EDITORIAL

Gastrointestinal Neuroendocrine Neoplasms

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What Every Surgeon Should Know

The neuroendocrine system consists of a glandular system (pituitary, parathyroid, paraganglia, and adrenal medulla) and a diffuse system comprising cells dispersed throughout the skin, lung, gastrointestinal tract (GIT), and urogenital tract.[1] These cells produce various biogenic amines, peptides, tachykinins, and prostaglandins that, in the GIT, influence gut motility, stimulation of digestive enzymes, and glucose storage. Since these cells share structural and regulatory properties with neural and endocrine cells, they have been called neuroendocrine cells, and tumors arising from them have been referred to in the literature as neuroendocrine neoplasms (NENs). The tumor cells are uniform, rounded with "salt-and-pepper" chromatin and amphophilic cytoplasm, and arranged in nests, cords, and/or trabeculae. Mitotic figures are generally sparse and necrosis is minimal or absent. They are positive for synaptophysin and/or chromogranin (CgA). The term NEN includes the well-differentiated types referred to as neuroendocrine tumors (NETs) and the poorly differentiated types referred to as neuroendocrine carcinoma (NEC) to emphasize the substantial clinical and prognostic difference between the two groups. The term, "carcinoid tumor" is used as a synonym for well-differentiated NETs of the luminal GIT.

This review looks at NENs arising from the luminal GIT and will not discuss pancreatic NENs. We shall attempt to answer questions like what is the scale of the problem overall and specifically in the stomach, small bowel, appendix, and colon and rectum and why every clinician needs to be aware of these tumors and their unique clinical characteristics, diagnostic challenges, and treatment paradigms. This knowledge becomes imperative in light of increased diagnosis of these tumors due to technical advances and increased use of cross-sectional imaging, long natural history of these neoplasms, and the overall satisfying results when treated appropriately as opposed to other neoplasms like adenocarcinomas.

Incidence

Majority of well differentiated remain asymptomatic and are incidentally diagnosed at autopsy after death from other causes. Recent studies, however, document rising incidence and even suggest that carcinoid tumors are actually the second most prevalent GI cancer, after colorectal cancer!! Factors like aging population, increased awareness of this entity, much improved and increasing use of diagnostic technologies, and more specific classification and grouping systems are probably responsible rather than a true change in incidence.

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Risk Factors

The specific risk factors for the development of sporadic NENs are still unknown. A systematic review suggests that the risk factor most significantly associated with the development of a NEN is the parental history of a carcinoid tumor in an extrapulmonary site, history of carcinoid tumor in a sibling,[2] and long-term history of diabetes mellitus, especially in women.[3] In contrast, there are four well-established genetic disorders that are strongly associated with the development of pancreatic neuroendocrine tumors (PNETs) like multiple endocrine neoplasia (MEN) 1 (65%), von Hippel-Lindau syndrome (15%), neurofibromatosis 1 (10%), and tuberous sclerosis (<5%).[4]

Classification and Staging Systems

The current World Health Organization (WHO) classification for NEN incorporates both grading and staging information in a single system to provide prognostic information irrespective of the site of origin (Table 1). Any suspected NEN has to be separated into well-differentiated (includes three grades) or poorly differentiated (includes two cell types) or mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) when either component accounts for at least 30% of the entire lesion. The grading scheme is determined by markers of the tumor's proliferative index: The mitotic rate (reported as the number of mitoses per 10 high-power fields) and the Ki67 labeling index, assuming that the higher the proliferation grade, the worse the patient outcome.[5] The Ki67 antigen is an important marker of cellular proliferation and mitotic activity and is detected in all phases of the cell cycle except G0.

