Gastric neuroendocrine tumor: A practical literature review

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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

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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.

**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 polypl 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 [19,22,23]. 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 [28,29]. 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 [20,21,23]. 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, IC 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 I 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[12,20,34]. 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. 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. 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.

Total or subtotal gastrectomy is performed together with lymphadenectomy, as recommended in gastric adenocarcinomas. 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. 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 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), Lu-OctreoTate or even chemotherapy regimens when G3 should be considered when possible. Despite the low response rates, the somatostatin analogue (Octreotide or Lanreotide) is usually the initial treatment of choice because it is well tolerated. 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. 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.

REFERENCES

1. Strosberg JR, Benson AB, Huynh L, Duh MS, Goldman J, Sahai V, Rademaker AW, Kultke MH. Clinical benefits of above-standard dose of octreotide LAR in patients with neuroendocrine tumors for control of carcinoid syndrome symptoms: a multicenter retrospective chart review study. Oncologist 2014; 19: 930-936 [PMID: 25096997] DOI: 10.1634/theoncologist.2014-0120
2. Berruti A, Fazio N, Ferrero A, Brizzi MP, Volante M, Nobili E, Tozzi L, Bodei L, Torta M, D’Avolio A,
Priola AM, Birocco N, Amoroso V, Biscio G, Papotti M, Dogliotti L. Bevacizumab plus octreotide and metronomic capcitabine in patients with metastatic well-to-moderately differentiated neuroendocrine tumors: the XELIHECO study. BMC Cancer 2014; 14: 184 [PMID: 24628963 DOI: 10.1186/1471-2407-14-184]

3 Wolin EM, Jarnaz B, Eriksson B, Walter T, Toumpanakis C, Morse MA, Tomassetti P, Weber MM, Fogelman DR, Ramage J, Poon D, Gadbaw B, Li J, Pasieka JL, Mahamat A, Swanf N, Newell-Price J, Mansoor W, Öberg K. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. Drug Des Devel Ther 2015; 9: 5075-5086 [PMID: 26366058 DOI: 10.2147/DDDT.S84177]

4 Yamaguchi T, Machida N, Morizane C, Kasuga A, Takahashi H, Sudo K, Nishina T, Tobimatsu K, Ishido K, Furuse J, Boka N, Okusa T. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. Cancer Sci 2014; 105: 1176-1181 [PMID: 24975505 DOI: 10.1111/cas.12473]

5 Yao JC, Guthrie KA, Moran C, Strosberg JR, Kulke MH, Chan JA, LoConte N, McWilliams RR, Wolin EM, Mattar B, McDonough S, Chen H, Blanke CD, Hochster HS. Phase III Prospective Randomized Comparison Trial of Depot Octreotide Plus Interferon Alfa-2b Versus Depot Octreotide Plus Bevacizumab in Patients With Advanced Carcinoid Tumors: SWOG S0518. J Clin Oncol 2017; 35: 1695-1703 [PMID: 28338065 DOI: 10.1200/JCO.2016.70.4072]

6 Al-Efraij K, Aljama MA, Kennecke HF. Association of dose escalation of octreotide long-acting release on clinical symptoms and tumor markers and response among patients with neuroendocrine tumors. Cancer Med 2015; 4: 864-870 [PMID: 25727756 DOI: 10.1002/cam4.435]

7 Bajetta E, Catena L, Fazio N, Puseceda S, Biondani P, Blanco G, Ricci S, Aieta M, Pucci F, Valente M, Bianco N, Mauri CM, Spada F. Everolimus in combination with octreotide long-acting repeatable in a first-line setting for patients with neuroendocrine tumors: an ITMO group study. Cancer 2014; 120: 2457-2463 [PMID: 24752410 DOI: 10.1002/cncr.28726]

8 Yao JC, Phan A, Hoff PM, Chen HX, Chansangavej C, Yeung SC, Hess K, Ng C, Abbruzzese JL, Ajani JA. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. J Clin Oncol 2008; 26: 1316-1323 [PMID: 18323556 DOI: 10.1200/JCO.2007.13.6374]

