World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2020 August 15; 12(8): 850-856

DOI: 10.4251/wjgo.v12.i8.850

ISSN 1948-5204 (online)

MINIREVIEWS

Gastric neuroendocrine tumor: A practical literature review

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Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Manuscript source: Unsolicited manuscript

Received: March 20, 2020
Peer-review started: March 20, 2020
First decision: April 26, 2020
Revised: May 5, 2020
Accepted: July 19, 2020
Article in press: July 19, 2020
Published online: August 15, 2020

P-Reviewer: Fernandes J

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Abstract

Gastric neuroendocrine tumors are gastric neoplasms originating from enterochromaffin type cells and are inserted in a larger group, named gastroenteropancreatic neuroendocrine tumors. They are considered rare and variable in terms of their clinical, morphological and functional characteristics and may be indolent or aggressive. They are classified into types I, II and III, according to their pathophysiology, behavior and treatment. Their diagnosis occurs, in most cases, incidentally during upper digestive endoscopies, presenting as simple gastric polyps. Most cases (type I and type II) are related to hypergastrinemia, can be multiple and are treated by endoscopic resection, whenever possible. The use of somatostatin analogs for tumor control may be one of the options for therapy, in addition to total or subtotal gastrectomy for selected cases. Adjuvant chemotherapy is only reserved for poorly differentiated neuroendocrine carcinomas. Although rare, gastric neuroendocrine tumors have an increasing incidence over the years, therefore deserving more comprehensive studies on its adequate treatment. The present study reviews and updates management recommendations for gastric neuroendocrine tumors.

Key words: Gastric neuroendocrine tumor; Gastroenteropancreatic tumor; Hypergastrinemia; Gastric carcinoid; Endoscopic resection

Core tip: Gastric neuroendocrine tumors are rare lesions that are part of the

S-Editor: Zhang L
L-Editor: Filipodia
P-Editor: Wang LL

gastroenteropancreatic neuroendocrine tumors group. They are classified into types I, II and III according to their clinical and pathophysiological characteristics. Their diagnosis is usually made incidentally by upper gastrointestinal endoscopy, and most cases are treated by endoscopic resection. Surgical resections, as well as somatostatin analog treatments, are reserved for selected cases. Although rare, gastric neuroendocrine tumors need further research as their incidence has increased over the years.

Citation: Roberto GA, Rodrigues CMB, Peixoto RD, Younes RN. Gastric neuroendocrine tumor: A practical literature review. *World J Gastrointest Oncol* 2020; 12(8): 850-856
URL: https://www.wjgnet.com/1948-5204/full/v12/i8/850.htm
DOI: https://dx.doi.org/10.4251/wjgo.v12.i8.850

INTRODUCTION

Gastric neuroendocrine tumors (G-NETs), once called gastric carcinoids, are neoplasms derived from enterochromaffin-like cells (ECF) of the stomach mucosa and correspond to less than 2% of all gastric neoplasms[1]. They are part of a larger group called gastroenteropancreatic NETs (GEP-NET), which comprise well-differentiated NETs from the gastrointestinal tract. Well-differentiated NETs, together with poorly differentiated neuroendocrine carcinomas (NECs) form the neuroendocrine neoplasms. In immunohistochemistry, like other GEP-NET, G-NETs usually express neuroendocrine markers, such as chromogranin and synaptophysin. They are considered rare and of heterogeneous spectrum with a wide variety of morphological, functional and clinical characteristics[2-4]. Their behavior is generally indolent, although may be highly aggressive[5].

The real prevalence of NETs is unknown due to a worldwide difficulty in standardizing and categorizing the data. Nonetheless, increasing incidence over time is certainly related to a greater access to endoscopic and imaging methods, favoring its diagnosis[1,6-9]. A 2015 multicenter study involving national registries from several countries estimated that the prevalence of G-NET in Europe is 0.32 per 10000 inhabitants, while in the United States it is 0.17 and 0.05 in Japan[10]. Most G-NETs are incidentally diagnosed as simple gastric polyps during endoscopies of the upper gastrointestinal tract, corresponding to 0.6% to 2% of gastric polyp cases[6,9,11-16].