Table 1: WHO 2019 classification and grading of NENs

Type of tumor	*Ki67%*	*Mitotic count (2 mm²)*
Well-differentiated neoplasms		
NET grade I	<3	<2
NET grade II	3–20	2–20
NET grade III	20	>20
Poorly differentiated neoplasms		
NEC large cell type	>20	>20
NEC small cell type	>20	>20
MiNEN		
Well- or poorly differentiated or both components	N/A	N/A

MiNEN, mixed neuroendocrine-non-neuroendocrine; N/A, not applicable; NET, neuroendocrine tumor

A monoclonal antibody (MIB-1) that binds to the Ki67 nuclear antigen is used to estimate the percentage binding to 2,000 cells in the area of highest nuclear activity.

MiNEN tumors are not pure NENs; grading is performed separately for the NEN component (according to this table) and for the non-neuroendocrine counterpart (adenocarcinoma or squamous cell carcinoma) according to specific cancer definitions by WHO 2019. They are staged following the staging system for non-neuroendocrine cancer.

It is believed that there is a size-dependent time course for metastasis development in NENs and this size can be substantially different according to the anatomical location of the NEN. A very small gastrin-producing cell NET of the duodenum of size 20.1 mm has a probability of developing metastasis in ~50%, but a probability of developing metastasis in the stomach and pancreas of only ~30%.[6] The American Joint Committee on Cancer staging system for NENs for each anatomic site is based on this understanding.

Stage I: Small tumors (≤1 cm for small bowel and stomach; ≤2 cm for colon and appendix) without invasion beyond the submucosa.
Stage II: Larger tumors and deeper depth of invasion than stage I, but still localized to the primary site.
Stage III: Advanced tumors (e.g., tumors that have penetrated the serosa in gastric and small bowel tumors; those that are growing into nearby structures in appendiceal and colon tumors) with nodal disease.
Stage IV: Any size tumor with distant metastases with or without regional lymph nodes.

Shared Clinical Characteristics of Tubular Nens

NET is a low-grade, usually non-functioning, malignant cancer characterized by long survival of patients with prognosis depending on grade and stage.[7] Ninety percent of tubular NETs are low grade (grade I or II), whereas 10% are high grade (grade III). High-grade NETs arise in stomach and colon.[7] Despite their predominant low grade, NETs of the tubular GIT, especially of the intestine, are generally advanced stage at the time of clinical diagnosis. This is in contrast to "high-grade amounts to high-stage rule" observed with other gastrointestinal neoplasms. Only 15% of all gastrointestinal-neuroendocrine neoplasms (GI NENs) are functional and secrete hormones that result in characteristic syndromes. The somatostatinoma syndrome is associated with duodenal and/or jejunal NETs but is exceedingly rare.[8] Most clinically relevant and frequent are Zollinger–Ellison syndrome, from unregulated gastrin hypersecretion by duodenal gastrin-producing cell NETs and often associated with a MEN type I,[9] and the carcinoid syndrome (CS) reported in stage IV enterochromaffin cell NEC with liver metastases.[10] The liver generally removes the excess hormones produced by functioning NETs from the blood (first-pass effect). Hence, hormonal symptoms from these tumors manifest only in the presence of extensive liver metastases and from retroperitoneal deposits when the excess hormones are able to enter the systemic circulation directly.

NECs account for less than 10% of all tubular NENs and are most commonly located in stomach and colon.[11] The poorly differentiated, proto-neuroendocrine cells display a large or small cell phenotype and retain expression of the general neuroendocrine markers. NEC is a very aggressive, highly malignant cancer characterized by short survival of patients and is usually in advanced stage at the time of diagnosis.

Salient Features of Nets by Organ of Origin

Although well-differentiated NETs look largely similar on histology, no matter their organ of origin, their behavior is markedly different from site to site.

Gastric NETs

Gastric NENs arise from enterochromaffin-like (ECL) cells and have been classified into four subtypes (Table 2). The fourth type of gastric carcinoids has been introduced more recently. They are similar to type III in being solitary, large tumors. But they arise from non-ECL cells and are associated with parietal cell hyperplasia and can arise anywhere in the stomach.

