MANAGEMENT OF GASTRIC NEUROENDOCRINE TUMORS: A REVIEW

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Abstract

Gastric neuroendocrine tumors (G-NET) are rare tumors arising from enterochromaffin-like cells of the gastric mucosa. They belong to a larger group called gastroenteropancreatic neuroendocrine tumors and are classified as low, intermediate, or high-grade tumors based on their proliferative indices. They are further categorized into three subtypes based on their morphologic characteristics, pathogenesis, and behavior. Type 1 and 2 tumors are characterized by elevated serum gastrin and are usually multifocal. They typically occur in the setting of atrophic gastritis or MEN1/Zollinger Ellison syndrome, respectively. Type 2 tumors are associated with the most symptoms, such as abdominal pain and diarrhea. Type 3 tumors are associated with normal serum gastrin, are usually solitary, and occur sporadically. This type has the most aggressive phenotype and metastatic potential. Treatment and prognosis for G-NET is dependent on their type, size, and stage, with Type 1 having the best prognosis and Type 3 having the worst. This review discusses the presentation, work-up, and surgical management of these tumors.

Keywords

gastric neuroendocrine; neuroendocrine carcinoma; high-grade; gastrinoma; NET; G-NET

1. Introduction

Gastric neuroendocrine tumors (G-NET), previously referred to as gastric carcinoids, are rare tumors arising from enterochromaffin-like (ECL) cells of the gastric oxyntic mucosa.[1,2] They are part of a larger group of tumors called neuroendocrine neoplasms (NEN) and include well-differentiated neuroendocrine tumors (NET), poorly differentiated NET, poorly differentiated neuroendocrine carcinomas (NEC), and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN).[3,4]

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G-NET comprise 1.9-2.2% of all NET and 5-15% of all gastroenteropancreatic NET.[5,6] According to recent analyses of the Surveillance, Epidemiology, and End Results (SEER) database in 2020, G-NET were found to have an annual incidence of 4.97 cases per 1,000,000 patients in the USA, with a median age of diagnosis of 59 years and 5-year overall survival of 81.1% for all stages combined.[7]

The clinical presentation of G-NET is not specific. They are usually diagnosed during an upper gastrointestinal endoscopy, and carcinoid syndrome is seldom seen in this subset of NETs.[8,9] After appropriate diagnostic, imaging, and staging procedures, treatment depends on the size, number, depth of invasion, metastasis, and differentiation of the tumor.[10] Treatment options include surveillance with or without excision, endoscopic therapy / resection, surgical resection, and systemic therapies. In this paper, we have reviewed the different types of G-NETs and provided insights into their management and surveillance based on the presenting type.

2. Types

As per the World Health Organization (WHO) in 2019, G-NET are classified based on their morphologic characteristics, behavior, and pathogenesis into histamine-producing ECL-cell NET, somatostatin-producing D-cell NET, gastrin-producing G-cell NET and serotonin-producing enterochromaffin (EC) cell NET.[4]

The majority of G-NET are histamine-producing ECL-cell NET which are categorized into three main types. Type 1 is associated with autoimmune atrophic gastritis, type 2 with Zollinger-Ellison syndrome (ZES) and Multiple endocrine neoplasia type 1 (MEN1) syndrome, and type 3 arises sporadically, usually with a unifocal lesion (Table 1). Rarely, ECL-cell NETs have been associated with an intrinsic defect in the acid secretion of the parietal cells.[1,2,4,11–13] Type 1 and type 2 G-NET are characterized by hypergastrinemia, whereas patients with type 3 tumors usually have normal serum gastrin levels.[1,2,4,14] Type 3 G-NET are frequently larger in size compared to the other two types and behave more aggressively.[2,14] Clinically, patients with G-NET are usually asymptomatic, but they can present with abdominal pain, nausea, vomiting, gastrointestinal bleeding or gastric outlet obstruction.[4,15,16]

3. Evolution of Nomenclature and Staging

In 2000, the WHO defined gastric carcinoids as "well differentiated neoplasms of the diffuse endocrine system". This change was undertaken to underline the malignant potential of these tumors and also separate them from other entities producing bioactive molecules, such as insulinomas, VIPomas and gastrinomas.[1,17] In 2010, the WHO classified well-differentiated gastroenteropancreatic NET into low grade (G1) or intermediate grade (G2), whereas the term high-grade (G3) was used to define poorly differentiated NEC. This grading system utilizes the tumor's proliferative characteristics to assign the appropriate grade, by taking into consideration the mitotic rate and Ki-67 index.[18] Since then, studies have revealed a subgroup of patients with well-differentiated high-grade NET.[19] For this reason, in 2019, WHO re-classified G-NET into three grades (low or G1, intermediate or G2 and high or

