Gastric neuroendocrine tumors: management and challenges

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Abstract: Gastric neuroendocrine tumors derive from enterochromaffin-like cells in the stomach mucosa. Based on histologic, serologic, and endoscopic findings, they may be further differentiated into types I, II, and III, with varying degrees of aggressiveness. In this article, diagnostic and classification strategies are reviewed, as are endoscopic, systemic, and surgical modalities for management. A multidisciplinary approach is advocated to provide the most effective patient care.

Keywords: neuroendocrine, tumor, carcinoid, gastrin, stomach

Background

First reported by Askanazy in 1923, gastric neuroendocrine tumors (NETs) comprise approximately 1.8% of all gastric tumors¹ and develop from enterochromaffin-like (ECL) cells in the gastric mucosa. Gastric NETs are also referred to as gastric carcinoids. The term karzinoide, or carcinoma-like, was coined by Oberndorfer in 1907 to describe this class of tumors, which behaves in a relatively benign fashion compared to adenocarcinomas.² Our understanding of NETs as a whole has evolved over time, and the World Health Organization (WHO) classification system now employs the term neuroendocrine tumor instead of carcinoid. As such, gastric NETs are part of a broad category of gastroenteropancreatic-neuroendocrine tumors (GEPNETs), which encompass well-differentiated NETs arising from the gastrointestinal tract. In an effort to standardize the system and assist clinicians to accurately predict clinical outcomes, GEPNETs are graded histologically based on mitotic count and/or Ki67 index. The 2010 WHO histologic classification describes well-differentiated NETs as having a Ki67 index <3% and <2 mitoses per 10 high-power fields (HPFs) (G1), moderately differentiated NETs with a Ki67 index 3–20% or 2–20 mitoses per 10 HPFs (G2), and poorly differentiated NETs with a Ki67 index >20% or >20 mitoses per 10 HPFs (G3).³,⁴

The prevalence of gastric NETs is difficult to establish due to a lack of uniform data collection from cancer registries worldwide. A study published in 2015 analyzing national cancer registries in 10 European countries, the US, and Japan determined the prevalence of gastric NETs per 10,000 population to be 0.32 in Europe, 0.17 in the US, and 0.05 in Japan.⁵ The authors of this study did note that their values may be underestimations due to a tendency of cancer registries to reflect the aggressive tumors that require treatment as opposed to benign tumors.

Clinically, gastric NETs are categorized into types I, II, and III (Table 1). The basis for these subtypes is rooted in gastric pathophysiology.⁶ Gastrin is produced by
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Table 1 Gastric carcinoid disease categories and characteristics

| Characteristics          | Type I (%) | Type II (%) | Type III (%) |
|--------------------------|------------|-------------|--------------|
| % among gastric carcinoids| 70–80      | 5–10        | 10–15        |
| Associated disease       | Atrophic gastritis | Gastrinoma | None         |
|                          | Helicobacter pylori | MEN1      |              |
| Gastric pH                | High (>4) | Low (<2)    | Normal       |
| Serum gastrin            | High      | High        | Normal       |
| Potential to metastasize | 2–5%      | 10–30%      | 50–100%      |

Figure 1 (A) Endoscopic image of multiple type I gastric neuroendocrine tumors (NETs) in the gastric body. (B) Close-up endoscopic image of a type I gastric NET in the gastric body. (C) Endoscopic ultrasound of a type I gastric NET. The lesion appears hypoechoic and confined to the submucosa, without any invasion of the muscularis propria.

Table 1 Gastric carcinoid disease categories and characteristics

- Type I tumors are most common and represent 70–80% of all gastric NETs. They tend to be multiple, smaller than 1 cm in size, and are often discovered incidentally or during endoscopic evaluation for anemia (Figure 1A and B). Their behavior is typically indolent, and metastases are infrequent (occurring in <10% of patients for lesions <2 cm in size).
- Type II gastric NETs represent 5–10% of gastric NETs and are typically nonfunctioning tumors. They are associated with hypergastrinemia, chronic atrophic gastritis (e.g., from type A autoimmune gastritis or vagotomy). Although long-term use of proton pump inhibitor (PPI) leads to chronic hypergastrinemia, there have only been case reports of gastric NETs associated with PPI use.
- Type III gastric NETs represent 10–15% of gastric NETs and are usually sporadic. They are associated with mutations in the tuberous sclerosis complex (TSC) genes, such as TSC1 and TSC2. Type III NETs are typically small, asymptomatic, and well-differentiated tumors. The risk of metastasis is slightly higher in type II gastric NETs compared to type I lesions but is still low.