9 McMullen T, Al-Jahdali A, de Gara C, Ghosh S, McEwan D, Schiller D. A population-based study of outcomes in patients with gastrointestinal neuroendocrine tumors. Can J Surg 2017; 60: 192-197 [PMID: 28322725 DOI: 10.1503/cjs.007616]

10 Boyce M, Thomas L. Gastric neuroendocrine tumors: prevalence in Europe, USA, and Japan, and rationale for treatment with a gastrin/CK2 receptor antagonist. Scand J Gastroenterol 2015; 50: 550-559 [PMID: 25975655 DOI: 10.3109/00365521.2015.1009941]

11 Massironi S, Zilli A, Fanetti I, Ciafardini C, Conte D, Peracchi M. Intermittent treatment of recurrent type-I gastric carcinoids with somatostatin analogues in patients with chronic autoimmune atrophic gastritis. Dig Liver Dis 2015; 47: 978-983 [PMID: 26321479 DOI: 10.1016/j.dld.2015.07.015]

12 Pavlova SI, Baulin JE, Zilitin VM, Reinert J, Dichtl E, Schöler HR, Klimovskij A, Lohse D, Jechl V. Evaluation of the efficacy of octreotide and radiolabeled somatostatin analogues in the management of metastatic neuroendocrine tumors. J Clin Oncol 2011; 39: 2005-2012 [PMID: 22165465 DOI: 10.1200/JCO.2010.31.6736 (Epub 2011)].

13 Strosberg J, El-Haddad G, Wolin E, Hendífar A, Yao J, Chesan B, Mitrata E, Kunz PL, Kulke MH, Jacene H, Bushnell D, O’Dorisio TM, Baum RP, Kulkarni HR, Caplin M, Lebthai R, Hohday T, Delpassand E, Van Cutsem E, Benson A, Srijakasanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregini E, Óberg K, Lopera Sierra M, Santoro P, Thevenet T, Erion JL, Ruszniewski P, Kwekkeboom D, Krenning E; NETTER-1 Trial Investigators. Phase 3 Trial of Lu-Dotatate for Midgut Neuroendocrine Tumors. J Clin Oncol 2017; 35: 767-769 [PMID: 28067709 DOI: 10.1200/NEJMoa1607427]

14 Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomassek J, Radermer H, Voss M, Paccard LB, Rosyere N, Sachs C, Vallee JW, Fave GD, Van Cutsem E, Tosselar M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME, RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016; 387: 126-135 [PMID: 26077094 DOI: 10.1016/S0140-6736(15)60707-7].

15 Kvol LS, Øberg KE, O’Dorisio TM, Mohideen P, de Herder WW, Arnold R, Hu K, Zhang Y, Hughes G, Anthony L, Wiedenmann B. Pasireotide (SOM230) shows efficacy and tolerability in the treatment of patients with advanced neuroendocrine tumors refractory or resistant to octreotide: results from a phase II study. Endocr Relat Cancer 2012; 19: 657-666 [PMID: 22807497 DOI: 10.1530/ERC-11-0367]

16 Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, Jacobs C, Maes JE, Landgraf AN, Rashid A, Meric-Bernstam F. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol 2008; 26: 4311-4318 [PMID: 18779618 DOI: 10.1200/JCO.2008.16.7858]

17 Klimstra DS, Kloppehl G, La Rosa S, Rindi G. Classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification of Tumours: Digestive System Tumours, ed, WHO Classification of Tumours Editorial Board (Ed), International Agency for Research on Cancer. Lyon: WHO, 2019; 16

18 Mikuchman CR, Metz DC. Gastric Neuroendocrine Tumors (Carcinoids). Curr Gastroenterol Rep 2019; 21: 33 [PMID: 30868282 DOI: 10.1007/s11886-019-0868-7]