G3) (Table 2). NEC are no longer graded as they are uniformly defined as high-grade, but continue to be separated into small-cell and large-cell subtypes. Well-differentiated NET may be high-grade, despite remaining well-differentiated morphologically, and distinct from poorly differentiated NEC.[3,4,20] Mutations in the p53 and RB1 genes are usually present in NEC, differentiating them from G3 NET.[4]

G-NET are staged according to the Tumor (T), Node (N) and metastasis (M) staging system of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) (Table 3,4).[4,11,21]

4. Type 1 Gastric Neuroendocrine Tumors

Type 1 G-NET comprise 80-90% of all G-NET.[2,4,6,12,13] These tumors have a female predominance with a male to female ratio (M:F) of 0.4:1.[4,13] This type is associated with chronic autoimmune atrophic gastritis, in which the formation of autoantibodies target the H+/K+ ATPase of the parietal cells in the gastric body and fundus, leading to achlorhydria and the decreased production of intrinsic factor (IF). Critically, only a subset of patients with autoimmune atrophic gastritis develop G-NET with an annual risk of 0.4-0.7%, indicating that other pathogenic processes may be at play, including mutations of the Regalpha gene.[22–24] The absence of hydrochloric acid causes a physiologic loss of the normal feedback inhibition via somatostatin producing D cells, which subsequently leads to increased gastrin production by G-cells in the antrum, leading to hypergastrinemia. The continuous production of gastrin causes hyperplasia of the ECL cells, acting as the nidus for the formation of type 1 G-NET via subsequent dysplasia and NET development, which appear as multiple small lesions (Figure 1). Furthermore, the decreased production of IF results in the decreased absorption of vitamin B12, leading to megaloblastic anemia (pernicious or macrocytic anemia).[1,2,4,13] Infection with H. Pylori is described as another etiologic factor for development of type 1 tumors.[4] Patients with type 1 G-NET have an excellent prognosis, where 5-year overall survival reaches 100%.[4,14]

Presentation and histologic evaluation

Type 1 G-NET usually present as multiple sub centimeter polyps or nodules in the gastric body or fundus that rarely metastasize (1-3%).[2,4,6,14] Histologically, they are low or intermediate grade monomorphic cells with round nuclei.[4,25] The gastric mucosa shows atrophy with intestinal and pseudopyloric metaplasia, ECL-cell hyperplasia and dysplasia, and absence of parietal cells.[4]

Diagnosis and work-up

Work-up of type 1 G-NET should include endoscopy with gastric polypectomy/biopsy and measurement of serum gastrin levels. High gastric pH, presence of anti-parietal cell and anti-IF antibodies, and low serum B12 supports the diagnosis.[26] Proton pump inhibitors (PPIs) may lead to falsely elevated serum gastrin levels, and thus levels should be checked after PPI cessation for at least 1 week. Once the diagnosis has been confirmed, endoscopic ultrasound (EUS) should be considered to evaluate lesions greater than 1cm to identify the depth of invasion and involvement of regional lymph nodes.[12] Additional computed

tomography (CT) of the chest and multiphasic CT or magnetic resonance imaging (MRI) of the abdomen and pelvis is only recommended in the presence of tumors greater than 2cm, as these lesions have an increased risk of metastasis. Additional imaging with 68Ga-Dotatate positron emission tomography (PET)-CT should only be considered in patients with high-risk or advanced disease. [27]

Treatment and follow-up

In the absence of metastatic disease, treatment usually involves endoscopic resection of the most prominent tumor and endoscopic observation of tumors less than 1cm.[6,28,29] Endoscopic surveillance should be tailored to the size and number of prominent lesions, annually or every two years with biopsy of the polyps, and mucosal resection for lesions larger than 1cm.[11,30,31] In a recent endoscopic surveillance study of 57 patients, 30% of patients who were monitored with surveillance progressed, requiring resection. Patients with disease progression had significantly higher serum gastrin levels than patients without progression. Fifty percent of patients with disease progression required reinterventions with a median follow up of 22 months after the first intervention.[32] Another study followed 84 patients with type 1 G-NET after initial endoscopic or surgical intervention. Fifty-two percent of patients developed local recurrence requiring reintervention during a mean follow-up period of 45 months.[33] No metastasis or death was reported during this period with a median recurrence-free survival of 31 months. Similar to the previously mentioned study, high serum gastrin at follow up was associated with recurrence.