The present review of the English literature presents updated definitions as well as epidemiology, diagnosis and management recommendations for G-NET.

DISCUSSION

In order to standardize the classification of GEP-NETs and facilitate their understanding, the World Health Organization in 2010 divided GEP-NETs (including G-NETs) into three histological grades (G1, G2 and G3) based on the mitotic index (number of mitoses per ten high magnification fields) and/or on the Ki-67 index (mitotic and cellular proliferative index) (Table 1). This division was important due to the clinical and prognostic variability between G1, G2 and G3 groups. G1 and G2 GEP-NETs were considered well differentiated while high-grade NECs (G3) were considered poorly differentiated with significantly more aggressive behavior. In 2019, World Health Organization revised the classification and recognized a new category of high-grade but still well-differentiated GEP-NET (G3 NET-Neuroendocrine Tumors) (Table 2). Unlike G3 NECs, G3 NETs usually have a Ki-67 index below 55% and a prognosis not as poor as G3 NECs[17]. In addition to the grade classification established by the World Health Organization, which is fundamental for all GEP-NETs, well-differentiated G-NETs are also clinically divided into three types according to their pathophysiology and behavior, which influences treatment recommendations (Table 3).

Below we will describe the three types of G-NETs with their clinical characteristics and approach to localized disease.

Type I

Type I tumors correspond to the majority of G-NETs. They constitute about 70%-80%

Table 1 Classification of gastroenteropancreatic neuroendocrine tumors according to the World Health Organization 2010

	Grade I	Grade II	Grade III
Tumor size in cm	≤ 2	> 2	Any
Mitoses/10 HPF	< 2	2–20	> 20
Ki 67 index, %	< 3	3–20	> 20
Differentiation	Well differentiated	Well differentiated	Poorly differentiated

Adapted from[18]. HPF: High-power fields.

Table 2 Classification of gastroenteropancreatic neuroendocrine tumors: Neuroendocrine neoplasms according to the World Health Organization 2019

Terminology	Differentiation	Grade	Mitotic rate	Ki 67 index, %
NET, G1	Well differentiated	Low	< 2	< 3
NET, G2	Well differentiated	Intermediate	2-20	3-20
NET, G3	Well differentiated	High	> 20	> 20
NEC, SCNEC	Poorly differentiated	High	> 20	> 20
NEC, LCNEC	Poorly differentiated	High	> 20	> 20
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

Adapted from[17]. NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; SCNEC: Small cell neuroendocrine carcinoma; LCNEC: Large cell neuroendocrine carcinoma; MiNEN: Mixed neuroendocrine non-neuroendocrine neoplasm.

of the lesions and are associated with chronic autoimmune atrophic gastritis[18-23].

The destruction of parietal cells leads to achlorhydria, which stimulates the production of gastrin. This results in hypergastrinemia as a physiological response to the demand generated by the shortage of HCl. The excess of gastrin generates hypertrophy and hyperplasia of the ECFs, favoring the appearance of innumerable small lesions, which are usually not very aggressive[18,20,22,23]. Serum gastrin is always elevated in type I G-NETs. Vitamin B12 deficiency with or without macrocytic anemia (pernicious or megaloblastic) may be present due to the reduction of the intrinsic factor, with a consequent reduction in the absorption of vitamin B12[18,20,22-24]. Parallel to this, serum antiparietal cell antibodies are positive in 80% of cases[20,24-26].

The diagnosis is made by upper digestive endoscopy with biopsy. There are pale, yellowish and transparent blood vessels that contrast with the smooth and red mucosa of areas not affected by the tumor, presenting as red, small and numerous polyps[11,19,20,22,24-26]. Histological analysis of the gastric mucosa shows atrophy of mucosal cells, hyperplasia of neuroendocrine cells and absence of parietal cells.

