform appendix. Cancer 1968; 21: 270-278 [PMID: 4952505 DOI: 10.1002/1097-0142(19680201)21:2<270::AID-cncr2820210217>3.0.CO;2-9]
108 Hsu C, Rashid A, Xing Y, Chiang YJ, Chagpar RB, Fournier KF, Chang GJ, You YN, Feig BW, Cormier JN. Varying malignant potential of appendical neuroendocrine tumors: importance of histologic subtype. J Surg Oncol 2013; 107: 136-143 [PMID: 22767417 DOI: 10.1002/jso.23205]
109 Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. N Engl J Med 1987; 317: 1699-1701 [PMID: 3696178 DOI: 10.1056/NEJM198712313170204]
110 Pöckinger U, Couvelard A, Falconi M, Sundin A, Salazar R, Christ E, de Herder WW, Gross D, Knapp WH, Knigge UP, Kulke MH, Pape UF, Frascati Consensus Conference participants. Consensus guidelines for the management of patients with digestive neuroendocrine tumours: well-differentiated tumour/carcinoma of the appendix and goblet cell carcinoma. Neuroendocrinology 2008; 87: 20-30 [PMID: 17934252 DOI: 10.1159/000109876]
111 National Comprehensive Cancer Network. NCCN Guidelines® & Clinical Resources. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx
112 Saha S, Hoda S, Godfrey R, Sutherland C, Raybok N. Carcinoid tumors of the gastrointestinal tract: a 44-year experience. South Med J 1989; 82: 1501-1505 [PMID: 2595419 DOI: 10.1097/00000761-198912000-00011]
113 Caplin M, Sundin A, Nilsson O, Baum RP, Klose KJ, Kelestimur F, Pöckinger U, Papotti M, Salazar R, Pascher A; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. Neuroendocrinology 2012; 95: 88-97 [PMID: 22261972 DOI: 10.1159/000335594]
114 Rosenberg JM, Welch JP. Carcinoid tumors of the colon. A study of 72 patients. Am J Surg 1985; 149: 775-779 [PMID: 2409828 DOI: 10.1016/s0002-9610(85)80184-7]
115 Anthony LB, Strohsberg JR, Klimstra DS, Maples WJ, O’Dorisio TM, Warner RR, Wiseman GA, Benson AB 3rd, Pommier RF; North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): well-differentiated net/s of the distal colon and rectum. Pancreas 2010; 39: 767-774 [PMID: 20664474 DOI: 10.1097/MPA.0b013e3181ec1261]
116 Basuroy R, Haji A, Ramage JK, Quagliola A, Srinajaskanthan R. Review article: the investigation and management of rectal neuroendocrine tumours. Aliment Pharm Ther 2016; 44: 332-345 [PMID: 27300283 DOI: 10.1111/apt.13697]
117 Yoon SN, Yu CS, Shin US, Kim CW, Lim SB, Kim JC. Clinico-pathological characteristics of rectal carcinoids. Int J Colorectal Dis 2010; 25: 1087-1092 [PMID: 20397020 DOI: 10.1007/s00384-010-0949-y]
Ahmed M. Gastrointestinal neuroendocrine tumors

118 **Modlin IM**, Sandor A. An analysis of 8305 cases of carcinoid tumors. *Cancer* 1997; 79: 813-829 [PMID: 9024720 DOI: 10.1002/(sici)1097-0142(19970215)79:4<813::aid-cncr19>3.0.co;2-2]

119 **Shim KN**, Yang SK, Myung SJ, Chang HS, Jung SA, Choe JW, Lee YJ, Byeon JS, Lee JH, Jung HY, Hong WS, Kim JH, Min YI, Kim JC, Kim IJ. Atypical endoscopic features of rectal carcinoids. *Endoscopy* 2004; 36: 313-316 [PMID: 15057680 DOI: 10.1055/s-2004-814202]

120 **Son HJ**, Sohn DK, Hong CW, Han KS, Kim BC, Park JW, Choi HS, Chang HJ, Oh JH. Factors associated with complete local excision of small rectal carcinoid tumor. *Int J Colorectal Dis* 2013; 28: 57-61 [PMID: 22821140 DOI: 10.1007/s00384-012-1538-z]

121 **Onozato Y**, Kakizaki S, Izuka H, Sobara N, Mori M, Itoh H. Endoscopic treatment of rectal carcinoid tumors. *Dis Colon Rectum* 2010; 53: 169-176 [PMID: 20087092 DOI: 10.1007/DCR.0b013e3181b9adb7b]

122 **de Mestier L**, Brixi H, Gincul R, Ponchon T, Cadiot G. Updating the management of patients with rectal neuroendocrine tumors. *Endoscopy* 2013; 45: 1039-1046 [PMID: 24163193 DOI: 10.1055/s-0033-1344794]

123 **Hauso O**, Gustafsson BI, Kidd M, Waldum HL, Drozdov I, Chan AK, Modlin IM. Neuroendocrine tumor epidemiology: contrasting Norway and North America. *Cancer* 2008; 113: 2655-2664 [PMID: 18853416 DOI: 10.1002/cncr.23883]