Endoscopic mucosal resection, endoscopic submucosal dissection, and band and slough technique are acceptable endoscopic techniques with a good safety profile.[34–36] Surgical intervention is usually not advised given the benign nature of this disease.[1,14] Indications for surgery include tumor extending beyond the submucosa, lymph node involvement, tumors larger than 2cm, recurrent tumors, and in patients with more than six polyps.[6,27,31] In these cases where surgery is indicated, the North American Neuroendocrine Tumor Society (NANETS) recommends tumor excision via wedge resection.[27,37,38] Antrectomy, particularly minimally invasive antrectomy, to remove the source of gastrin may be used very selectively in symptomatic patients with multifocal disease and can often result in regression of type 1 G-NETs.[39–41] Total gastrectomy is largely no longer used in the treatment of type 1 G-NETs, and may be performed rarely in cases with extensive fundal disease or widespread recurrence not amenable to endoscopic resection.[42,43]

Somatostatin analogs can be used in the setting of recurrence following endoscopic resection or multiple lesions not amenable to endoscopic resection to reduce serum gastrin.[44] Netazepide is a gastrin/cholecystokinin-2 receptor antagonist which has shown to reduce the size and number of type 1 G-NET, along with a reduction in plasma chromogranin A levels.[45,46] It is a potential alternative systemic treatment strategy either alone or with endoscopic surveillance, although large scale randomized trials are required to validate its effectiveness.

5. Type 2 Gastric Neuroendocrine Tumors

Type 2 tumors represent 5-7% of G-NET.[4,6,12,13] A gastrinoma, an ectopic gastrin producing G-cell neoplasm commonly found in the duodenum or pancreas, is responsible for the hypergastrinemia that drives the pathogenesis of type 2 G-NETs. This type is associated with elevated serum gastrin (>1000 pg/ml is considered diagnostic), low gastric pH (hyperchlorhydria, pH <2), and hypertrophic hypersecretory gastropathy that can develop in the setting of MEN-1 syndrome.[4] The long-term risk of developing a type 2 G-NET is at least 100 times less in patients with sporadic gastrinomas compared to MEN-1 patients with ZES.[47] The risk of metastasis is approximately 10-30%, higher than type 1, but less than type 3.[2,4] The 5-year overall survival ranges from 60% to 90%.[4]

Presentation and histologic evaluation

Type 2 G-NET usually present as multiple tumors in the gastric fundus / body that are less than 2cm in size.[2,4,6] Patients may present with symptoms of ZES, including abdominal pain, pepticulcers, and secretory diarrhea due to excessive gastric acid production.[48] The diagnosis is often delayed due to the nonspecific nature of these symptoms, with an average time between onset of symptoms to diagnosis being longer than 5 years.[49] Histologically, there is evidence of parietal cell hyperplasia and hypertrophy with the presence of monomorphic cells with extracellular mucoid-like material and formation of enlarged trabeculae and ribbons.[4]

Diagnosis and work-up

Diagnosis should include endoscopy with gastric polypectomy / biopsy, and measurement of serum gastrin and chromogranin A levels. Once the diagnosis is confirmed, EUS may be considered to investigate the depth of the lesion. Patients should undergo multiphasic abdominal CT or MRI and cross-sectional imaging of the chest and pelvis to assess the location of the gastrinoma and evaluate for metastatic disease.[28,29] Somatostatin receptor imaging with gallium-68 or 68Ga-Dotatate is a useful study with a higher sensitivity and specificity (91% and 94%, respectively) than somatostatin receptor scintigraphy, as patients with stage IV disease may benefit from systemic therapy if a receptor-positive tumor is identified.[50] Type 2 G-NET are associated with MEN1 syndrome, which demonstrates an autosomal dominant pattern of inheritance. Genetic work-up should be performed in patients meeting clinical criteria for MEN1, due to implications related to other MEN1-associated tumors, as well as genetic counseling.[11,51,52]