Incidence

Gastric NENs are being increasingly diagnosed due to increasing use of upper GI endoscopies (UGIEs). Due to widespread use of proton pump inhibitors (PPIs), the proportion of gastric carcinoids among all carcinoid tumors has increased from 2.4 to 8.7% and they are also increasing in frequency relative to other gastric malignancies—from 0.3 to 1.8%.[12]

Diagnosis

Majority of gastric neuroendocrine neoplasms (G-NENs) are diagnosed on histological examination of biopsy samples from incidental gastric polyps at screening endoscopy. They can also cause abdominal pain, gastrointestinal bleeding, and anemia from peptic ulcers. One should obtain biopsies from the largest lesion and also two biopsies from antrum and four biopsies from fundus to confirm histology and diagnose-associated atrophic gastritis. If there is associated gastritis or symptoms suggestive of hyperacidity, one should measure serum gastrin and gastric pH. Serum CgA is measured as a tumor marker for assessing disease progression, response to therapy, or disease recurrence in patients with resected stage II or III tumors. False-positive elevations in the serum CgA are seen with the use of PPIs in chronic gastritis, renal insufficiency, and other inflammatory diseases. Endoscopic ultrasound (EUS) and cross-sectional imaging are done for tumors >1 cm for tumor depth and to assess locoregional spread.

Table 2: Characteristics of gastric NENs

Characteristics	*Type I G—NEN*	*Type II G—NEN*	*Type III G—NEN*
Proportion	70–80%	5–10%	10–15%
Associated diseases	Chronic atrophic gastritis	MEN type I, Zollinger–Ellison syndrome	None, sporadic
Gender	Females >males	Females = males	Females >males
Location	Fundus or body	Fundus or body	Body and fundus
Tumor number	Multiple	Multiple	Single
Tumor size	<10 mm	<10 mm	10 mm, usually large size by the time of diagnosis
Histology	Usually grade I NET	Usually grade I or II NET	Grade III NEC
Depth of invasion	Mucosa and submucosa	Mucosa and submucosa	Any depth
Serum gastrin levels	High	High	Normal
Gastric pH	High	Low	Normal
Risk of metastases	2–5%	10–20%	50%
Prognosis	Excellent	More often associated with distant disease and course influenced more by the presence of MEN than by the NET itself	Worse prognosis. These tumors produce 5-hydroxytryptophan and can be associated with the development of an atypical carcinoid crisis (flushing, hypotension, lacrimation, edema, and bronchoconstriction)

Treatment

Management of G-NENs is based on the type of tumor and surrogates of poor tumor biology such as size, muscular wall infiltration, presence of lymph nodes (LNs), increased tumor proliferation, and metastasis.

Type I Gastric Neuroendocrine Tumors (G-NET): Guidelines suggest simple surveillance or endoscopic mucosal resection (EMR) for tumors that are smaller than 20 mm in size [European NET society (ENETS) says for <1 cm], and without features of invasion of muscularis propria or metastasis. If the tumor extends till submucosa, endoscopic submucosal dissection (ESD) provides better tumor clearance. In cases of recurrence or persistent G-NETs after endoscopic or local resection or lesions >2 cm and more than 6 in number, antrectomy or partial/total gastrectomy along with lymphadenectomy is recommended. This alleviates G-cell-mediated hypergastrinemia that drives enterochromaffin cell hyperplasia and thus decreases the risk of recurrence.

Type II G-NET: Their treatment is driven more by assessment of the advisability of proceeding with resection of the gastrinoma, usually in the setting of MEN. The principles for the management of gastric lesions are similar to type I G-NETs. The ENET guidelines suggest surgical excision with lymphadenectomy because of the higher rate of metastasis.[13] Somatostatin analogues (SSAs) can provide symptomatic relief when surgery is not possible.[14]

Types III and IV gastric NENs: These are treated similar to gastric adenocarcinoma—resection with widely negative margins and formal D2 lymphadenectomy. Those with metastatic disease can be considered for surgical resection of primary with surgical excision of metastatic disease or locoregional therapy for unresectable metastatic disease. Patients with widespread metastatic disease can be offered palliative therapy, and gastric surgery is done only for local symptom control. There is a suggestion that small, well-differentiated type III NENs <2 cm confined to submucosa without lymphovascular invasion (LVI) can be treated with EMR.[15]