Diagnosis and evaluation

Studies used to diagnose and differentiate gastric NET disease may be broadly divided into endoscopic, biochemical,
histopathologic, and imaging studies. As symptoms related to carcinoid syndrome are rare, endoscopy is the gold standard for diagnosing gastric NETs. During esophagogastroduodenoscopy (EGD), aspiration of gastric fluid may be performed to assess a gastric pH, though this value can be artificially elevated by PPI use. Endoscopic ultrasound (EUS) may be performed on larger lesions to evaluate the depth of gastric wall involvement and for lymphadenopathy. In type I disease, tumors are often found in the gastric fundus and described as subcentimeter and multifocal. Biopsies of the rest of the stomach may detect atrophic gastritis or Helicobacter pylori (HP). Type II disease may also appear as multifocal subcentimeter polypoid lesions, but there may be concurrent peptic ulcer disease in the setting of a hypersecretory state. The gastric pH is generally high (>4) in type I disease and low (<2) in type II tumors. Tumors in type III disease typically appear as solitary larger lesions that may be ulcerated with hemorrhage. Gastric pH is typically normal, and there is an association with HP infection but not atrophic gastritis or peptic ulcer disease.

Biochemical testing is often performed to differentiate between the subtypes of gastric NETs. Gastrin levels are elevated in type I and II gastric NETs, while they are normal in type III. However, concurrent or recent PPI use may elevate gastrin levels; therefore, PPIs should be withdrawn at least 1 week before obtaining accurate fasting gastrin levels. In cases of ZES, abrupt PPI withdrawal can lead to serious consequences, including gastrointestinal perforation, and a careful PPI wean may be recommended when this entity is suspected. During weaning, PPIs are replaced by histamine H2-receptor antagonists such as ranitidine 1–2 weeks before formal testing. The H2-receptor antagonist should be dosed as 450–750 mg every 6 hours and then stopped in the final 24–30 hours before testing. Antacids may be taken as needed until the midnight before testing. Patients should be given explicit instructions to seek medical attention during this period should they develop diarrhea, nausea, vomiting, or severe abdominal pain. Further differentiation between type I and II gastric NETs may be established by incorporation of the gastric pH as gastrin level alone cannot determine type I or type II disease. Finally, given the association of chronic atrophic gastritis with type I gastric NETs, a low serum vitamin b12 and positive parietal cell and/or intrinsic factor antibodies may be found. While genetic testing for MEN1 may be considered when there is suspicion of type II disease, it is not considered a diagnostic tool for gastric NETs. A small case series of type II gastric NET in the setting of a confirmed germline MEN1 mutation has recommended screening for parathyroid and pituitary tumors.

Conventional cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used to assess for disease spread and for staging of advanced lesions. However, their value is limited in type I and II diseases as these are frequently characterized by small tumors. Similarly, functional imaging with somatostatin receptor scintigraphy, fluoro-D-glucose positron emission tomography, Ga-DOTATOC PET/CT, or MRI is of limited use in smaller tumors. That said, 68Ga-DOTATOC may be helpful in localizing occult gastrinomas in the setting of type II gastric NETs. In type III disease where tumors are larger with a tendency to metastasize, conventional CT or MRI studies are helpful for tumor detection and staging. Larger studies are needed to determine the precise role of functional imaging in gastric NETs, though early data on Ga-DOTATOC imaging are promising.

Endoscopic management

Endoscopic management is predominantly utilized in type I and localized type II disease. In type III disease, endoscopy plays a smaller role given the higher likelihood of concurrent metastatic disease. The lack of consensus surrounding the management of gastric NETs is highlighted by discrepancies between the published guidelines of the National Cancer Comprehensive Network (NCCN) and European Neuroendocrine Tumor Society (ENETS). Beyond a conventional EGD, EUS may also be performed to evaluate tumor depth (Figure 1C), though the cutoff size to prompt this procedure is not yet defined. Generally, lesions smaller than 8–10 mm are not amenable to fine needle biopsy during EUS and lesions smaller than 5 mm may be challenging to visualize endosonographically. The potential benefits of EUS include determination of any muscularis propria invasion that may preclude a complete endoscopic resection and evaluation of lymphadenopathy. The NCCN recommends EUS in type III disease to evaluate for lymphadenopathy and tumor depth, while an EUS is recommended in type I and II disease as clinically indicated. The ENETS guidelines mention the role of EUS for staging tumors but are less specific with respect to subtype of gastric NETs, and emphasize the need of further investigation to determine the cutoff size for endosonographic examinations of tumors.