Treatment and follow-up

Treatment of type 2 G-NET usually consists of surgical resection of the primary gastrinoma. Appropriate patients with sporadic gastrinoma without unresectable metastatic disease should undergo surgery to remove the gastrinoma.[53] Primary gastrinoma resection often results in regression of the type 2 G-NET.[54] If resection is not feasible due to metastatic disease or multifocal gastrinomas, endoscopic resection of the most prominent G-NET followed by surveillance is a viable option. Somatostatin analogs should be considered for the management of symptoms or when disease control is required.[55] High dose PPIs may help in decreasing gastric acid hypersecretion. In patients with type 2 G-NET as a

result of MEN1, resection of the primary gastrinoma is only recommended in the setting of gastrinomas larger than 2cm.[53] Medical management of hypergastrinemia is the mainstay of therapy in patients with MEN1 due to the multiplicity of tumors, extra-pancreatic location, co-existent metastatic disease, and low chance of surgical cure. Following resection, imaging surveillance should continue for at least 10 years in the majority of patients.[6,11,55] Netazepide as a treatment option has not been validated in type 2 G-NETs.

6. Type 3 Gastric Neuroendocrine Tumors

Type 3 tumors represent 10%-15% of G-NET.[4,6,12,13] They develop sporadically and are non-gastrin dependent.[2,4,6,14,16] Type 3 tumors have strong male predominance with M:F ratio 2.8:1.[4] The 5-year overall survival is <50%.[4] Factors associated with worse overall survival are tumor size > 2cm, angio-lymphatic invasion, invasion of the gastric wall, and distant metastasis.[14]

Presentation and histologic evaluation

Type 3 tumors present as a single, large (usually > 2cm) tumor. Approximately half of patients (51%) have distant metastases at the time of diagnosis.[6] Patients usually present with nonspecific symptoms including pain, weight loss, and melena related to tumor progression and metastatic spread. Histologic examination of the normal gastric mucosa is usually unrevealing.[2,4,14]

Diagnosis and work-up

Endoscopy with histologic examination of the biopsy confirms the diagnosis. Given the aggressive nature of this tumor with a tendency to invade the lymphovascular and submucosal tissue, all patients should be considered for 68Ga-Dotatate PET-CT along with multiphasic CT or MRI abdominal imaging to assess the extent of disease.[56] EUS may be considered to determine T-stage, especially for smaller tumors.[11,28,29]

Treatment and follow-up

Due to its advanced stage at the time of diagnosis and metastatic potential, radical resection, including partial or total gastrectomy, with regional lymphadenectomy is the treatment of choice for non-metastatic lesions >2cm recommended by the European Neuroendocrine Tumor Society (ENETS) and NANETS.[27,30] The role of endoscopic resection and surveillance for small and low-grade type 3 G-NET has been explored. A study by Min *et al.* included 32 patients with type 3 G-NETs, and 22 patients with grade 1 NETs without lymphovascular invasion were treated with wedge or endoscopic resection.[57] After a median follow up of 59 months, only patients with tumor size >1.5 cm developed recurrence, and no patients with a grade 1 NET of 1.5 cm or smaller developed recurrence. Another study by Kwon *et al.* investigated 50 patients with well-differentiated type 3 G-NETs with a mean tumor size of 1cm that were treated with endoscopic resection, and no recurrence was noted in either the pathologically complete resection group (80%) or the incomplete resection group (20%) with a median follow up of 46 (13-60) months.[58] A more recent analysis by Hanna *et al.* compared outcomes between patients presenting with type 1 and type 3 G-NET.[59] Patients with type 1 G-NET had a median tumor size of 0.6cm, and patients with

type 3 G-NET had a median tumor size of 1.0cm. The majority (88%) of patients with type 1 G-NET had grade 1 lesions, while 53% of patients with type 3 G-NET had grade 2/3 lesions. They found no difference in overall survival between patients presenting with type 1 and type 3 G-NET.

Higher tumor grade and presence of nodal or distant metastases was associated with worse survival. Among type 3 G-NET patients, those with small (< 0.5 cm), grade 1 lesions were less likely to develop metastases (0% versus 33%, p < 0.01) and more likely to survive (100% versus 67%, p < 0.01) at 5 years compared to patients with larger or higher-grade tumors. Patients with grade 1 tumors <0.5cm were largely treated with endoscopic resection (67%).[59] Consistent with these studies, the recent National Comprehensive Cancer Network (NCCN) guidelines indicate that small and low grade type 3 G-NETs can be treated with endoscopic resections (< 1 cm) or surgical wedge (< 2 cm).[38] Post-operative surveillance with imaging studies should continue for at least 10 years.[11]