Duodenal NENs (D-NENs)

Incidence and Presentation

Around 80% of D-NENs occur in the first or second part, whereas 20% occur in periampullary region.[16] Ninety percent of these tumors are nonfunctional and detected incidentally on UGIEs. Ampullary D-NENs differ from D-NENs in other locations in that they present at a more advanced stage and have poorer overall survival.[17]

Management of D-NENs

The management of D-NENs is based on tumor size, location, histological grade, stage, and tumor type. The management protocol of D-NENs based on the ENETS guidelines is summarized in Flowchart 1.[13]

Follow-up

Following complete endoscopic resection, patients are followed up for recurrence with UGIEs, abdominal USG (USG), and serum CgA levels at 6 months, 2 and 3 years. The patients who undergo surgical resection require follow-up computed tomography (CT) scans, somatostatin receptor scintigraphy (SRS), and serum CgA levels at 6 months and then annually for 3 years.

Small Bowel NENs (SB-NENs)

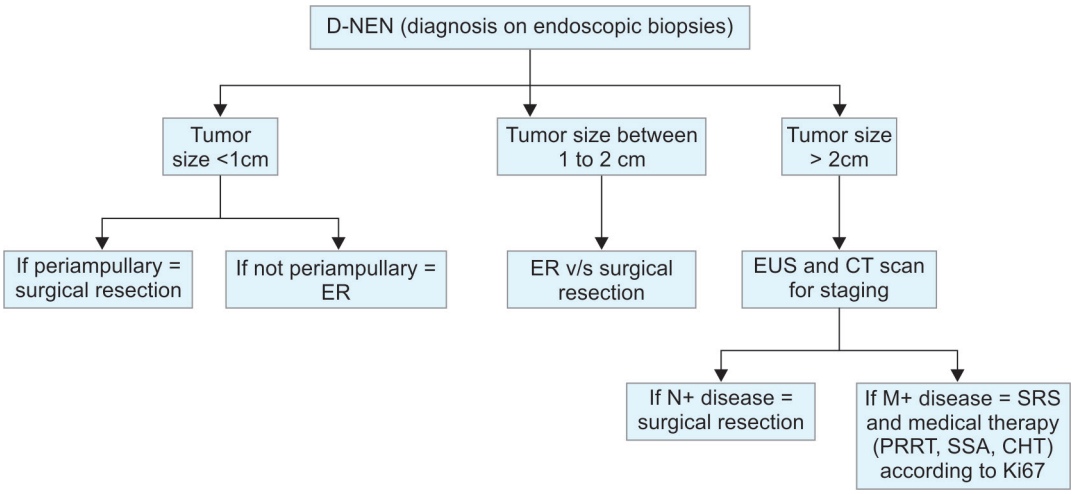
Incidence

SB-NENs account for 38% of all GIT NENs.[18] Ileum accounts for 50% of all SB-NENs. Carcinoid tumors are the most common small bowel tumor, representing 35% of the total, whereas adenocarcinomas account for 31%. CS is more commonly associated with SB-NENs (36% with jejunoileal carcinoids and 24% with ileocecal carcinoids). These tumors are multifocal in 25%, particularly in the ileum, and multifocal tumors have a more aggressive phenotype than solitary tumors.[19]

Presentation

SB-NENs can present with diverse symptoms like vague abdominal pain, bloating, diarrhea, weight loss, intermittent bowel obstruction, bowel ischemia, or bleeding. However, the most common presentation is nonspecific abdominal pain that leads to cross-sectional imaging. Bowel obstruction can be due to the tumor acting as a lead point for intussusception or extensive fibrosis and kinking of small bowel produced by changes in the subjacent mesentery by neurohormonal factors. They can also present with features of CS due to excess circulating serotonin in the presence of extensive hepatic metastases or retroperitoneal involvement.