For type I G-NETs, treatment is generally more conservative to avoid gastrectomy because they are smaller and more defined lesions. The prognosis is good. The treatment of choice is endoscopic resection for lesions ≥ 0.5 cm and endoscopic observation in smaller ones. In lesions smaller than 2 cm, the risk of metastasis is less than 10%[27]. In general, for lesions smaller than 1 cm, no other complementary imaging exam is necessary. However, for lesions ≥ 1 cm, echo-endoscopy is recommended to identify the depth of tumor invasion in the gastric wall and the possible involvement of regional lymph nodes. Gastrectomy is reserved for submucosa tumors and/or lymph node involvement and/or positive margin in the polypectomy sample[19,22,28]. Patients with small type I G-NETs are managed by regular endoscopic follow-up.

When the lesions are multiple and impossible to resect endoscopically or when there are repeated recurrences after endoscopic treatment, both gastrectomy and prescription of somatostatin analogs can be used to reduce serum gastrin and tumor control[29,30]. Reports of the use of somatostatin analogues in small groups of patients showed that the interruption after 12 mo caused the serum gastrin to rise again without the reappearance of new lesions[11,31,32]. However, data are still insufficient to show the long-term efficacy of pharmacological treatment of localized type I G-NETs[21,22]. More rarely, antrectomy may be indicated in an attempt to reduce

Table 3 Types of gastric neuroendocrine tumors

	Type I	Type II	Type III
Prevalence, %	70-80	5-10	10-20
Background	Chronic atrophic gastritis	Gastrinomas (Zollinger-Ellison syndrome)	Normal mucosa
Other syndromes	Autoimmune polyglandular syndrome	MEN-1 syndrome	
Number of lesions	Multiple	Multiple	Single
Site of tumor	Fundus/body	Fundus/body	Fundus/body
Cell of origin	ECL	ECL	ECL, EC or X cell
Serum gastrin levels	Elevated	Elevated	Normal
Gastric PH	High	Low	Normal
Underlying mucosa	Atrophic	Hypertrophic	Normal
Size of tumors, usual	1-2 cm	1 cm	> 2 cm
Invasion	Rare	More common	Common
Metastases			
Lymph nodes	5%-10%	10%-20% (duodenal tumors)	50%-100%
Liver	2%-5%	10%	22%-75%
Prognosis	Excellent	Very good	Similar to gastric adenocarcinoma

Adapted from[18]. ECL: Enterochromaffin-like; EC: Endocrine.

hypergastrinemia.

Type II

They correspond to 5%-10% of G-NETs. In type II, hypergastrinemia also occurs, but it is due to the presence of Zollinger-Ellison syndrome mostly in the context of MEN-1 syndrome. Therefore, in the suspicion of a type II G-NET, it is recommended to determine the serum concentration of both pituitary and parathyroid hormones as well as serum calcium and gastrin levels to assess the possibility of MEN-1 syndrome. The patient may experience abdominal pain and diarrhea in addition to peptic ulcers. Similar to type I G-NETs, excess gastrin causes hypertrophy and hyperplasia of the ECFs. In these cases, it is also common for lesions to be small and multiple[2,18,33-35].

Upon diagnosis, upper endoscopy reveals normal or hypertrophic gastric mucosa in addition to hypergastrinemia and low pH due to hyperchlorhydria. Unlike type I, type II G-NETs tend to be slightly larger, affect younger patients and have a slightly worse prognosis with the risk of lymph node metastases reaching 30%[27].

In general, the management of type II G-NETs is similar to type I, except for the need to also resect the gastrinoma. Most cases are treated endoscopically with resections. Surgery is rarely necessary. The use of somatostatin analogues is still debated as well as in type 1 G-NETs[20,22].

When confirming the diagnosis, the primary gastrinoma should be located and resected, although it is not always possible to locate it and multiple lesions may exist. For that, we include computed tomography, magnetic resonance imaging, endoscopic ultrasound, scintigraphy with octreotide, selective angiography, positron emission tomography and/or intraoperative ultrasound in the workup. It is also possible to use an anatomical reference known as the gastrinoma triangle composed of the junction of the cystic duct with the common liver, the transition from the second to the third duodenal portion and the pancreatic neck[11,20,35].