In type I gastric NETs, the cutoff size for a tumor to harbor metastatic potential is thought to be 10 mm. Assuming there is no muscularis propria or lymph node involvement, endoscopic resection of lesions >10 mm is favored in the ENETS guidelines as this is considered the least invasive approach. The 2017 NCCN guidelines are less specific and
Medical management

In type I and II gastric NETs, somatostatin analogs (SSAs) have been shown to decrease levels of gastrin and have an antiproliferative effect on ECL cells. Limited studies, including a few small prospective studies, have demonstrated regression or complete disappearance of tumors and marked decrease in serum gastrin, lasting up to several years. SSAs (e.g., octreotide and lanreotide) can be considered in cases in which endoscopic resection is not feasible due to extensive multifocal disease, or submucosal/lymph node involvement, as well as recurrent disease after repeated endoscopic resection. However, small studies have shown that this antiproliferative effect is not durable, since a rebound in serum gastrin to pretreatment levels and tumor recurrence is possible after cessation of therapy.

A repeat cycle of SSA after disease recurrence may again induce tumor regression. Given the lack of randomized clinical trials with SSAs for this indication, their high cost, and the comparatively benign course of type I/II gastric NETs with endoscopic resection, ENETS recommends their use be restricted to cases of metastatic type I gastric NETs with proven somatostatin receptor 2 (SSTR2) expression and a low Ki67 index, and NCCN guidelines recommend consideration of SSAs only for type II gastric NET cases in which the primary tumor has not been resected (i.e., to control gastrin secretion), in conjunction with endoscopic surveillance and resection of prominent tumors. Furthermore, the oral gastrin receptor antagonist netazepide (YF476) is under study as an alternative therapeutic option for patients with type I gastric NETs and has been shown to cause tumor regression and normalize chromogranin A levels in 2 small prospective studies.

As in type I and II gastric NETs, systemic therapy in type III is warranted only in locoregional disease that is unresectable or metastatic. Management in these cases is identical to that of all unresectable or metastatic gastrointestinal NETs and is based on a multitude of factors, including the patient’s symptoms, tumor grade, tumor burden, and progression of disease during imaging-guided surveillance. Systemic options for well-differentiated NETs typically include SSAs and everolimus; interferon alfa-2b is less commonly employed. Treatment is often multimodal, particularly in cases of liver metastases, for which liver-directed therapies such as hepatic arterial embolization are commonly employed. Peptide receptor radionuclide therapy is an emerging tool for somatostatin receptor-expressing tumors, but is not approved for use in the US. The role of systemic chemotherapy in the treatment of well-differentiated gastric
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Type III gastric NETs may be well differentiated (G1, G2) or poorly differentiated (G3). Well-differentiated type III gastric NETs are frequently invasive and metastasize to regional lymph nodes; therefore, patients are typically managed with an oncologic resection of the primary tumor and regional lymph nodes. In carefully selected patients with type III gastric NETs with low-risk features (<2 cm, confined to submucosal layer, no lymphovascular invasion), favorable results with endoscopic resection (EMR, ESD) have been reported in South Korea. The outcome of patients with poorly differentiated type III gastric NETs is extremely poor, resembling that of patients with small-cell lung cancer; therefore, the role of surgery is quite limited. A reasonable approach is to treat patients with poorly differentiated type III gastric NETs with upfront platinum-based systemic therapy, and perhaps consider surgical resection in only those who have locoregional disease.

Conclusion

Gastric NETs are clinically categorized into types I, II, and III. A combination of fasting serum gastrin levels, gastric pH, and endoscopic and imaging findings is necessary to differentiate among the types of gastric NETs as their prognoses all vary. While some gastric NETs are indolent and can be managed by endoscopic resection and surveillance, refractory disease may require treatment with an SSA. Liver-directed therapy and/or systemic therapy with everolimus or chemotherapy is typically reserved for advanced disease. Surgical resection is reserved for type I and type II NETs that are endoscopically unresectable, or carefully selected patients with well-differentiated type III disease. While the NCCN and ENETS provide guidelines, the diagnosis and management of gastric NETs remains challenging in some areas, and a multidisciplinary approach is preferred to ensure consideration of all therapeutic options.

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