Flowchart 1: Management of D-NEN. CHT, chemotherapy; CT, computed tomography; D-NETs, duodenal neuroendocrine tumors; EUS, endoscopic ultrasound; N+, lymph node metastasis; M+, distant metastasis; PRRT, peptide receptor radionuclide therapy; SRS, somatostatin receptor scintigraphy; SSAs, somatostatin analogues



SB-NENs can be associated with two distinct types of metastasis formation. Lymphatic type (L-type) wherein large abdominal lymph node metastases (N+) are present in the absence of synchronous hepatic deposits and hepatic type (H-type) wherein hematogenous liver metastases are present in the absence of synchronous lymph node deposits.[20]

Diagnosis

Since SB-NENs generally produce only vague symptoms, they are only diagnosed when the patient is evaluated by cross-sectional imaging. If SB-NET is suspected clinically, measure urinary 5 hydroxyindoleacetic acid (5-HIAA) that has a sensitivity of 75%, a specificity of 88%, and serum CgA (less specific marker for midgut NET). After injection of intravenous contrast, timed images obtained in arterial and venous phases will show SB-NET lesions to be hyperenhancing on arterial phase and iso-enhancing in later phases. A mesenteric mass with radiating spokes is pathognomonic for a mesenteric midgut tumor. In addition, liver should be evaluated for metastases and the rest of the bowel carefully imaged for multifocal lesions. CT enteroclysis may be necessary to look for a small intraluminal lesion causing intermittent symptoms. One might consider capsule endoscopy for the evaluation of obscure GI bleed from suspected SB-NETs. But in patients with significant small bowel tethering and luminal disease from carcinoid, it may lead to obstruction. When routine imaging studies are unrevealing and clinical suspicion is high, one can consider adjunctive tests like gallium DOTA PET or even diagnostic laparoscopy.

Management

Always look for a concomitant second tumor (identified in 12–46% cases)[21] when treating small bowel carcinoids. Accordingly, obtain preoperative UGIE and colonoscopy in all patients and at laparotomy perform a thorough evaluation of abdominal cavity for associated second neoplasm. Surgery for small bowel carcinoids entails segmental resection with wide mesenteric lymphadenectomy. If mesenteric LNs in SB-NETs are left behind, they can cause mesenteric vascular compromise later. Technically this surgery is more challenging than similar resection in adenocarcinomas of small bowel due to the extensive fibrotic changes and significantly foreshortened mesenteries. Mobilizing the right colon and small bowel mesenteries off the retroperitoneum upfront and isolating the mesenteric vessels as they exit near the pancreatic neck can provide control of the main vessels in a relatively less hazardous area. The vessels are dissected from the root out into the mesentery, peeling the nodes carefully away from the vasculature. The bowel resection is delayed until after the mesenteric dissection is completed to preserve a maximum length of well-perfused bowel.[22]

Prophylactic Cholecystectomy

During exploration for midgut carcinoid tumors, prophylactic cholecystectomy can be considered to prevent biliary complications from possible subsequent use of SSAs.[23]

Colon and Rectal NENs (CR-NENs)

Incidence and Presentation

CR-NENs make up 12% of all gastrointestinal neuroendocrine tumors (GI NETs), whereas rectal carcinoids are more common accounting for 21% of all GI NETs.[24] Colonic carcinoids are more frequently diagnosed in older patients when they present with weight loss or abdominal pain, whereas rectal carcinoids are detected incidentally when patients undergo evaluation for rectal pain or bleeding. It is not surprising then that at presentation, colonic NETs measure 5 cm or more and are metastatic in 40%, whereas 80% of rectal carcinoids are localized and less than 1 cm in size.