Type III

G-NETs of this type are sporadic and not associated with any known clinical condition. They correspond to 10%-15% of all G-NETs. The production of gastrin and HCl is within normal values, except in rare cases where the tumor itself can produce gastrin[36]. They are generally characterized by being single lesions, larger than 1 cm in size and with greater likelihood of evolving to regional and systemic metastases[2,20,33,34]. More than half of patients with type III G-NET are metastatic at

diagnosis, mainly to the liver. In these cases, carcinoid syndrome may be present, which is a paraneoplastic syndrome caused by endogenous secretion of serotonin and kallikrein secondary to carcinoid tumors. It becomes manifest when those vasoactive substances from the tumors enter the systemic circulation escaping hepatic degradation. Clinical components of the typical carcinoid syndrome are flushing, diarrhea and abdominal pain. It occurs more frequently in the context of high-volume hepatic metastases and primary tumors located in the small bowel, although it may happen with G-NETs, when atypical symptoms, such as bronchoconstriction, may be present due to the release of histamine.

Recently, some groups have suggested the existence of a type IV G-NET, which consists of the same characteristics described above for type III but being neuroendocrine carcinomas or mixed neuroendocrine non-neuroendocrine neoplasm. Therefore, they have a more aggressive behavior and even worse prognosis[37]. However, the subclassification of type IV is still not well established.

Type III lesions are also investigated by upper endoscopy with biopsy, which shows a single lesion with normal mucosa. The pH is < 4, which is normal for the gastric pattern[2,18,20,33,34]. In addition to the neoplastic lesion, the adjacent normal mucosa should also be biopsied in order to assess whether there is atrophic gastritis, intestinal metaplasia and ECF hyperplasia, which are not usually present[2,18,19,33,34].

Total or subtotal gastrectomy is performed together with lymphadenectomy, as recommended in gastric adenocarcinomas[22,38]. For patients with any surgical contraindication, endoscopic resection may be an alternative, but the risk of regional lymph node spread is high. When the anatomopathological part of the resection specimen shows a slightly differentiated NEC, adjuvant chemotherapy based on platinum, such as cisplatin and etoposide, is used (similar to small-cell lung carcinomas).

Treatment of metastatic disease

The goal of metastatic G-NET therapy is to control symptoms by reducing circulating hormones (when present) and tumor growth in order to increase quality of life and ensure greater survival[39]. In general, the treatment of well-differentiated metastatic disease (G1, G2 or G3 NET) is usually similar to other NETs, taking into account the patient's performance, available drugs, toxicity profile, the volume and extent of the metastatic disease, the expression of somatostatin receptors in functional images (Octreoscan or ^{68}Ga-Dotatate) and the presence/lack of a functioning syndrome. Surgical resection of metastases, local-regional therapies such as embolization or ablation when there is exclusive liver involvement, somatostatin analogs, target-molecular drugs (everolimus), ^{177}Lu-OctreoTate or even chemotherapy regimens when G3 should be considered when possible[40]. Despite the low response rates, the somatostatin analogue (Octreotide or Lanreotide) is usually the initial treatment of choice because it is well tolerated[41,42]. In the presence of carcinoid syndrome (8% to 35% of G-NETs), the use of the somatostatin analog is mandatory to reduce symptoms and decrease the long-term risks of an uncontrolled carcinoid syndrome. The ideal sequencing for patients with G-NETs, as in other NETs, remains unknown.

In the case of metastatic NEC, the treatment usually follows the protocols of small-cell lung carcinomas, in which the most commonly administered regimen is the combination of cisplatin and etoposide[43]. In these cases, despite good initial response rates, the prognosis is often poor.

CONCLUSION

Although relatively rare, the incidence of G-NETs has increased over time. They comprise a diverse entity of three subtypes with different pathophysiology, prognosis and management. Further studies are needed for further advances in the treatment of G-NETs.

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