19 Murugesan SV, Steele IA, Dinaline R, Poston GJ, Shrotri M, Campbell F, Varro A, Pritchard DM. Correlation between a short-term intravenous octreotide suppression test and response to antrectomy in patients with type 1 gastric neuroendocrine tumours. Eur J Gastroenterol Hepatol 2013; 25: 471-474 [PMID: 23249603 DOI: 10.1097/EJGH.0b013e282383cec52]

20 Gladys RA, Strong VE, Coit D, Allen PJ, Gerdes H, Shia J, Klimstra DS, Brennan MF, Tang LH. Defining surgical indications for type I gastric carcinoid tumor. Ann Surg Oncol 2009; 16: 3154-3160 [PMID: 2008; 26: 657-666]
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DOI: 10.1200/JCO.2014.60.2532

21 Uygur A, Kadayifci A, Polat Z, Yilmaz K, Gural N, Demir H, Bagci S. Long-term results of endoscopic resection for type I gastric neuroendocrine tumors. J Surg Oncol 2014; 109: 71-74 [PMID: 24165913 DOI: 10.1002/jso.23477]

22 Manfredi S, Walter T, Braunf W, Coriat R, Ruszniewski P, Lecomte T, Laurenty AP, Giochot B, Rohmer V, Roquin G, Cojocarau OZ, Lombard-Bohas C, Lepage C, Mercet J, Cadot G. Management of gastric neuroendocrine tumors in a large French national cohort (GTE). Endocrine 2017; 57: 504-511 [PMID: 28664309 DOI: 10.1007/s12020-017-1355-9]

23 Pellet A, Dreyer C, Couffignal C, Walter T, Lombard-Bohas C, Niccoli P, Seitz JF, Hentz O, André T, Coriat R, Favier S, Zappa M, Ruszniewski P, Pote N, Couvelard A, Raymond E. Clinical and Biomarker Evaluations of Somitinh in Patients with Grade 3 Digestive Neuroendocrine Neoplasms. Neuroendocrinology 2018; 107: 24-31 [PMID: 29518779 DOI: 10.1159/000487237]

24 Hung OV, Maithel SK, Willingham FF, Farris AB 3rd, Kauh JS. Hypergastrinemia, type 1 gastric carcinoid tumors: diagnosis and management. J Clin Oncol 2011; 29: e713-e715 [PMID: 21747088 DOI: 10.1200/JCO.2011.35.3235]

25 Liu Y, Uemura N, Xiao SD, Tytgat GN, Kate FF. Agreement between endoscopic and histological gastric atrophy scores. J Gastroenterol 2005; 40: 123-127 [PMID: 15770394 DOI: 10.1007/s00535-004-1511-x]

26 Soga J. Early-stage carcinoids of the gastrointestinal tract: an analysis of 1914 reported cases. Cancer 2005; 103: 1587-1595 [PMID: 15743238 DOI: 10.1002/cncr.20939]

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

28 Delle Fave G, O’Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, Ferone D, Ito T, Weber W, Zheng-Pei Z, De Herder WW, Pascher A, Ruszniewski P, Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for Gastrointestinal Neuroendocrine Neoplasms. Neuroendocrinology 2016; 103: 119-124 [PMID: 26784941 DOI: 10.1159/000443168]

29 Campagna D, Neri F, Pezzielli R, Piscitelli L, Santini D, Brocchi E, Corinaldesi R, Tomassetti P. Gastric endocrine tumors type I: treatment with long-acting somatostatin analogs. Endocr Relat Cancer 2008; 15: 337-342 [PMID: 18310299 DOI: 10.1677/ERC-07-0251]

30 Jianu CS, Fossmark S, Syversen U, Hauso O, Fykse V, Waldum HL. Five-year follow-up of patients treated for 1 year with octreotide long-acting release for enterochromaffin-like cell carcinoids. Scand J Gastroenterol 2011; 46: 456-463 [PMID: 21133821 DOI: 10.3109/00365521.2010.539255]

31 Grazzini-Glasberg S, Kalisaa G, Gur C, Giel E, Thomas D, Fichman S, Alexandraki K, Baron D, Glaser B, Shimony I, Gross DI. Long-acting somatostatin analogues are an effective treatment for type I gastric carcinoid tumours. Eur J Endocrinol 2008; 159: 475-482 [PMID: 18662978 DOI: 10.1530/EJE-08-0420]