Diagnosis

These tumors rarely produce amines or other measurable hormones; hence, urinary 5-HIAA is of no value. Serum CgA is, however, sensitive and can be measured when there is clinical suspicion. The primary method of diagnosis is endoscopy wherein these lesions appear as sessile, submucosal polyps with discolored, yellow overlying mucosa. At histology, the diagnosis is straightforward but the margins have to be evaluated for completeness of polypectomy. If upfront complete endoscopic polypectomy in rectal carcinoids appears difficult, EUS can assist in determining the depth of invasion and hence suitability for ER. Colonic NETs require a metastatic workup after histology

with a cross-sectional imaging of the chest and abdomen and an octreotide scan. For the poorly differentiated colonic NENs that do not label with octreotide, a traditional fluorodeoxyglucose (FDG)-PET scanning may be more fruitful.[25]

Treatment

The operative approach to colonic carcinoids is similar to colonic adenocarcinomas. For small, incidentally detected colonic carcinoids completely removed with polypectomy, endoscopic surveillance alone can be considered. Tumors that are larger than 2 cm and invade the muscularis propria warrant a formal colectomy with lymphadenectomy.

Rectal tumors should be carefully staged with EUS or endorectal magnetic resonance imaging (MRI) prior to resection to decide the most appropriate strategy. After polypectomy if NET is the unexpected histology, immediate repeat endoscopy and tattooing of the region should be done for detailed reevaluation and re-excision if required later. Polyps with positive margins require ESD or full-thickness transanal excision. Similar to D-NET, rectal tumor <1 cm can be considered for ER and >1 cm should have a formal surgical resection particularly if the tumor penetrates the muscularis or has adverse features such as a high proliferative index, LVI, or gross ulceration.[26]

Appendiceal NENs (A-NENs)

Incidence and Presentation

Appendiceal NEN (A-NEN) account for 18% of all GI NENs.[21] Most A-NENs (referred to as carcinoid of the appendix in past) are detected incidentally at appendectomy (in 0.3–0.9% of all appendectomies) as they rarely cause specific symptoms. Three-fourths of appendiceal carcinoids are located at the tip of the appendix, and 95% of appendiceal carcinoids are less than 2 cm in diameter. Although small appendiceal tumors are considered benign, even 1 cm appendiceal tumors are associated with a mortality rate of 5% at 5 years, which increases to 22% for those with regional disease.

Diagnosis

Due to a lack of specific symptoms, it is not suspected preoperatively unless a large appendiceal mass is detected on cross-sectional imaging. Generally, the patient is operated on for appendicitis, and intraoperatively, one might notice a mass lesion. In all other cases, the diagnosis is revealed only at the histology of the resected specimen.

Management

It is unusual to find or suspect an appendiceal carcinoid prior to operative intervention. At the time of operative inspection during appendicectomy, if there is a concern for an appendiceal mass, it is helpful to resect as much mesoappendix as possible and to ensure that the base of the appendix is included in the specimen.

Conventionally performed appendectomy alone is an adequate oncological surgery for appendix carcinoid tumors if they are less than 1 cm in size, confined to the tip, well differentiated, have no evidence of LVI, and do not invade the mesoappendix. After appendectomy for presumed appendicitis with histology unexpectedly suggesting a NEN, one should carefully look at the tumor dimensions, depth of invasion, mitotic rate, and the presence or absence of LVI[27] to ensure that appendectomy alone is an adequate oncological surgery. Formal right hemicolectomy is recommended for tumors greater than 2 cm in size, invasion at the appendiceal base, evidence of LVI, any invasion of the mesoappendix, mixed histology (goblet cell carcinoids and adenocarcinoids), and intermediate- to high-grade tumors.[21]

Carcinoid Syndrome

The CS is a paraneoplastic syndrome and refers to a constellation of symptoms that result from excess neurohumoral factors released by some NENs. It is characterized by episodic flushing of face and torso described by patients as developing a dark red to purple hue accompanied by a burning sensation of the skin lasting for a few minutes and diarrhea with abdominal cramping. Atypical signs and symptoms can include wheezing, abdominal pain, valvular heart disease, telangiectasias, pellagra, and the complications of mesenteric fibrosis, including ureteral obstruction, bowel obstruction, and bowel ischemia. The hormones implicated are serotonin, histamine, bradykinin, kallikrein, prostaglandins, and tachykinins. This syndrome occurs in a patient with GI NENs in the presence of extensive liver or retroperitoneal NET metastases when these bioactive products escape degradation in the liver or directly reach the systemic circulation. The diagnosis of CS requires these symptoms and corresponding elevations in laboratory tests.