7. Grade 3 G-NET and NEC

Together, grade 3 G-NETs and NEC are classified as high-grade neuroendocrine neoplasms. They are extremely rare, comprising approximately 0.5% of all malignant gastric neoplasms.[60] Given their low incidence, there is a paucity of literature regarding the workup and management of high grade gastric NENs. Recently, the North American Neuroendocrine Tumor Society published consensus practice recommendations to provide guidance on best treatment practices for these rare tumors.[61]

Diagnosis and workup

The workup of G3 G-NET and G-NEC follows a comprehensive approach to establish an accurate diagnosis and assess the extent of the disease. Gastrointestinal endoscopy remains a fundamental step in the evaluation, allowing direct visualization of the tumor and obtaining biopsies for histopathological analysis. Immunohistochemistry is crucial to determine neuroendocrine differentiation and confirm the high-grade nature of the tumor. As previously discussed, G3 G-NETs are well-differentiated or moderately differentiated, whereas G-NEC are poorly differentiated.[20] Histologically, G-NEC are nearly identical to gastric adenocarcinoma except that endocrine cells are present in the tumor matrix.[62] The diagnostic criteria for G3 NENs includes a Ki-67 proliferation index greater than 20% and/or a mitotic count surpassing 20 per $2mm^2$, although the majority of NECs significantly surpass these thresholds.[63,64] G3 G-NETs are almost always positive for synaptophysin and chromogranin A, while up to 25% of G-NEC are negative for the traditional neuroendocrine markers.[61]

Due to their aggressive behavior, advanced imaging techniques play a critical role in staging these tumors. EUS provides valuable information on tumor depth and regional lymph node involvement. CT / MRI are essential for assessing local and distant spread. Key imaging characteristics, including larger size, arterial and portal enhancement, ill-defined features, and textural analysis, can be used to differentiate high grade G-NET and NEC from lower-grade lesions.[65] PET-CT with 68Ga-Dotatate can also be employed to detect somatostatin receptor expression and assess the potential for targeted therapy, especially in high-grade

G-NET. PET-CT with FDG can be used to differentiate G1/G2 lesions from G3. Several studies have shown that the degree of FDG uptake differs in lower versus higher grade lesions, and the degree of uptake is correlated with prognosis.[66–68] FDG-PET can be used as the functional imaging of choice in the case of high grade NETs or NEC with low somatostatin receptor expression.[61] The utility of brain imaging in the setting of high grade NET or NEC is low. The incidence of brain metastases in extra-pulmonary G3 G-NET and NEC is less than 2%, and patients with a higher disease burden are at higher risk of brain metastasis.[69,70] Brain MRI for patients with G3 G-NET or NEC should be reserved for symptomatic patients or patients with a high burden of systemic disease per expert consensus recommendations.[61]

Treatment and follow-up

Managing G3 G-NET and G-NEC demands an aggressive and individualized treatment approach. The management decisions are influenced by factors such as tumor stage, differentiation, patient's performance status, and the presence of distant metastases. There is little data to direct the management of G3 G-NET, so treatment recommendations are based on studies that have analyzed the management of G3 NET at other sites along that gastrointestinal tract.[71–73] Surgery with thorough lymphadenectomy remains the mainstay of curative treatment for localized G3 G-NET, with a reported median survival of 43-55 months.[74] There is currently no consensus regarding the use of definitive, neoadjuvant, or adjuvant radiotherapy or chemotherapy in the management of G3 G-NET. For G-NEC, surgery is recommended for resectable disease, with the understanding of poor prognosis.[75–80] Multiple studies compare outcomes between patients undergoing surgical resection of G-NEC versus gastric adenocarcinoma revealing neuroendocrine differentiation as an independent predictor of poor overall survival.[81,82] These studies are mainly from Asia, and more studies are needed to examine survival of patients with G-NEC across a more diverse population. A retrospective study of 69 patients with G-NEC by Ma *et al.* demonstrated that receipt of neoadjuvant chemotherapy was associated with significantly higher overall survival than patients undergoing upfront surgical resection (57.4% vs. 28.5% 5-year OS, p=0.032), indicating a possible benefit.[83] Consensus guidelines recommend the consideration of adjuvant therapy after the surgical resection of localized NEC.[84] Postoperative surveillance with imaging studies should be completed every 3 months for 3 years, and then every 6-12 months for at least 10 years for patients treated for localized high grade G-NET or G-NEC.[61]

8. Metastatic G-NET

Patients with metastatic G-NET should have a complete work-up that includes multiphasic CT or MRI abdominal imaging, chest CT, and 68Ga-Dotatate PET-CT. Depending on the disease burden and symptomatology, the following guidelines have been established per the NCCN:[85]

- If complete resection is possible, then patients should undergo resection of the primary tumor and metastasectomy.