32 Khuroo MS, Khuroo NS. Management of type I gastric neuroendocrine tumours with somatostatin analogs. J Gastroenterol Hepatol 2010; 25: 548-554 [PMID: 20074162 DOI: 10.1111/j.1440-1746.2009.06131.x]

33 Min BH, Hong M, Lee JH, Rhee PL, Sohn TS, Kim S, Kim KM, Kim JH. Clinicopathological features and outcome of type 3 gastric neuroendocrine tumours. Br J Surg 2018; 105: 1480-1486 [PMID: 29893488 DOI: 10.1002/bjs.10901]

34 Fykse V, Sandvik AK, Waldum HL. One-year follow-up study of patients with enterochromaffin-like cell carcinoids after treatment with octreotide long-acting release. Scand J Gastroenterol 2005; 40: 1269-1274 [PMID: 16334435 DOI: 10.1080/00365520510023684]

35 Pritchard DM. Zollinger-Ellison syndrome: still a diagnostic challenge in the 21st century? Gastroenterology 2011; 140: 1380-1383 [PMID: 21443889 DOI: 10.1053/j.gastro.2011.03.026]

36 Wardlaw R, Smith JW. Gastric carcinoid tumors. Ochsner J 2008; 8: 191-196 [PMID: 21603501]

37 Tan HY, Luo YN, Luo J, Liu JX, Jia LQ. The typing and treatment of gastric neuroendocrine tumors. Zhongguo Yiye Xue Qianyan Zazhi 2014; 6: 4-8

38 Shah MH, Goldner WS, Halfdanarson TR, Bergsland E, Berlin JD, Halperin D, Chan J, Kulke MH, Bensson AB, Blaszkowsky LS, Eads J, Engstrom PF, Fanta P, Giordano T, He J, Heslin MJ, Kalemkerian GP, Kandel-F, Khan SA, Kidwai WZ, Kunz PL, Kuvshinoff BW, Lieu C, Pillarsetty VG, Saltz L, Sosa JA, Strosberg JR, Sussman CA, Talwalkar SA, Whisenant J, Wong T, Yao JC, Burns JL, Ogba N, Khuroo MS, Kadayifci A, Polat Z, Yilmaz K, Gunal A, Demir H, Bagci S. Long-term results of endoscopic microparticles every 6 weeks compared with Lanreotide microparticles every 3 weeks in patients with well differentiated neuroendocrine tumors: a Phase III Study. Cancer 2006; 107: 2474-2481 [PMID: 17054107 DOI: 10.1002/cncr.22272]

39 Kunz PL. Carcinoid and neuroendocrine tumors: building on success. J Clin Oncol 2015; 33: 1855-1863 [PMID: 25918282 DOI: 10.1200/JCO.2014.60.2532]

40 Baldelli B, Barnabei A, Rizza L, Isidori AM, Rota F, Di Giacinto P, Paolini A, Torino F, Corsello SM, Lenzi A, Appetecchia M. Somatostatin analogs therapy in gastroenteropancreatic neuroendocrine tumours: current aspects and new perspectives. Front Endocrinol (Lausanne) 2014; 5: 7 [PMID: 24570674 DOI: 10.3389/fendo.2014.00007]

41 Caplin ME, Pavel M, Čwiklib JB, Phan AT, Raderer M, Sediáková E, Cadot G, Wolin EM, Capdevila J, Wall L, Randi G, Langley A, Martinez S, Blumberg J, Ruszniewski P. CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumours. N Engl J Med 2014; 371: 224-233 [PMID: 25046878 DOI: 10.1056/NEJMoa1316158]

42 Strosberg JR, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA, Kvols LK, North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapancreatic neuroendocrine carcinomas. Pancreas 2010; 39: 799-800 [PMID: 20664477 DOI: 10.1097/MPA.0b013e3181eb5d6]