Diagnosis

Although the CS is a dramatic and well-known presentation of NETs, it is uncommon and occurs in only 10–20% of patients. The primary tumor is asymptomatic in up to 30% and detected incidentally.[28] Midgut carcinoid tumors that are more frequently associated with the CS are submucosal, grow extrinsically, are located in the segment of the GI tract that is not easily accessed endoscopically and the presenting symptoms such as flushing and dyspnea may not be easily referable to the abdomen. Hence, unless the primary physician is aware of its possibility, such patients often experience delays in diagnosis and treatment.

Laboratory Evaluation

In patients in whom other diagnoses have been excluded and there is a high possibility of a GI-NET obtain a 24 hour urine sample for 5-HIAA (sensitivity of 75% and specificity of more than 90%). This requires adequate preparation like avoiding food with high tryptophan content like avocados, bananas, walnuts, and medications like acetaminophen, guaifenesin, nicotine, heparin, aspirin, and isoniazid. It is useful for tumors of midgut and less for tumors of foregut and hindgut.[29] If urinary 5-HIAA results are equivocal, blood levels of serotonin can be obtained to clinch the diagnoses. Foregut NENs are associated with atypical CS. Serum Cg A is elevated in both functional and nonfunctional tumors, and its sensitivity varies according to the tumor site and burden. When elevated in isolation keep in mind the non-neoplastic causes of elevated CgA-like impaired renal and hepatic function, hypergastrinemia secondary to PPI or atrophic gastritis, and inflammatory bowel disease.

Investigations to Localize and Stage GI NETs in CS

A gastric, duodenal, or rectal carcinoid is best evaluated at endoscopy and by EUS. Routine abdominopelvic CT imaging may detect large NETs (hypervascular masses on arterial phase imaging), but small bowel luminal lesions are better seen on CT enterography, magnetic resonance enterography, or enteroclysis. SRS using radiolabeled octreotide can help locate small tumors that overexpress somatostatin receptors (particularly subtypes 2 and 5).

It is the most sensitive imaging modality for detecting metastatic disease.

Considerations in Management of Suspected CS

The biggest challenge in managing these patients is avoidance or dealing with carcinoid crises, which can be provoked by the induction of general anesthesia as well as manipulation of the tumor. This manifests intraoperatively as severe resistant hypotension, bronchospasm, and flushing. It can be avoided by pretreating the patient with octreotide (200 µg subcutaneously three times a day) for 2–3 weeks prior to surgery and with continuous intravenous therapy intraoperatively (50 µg/hour). It is essential to avoid drugs that release histamine or activate the sympathetic system. One should avoid adrenergic drugs to treat hypotension as they may exacerbate the crisis. Antihistamines, corticosteroids, and bolus intravenous octreotide may be used in event of carcinoid crises. An optimal communication between the surgeon and anesthesiologist is essential to provide optimal intraoperative care.[30]

Carcinoid Heart Disease

Carcinoid heart disease is seen in 40–50% of patients with the CS and in 3–4% of patients with NET without CS. Serotonin and other vasoactive amines circulating in the blood are believed to cause fibrosis of the right-sided cardiac structures. Tricuspid valve disease is seen in 90% and pulmonary valve stenosis in 50%. Right heart dysfunction particularly tricuspid regurgitation can present significant intraoperative challenges and even contraindicate hepatic surgeries. Hence, routine echocardiography should be done in all patients.[31] If significant valve disease is found, valve replacement should be considered prior to abdominal surgical intervention.

Atypical CS manifesting mainly as flushing and wheezing is seen in well-differentiated NET of foregut that releases excess histamine.