- If patients are asymptomatic and the disease burden is low, then they can be observed with serial imaging. Alternatively, for somatostatin receptor positive tumors, administration of somatostatin analogs may be considered.

- If patients are symptomatic from the primary tumor, then debulking or resection of the primary tumor is recommended.

- For patients with unresectable or significant disease burden, somatostatin analogs should be considered as first-line. For this group of patients, who progress on first-line therapy and have significant uptake on Dotatate PET-CT, Peptide Receptor Radionuclide Therapy (PRRT) is considered standard of care. PRRT, a molecular therapy that combines a somatostatin analog with a radionuclide and targets somatostatin receptor positive tumors, is efficacious with some patients achieving complete remission.[86,87] Administration of cytotoxic chemotherapy remains controversial and may be considered in patients with progressive disease. Liver-directed therapy (surgical resection, hepatic arterial embolization and ablation) may be considered for control of liver metastases. For symptomatic bone metastases, palliative radiation therapy may be helpful.[11,55]

9.   Other types

Gastrin producing G-cell NET:

These tumors usually present as small non-functioning mucosal or submucosal lesions that develop in the antrum, frequently close to the pylorus. Histologically, they appear as uniform cells with scant cytoplasm and usually demonstrate a trabecular and gyriform pattern.[4]

Serotonin-producing EC-cell NET:

Usually presents as a non-functioning mass. Rarely, it can be associated with symptoms of carcinoid syndrome. Histologically, they appear as rounded nests of uniform cells with peripheral palisading and eosinophilic cytoplasm. They demonstrate serotonin, somatostatin receptor type 2A (SSTR2A) and caudal type homeobox 2 (CDX2) protein reactivity.[4]

Somatostatin-producing D-cell NET:

These tumor cells appear as monomorphic cells that are positive for somatostatin, SSTR2A, chromogranin A and synaptophysin.[4]

10.   Future trends

As the endoscopic evaluation of GI symptoms increase and advanced endoscopy becomes more accessible to an increasing proportion of the population, it is likely that the incidence of G-NET will keep increasing. Given the characteristics and unique behavior of G-NET compared to other gastroenteropancreatic NET, it is possible that a G-NET-specific TNM staging and histologic grading system will be developed in the future. In somatostatin receptor positive NET, PRRT has shown exciting results warranting further studies to identify the optimal timing and sequence of therapy.

11. Conclusion

Gastric neuroendocrine tumors pose significant challenges to clinicians due to their diverse origins, outcomes, and treatment demands. The pathogenesis of each is unique: type 1 is associated with hypergastrinemia and atrophic gastritis, type 2 is linked to gastrinoma with Zollinger-Ellison syndrome, while type 3 is sporadic, with no correlation with gastrin levels. The prognosis of gastric neuroendocrine tumors vary significantly: type 1 and 2 tend to have a more favorable outcome with lower metastatic potential, whereas type 3 is associated with a higher risk of metastasis. The role of resection via endoscopic or surgical intervention varies across type. Surveillance often suffices for type 1 lesions, while the surgical management of type 2 is largely focused on treatment of the underlying gastrinoma. Type 3 often requires a more comprehensive surgical approach. In light of these intricacies, it becomes paramount to tailor the management strategy to each patient′s specific gastric neuroendocrine tumor type and symptom presentation. Integrating well-established and innovative treatment methods holds the potential to mitigate disease progression and improve patients′ quality of life.

Disclosure:

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SYNOPSIS

Gastric neuroendocrine tumors are rare tumors of the stomach. As endoscopic evaluation of gastrointestinal symptoms increases, it is likely that the incidence of these neoplasms will increase. This review discusses the presentation, work-up, and surgical management of these tumors.
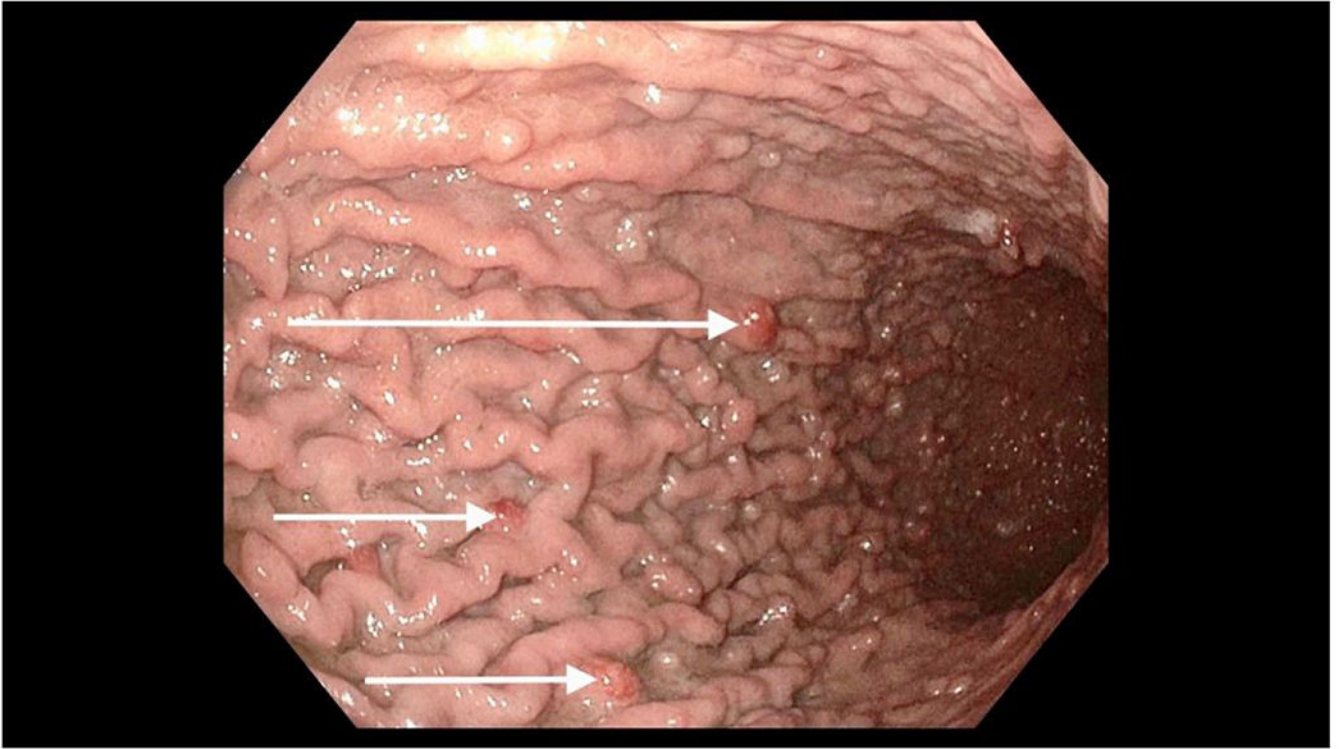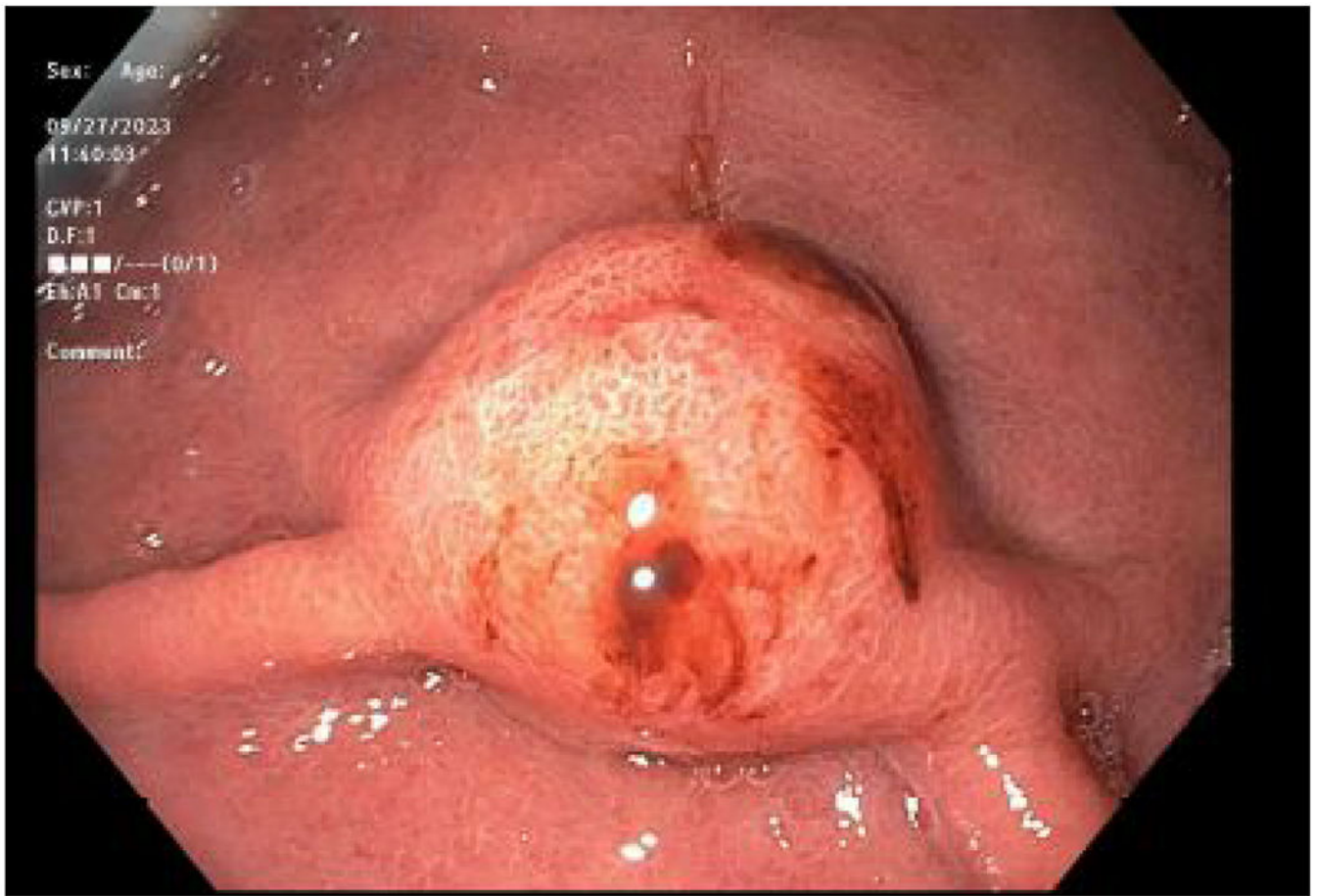
Figure 1.
Endoscopy View of Gastric Neuroendocrine Tumors