Metastatic GI NETs

Since a significant portion of patients with GI NETs will present with metastatic disease, it is essential to understand the optimal therapies in this subgroup. Patients with jejunoileal carcinoids present with metastatic disease in 30% of cases, whereas cecal NETs present with metastatic disease in 44%.[32]

The somatostatin analogue octreotide is an effective treatment for patients with symptomatic carcinoid disease. It has also been shown to have antiproliferative activity and is advocated even in asymptomatic metastatic midgut carcinoid tumors. The PROMID trial suggested a significant difference in time to tumor progression from 6 months in the placebo group to 14 months in the treatment group.[33] Lanreotide, a long-acting somatostatin analogue, is now recommended for the treatment of patients with unresectable, well or moderately differentiated, locally advanced, or metastatic gastropancreatic-NETs since it only requires monthly injections. Peptide receptor radionuclide therapy (PRRT) with lutetium-177–labeled SSAs can extend the overall survival of metastatic midgut NETs to 60 months.[34] PRRT response can be predicted by the maximum standardized uptake value (max SUV) on SSRT-PET imaging and is not beneficial for tumors with a max SUV less than 16.[35]

Resectable Hepatic Metastatic Disease

Hepatic resection is recommended for patients with well-differentiated NENs and resectable hepatic metastases if the tumor is well differentiated, there is no peritoneal or extraabdominal disease, and the patient can tolerate the planned procedure with acceptable morbidity and mortality. This strategy improves 5-year survival (50–60 vs 30%).[36]

Unresectable Hepatic Metastatic Disease

Symptomatic unresectable hepatic metastatic disease: Patients with GI NET and unresectable hepatic metastatic disease and no other disease who continue to be symptomatic despite somatostatin therapy can be considered for debulking surgery. Although this strategy (90% cytoreduction in tumor burden) may not yield survival benefits, it does bring about symptomatic improvement. This improvement may not be sustained beyond 24 months.[37] An alternative approach in some of these patients is hepatic artery embolization.

Asymptomatic Unresectable Hepatic Metastatic Disease

Some groups suggest resection of primary and hepatic debulking if more than 90% of the tumor burden can be removed with the goal of prolonging survival.[38] The role of liver transplantation in patients with unresectable hepatic disease has been explored in few well-selected patients in only a handful of centers. There can be a significant prolongation of survival if done in patients with complete resection of the primary tumor, isolated hepatic metastatic disease, low proliferative index (Ki67 less than 5% and staining for E-cadherin), absence of significant hepatomegaly, and primary tumor not of pancreatic or rectal origin.[39]

Role of Resection of Primary Tumor in Setting of Unresectable Metastatic Disease

If the primary tumor is symptomatic, it should be resected even in the presence of metastatic disease. There is confusion regarding management of asymptomatic primary GI NET in the presence of unresectable metastatic disease. But now there is emerging evidence to suggest resection of the primary for prolonging progression-free survival and enhance/supplement the antiproliferative effects of SSAs.[40]

Role of Systemic Chemotherapy (CHT)

There are very few effective CHT agents for patients with advanced, well-differentiated NETs. Interferons and alkylating agents have been tried in patients with progressive disease, but they have limited effectiveness and are associated with significant side effects. Targeted agents like sunitinib, a tyrosine kinase inhibitor, and everolimus, a mammalian target of rapamycin (mTOR) inhibitor, have been shown to result in a significant improvement in progression-free survival.[41]

Conclusion

The GI NENs are being increasingly diagnosed due to the widespread application of diagnostic endoscopies and cross-sectional imaging. Every surgeon should be aware of their natural history and treatment paradigms because they differ substantially from other epithelial neoplasms of the GIT. Since these neoplasms have a long natural history and are more often discovered incidentally, they offer the possibility of a cure if treated appropriately and also provide the option of less invasive excision strategies in elderly individuals with comorbidities. Ideally, these neoplasms should be managed by experienced multidisciplinary surgical teams for optimal results. But in view of the fact that most of these lesions are discovered incidentally, every clinician should acquaint himself/herself with recent developments in their

diagnosis and management before referring to a more dedicated later if required.

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