A. White arrows reveal few of the multiple tumors seen in Type 1 gastric neuroendocrine tumors.

B. Focused and magnified view of Type 1 gastric neuroendocrine tumors.

C. Focused and magnified view of a Type 3 gastric neuroendocrine tumor.

Table 1

Distinctive characteristics of different types of G-NET.

	Type 1	Type 2	Type 3
% among G-NET	80%-90%	5%-7%	10%-15%
Association with	Atrophic gastritis	MEN1-gastrinomas	-
Gastrin levels	Elevated	Elevated	Normal
Gastric pH	High	Low	Normal
Tumor size	<1cm	<2cm	>2cm
Number of tumors	Multifocal	Multifocal	Solitary
Sex predominance	Female	Equal	Male
Risk of metastasis	1-3%	10-30%	50%
Prognosis	Excellent	Very Good	Poor

Table 2

Classification of gastroenteropancreatic neuronendocrine neoplasms (WHO, 2019) [4].

Terminology	Differentiation	Grade	Ki-67 index	Mitotic rate (mitoses/10HPF)
G1 NET		Low	<3%	<2
G2 NET	Well differentiated	Intermediate	3-20%	2-20
G3 NET		High	>20%	>20
NEC	Poorly differentiated	High	>20%	>20

In cases of disparity between Ki-67 index and mitotic rate, the result that indicates a higher grade tumor should be selected.

Table 3

TNM staging for gastrointestinal NET per AJCC 8th edition [21].

T	Primary Tumor	N	Regional lymph nodes
TX	Primary tumor cannot be assessed	Nx	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis
T1	Invades the lamina propria or submucosa and less than or equal to 1 cm in size	N1	Regional lymph node metastasis
T2	Invades the muscularis propria or greater than 1 cm in size	**M**	**Distant metastasis**
T3	Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa	M0	No distant metastasis
T4	Invades visceral peritoneum (serosa) or other organs or adjacent structures	M1	M1a: Metastasis confined to liver M1b: Metastases in at least one extrahepatic site M1c: Both hepatic and extrahepatic metastases

Table 4

Prognostic stage groups for G-NET per AJCC 8th edition.[21]

	T	N	M
Stage 1	T1	N0	M0
Stage 2	T2,T3	N0	M0
Stage 3	T1,T2,T3 T4	N0 N1	M0 M0
Stage 4	Any T	Any N	M1