Gastric Neuroendocrine Tumors

13

Davide Ravizza and Giancarla Fiori

13.1 Introduction

Gastric neuroendocrine neoplasms (g-NENs) should be defined according to the World Health Organization classification and staged according to the Tumor Node Metastasis system. The former is based on histological differentiation and grade, which relies on the proliferation index assessed by the Ki67 and mitotic index [1, 2]. Therefore, g-NENs are classified in well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). NETs show a low to high proliferation grade, whereas NECs, by definition, are high-grade neoplasms [1].

Gastric neuroendocrine tumors (g-NETs), known as gastric carcinoid, were originally regarded as rare, but over the last few decades, their incidence has been growing (sevenfold to tenfold over the last 30 years) [3–5]. The increased incidence, frequently with lesions at early stage, may essentially be a consequence of the widespread use of endoscopy and imaging studies, improved immunohistochemical staining and increased awareness of the diagnosis [5, 6].

Recent epidemiological data show that g-NETs represent 6.9–8.7% of all gastrointestinal (GI) NETs and 0.3–1.8% of all gastric tumors [3, 6–11]. However, in a prospective Austrian study, g-NETs accounted for 23% of all NETs [10]. According to the last US epidemiological data (Surveillance, Epidemiology, and End Results - SEER), the age standardized incidence rate of g-NETs is approximately 0.4/100,000/year [12].

Most of the g-NETs develop from enterochromaffin-like (ECL) cells while a small proportion develop from non-ECL cells of gastric mucosa. Histologically, the diagnosis is confirmed by positive immunohistochemical staining of chromogranin A (CgA) and synaptophysin [13].

Gastric NETs are generally slow growing and often indolent neoplasms but can also be very aggressive and metastasize widely [11, 14–16]. They are divided into three types with different pathophysiology, clinical characteristics, aggressiveness, and prognosis (Tables 13.1 and 13.2) [17]. Type I and type II are associated with chronic hypergastrinemia causing ECL cells hypertrophy/hyperplasia and, ultimately, ECL cell NETs development [18]. In the former, the presence of a body chronic atrophic gastritis (CAG), mainly autoimmune, leads to achlorhydria which induces an appropriate hypergastrinemia [19, 20]. In the latter, the hypergastrinemia is inappropriate because it occurs in the presence of gastric acid hypersecretion, and it is due to an ectopic gastrin-producing G cell neoplasia

D. Ravizza (✉) · G. Fiori
Division of Endoscopy, European Institute of Oncology (IEO), IRCCS, Milan, Italy
e-mail: davide.ravizza@ieo.it

G. Beretta et al. (eds.), *Neuroendocrine Neoplasia Management*,
https://doi.org/10.1007/978-3-030-72830-4_13

Table 13.1 Clinical characteristics of gastric neuroendocrine tumors

	Type I	Type II	Type III
Prevalence (%)	70–80	5–6	15–20
Gender	Females	Females = males	Males
Age at diagnosis (years)	50–70	>50	>50
Associated conditions	CAG	Gastrinomas (ZES)	None
Other syndromes	Autoimmune polyglandular syndrome	MEN-1	None
Serum gastrin levels	Very high	Very high	Normal
Gastric pH	High	Low	Normal
Risk of metastases (%)	<10	10–30	50–100
Treatment	EMR, ESD or surgery	EMR, ESD or surgery	ESD or surgery
Tumor-related deaths (%)	None	<10	25–30

CAG chronic atrophic gastritis, *ZES* Zollinger–Ellison syndrome, *MEN-1* multiple endocrine neoplasia type 1, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

Table 13.2 Endoscopic and pathological characteristics of gastric neuroendocrine tumors

	Type I	Type II	Type III
Cell of origin	ECL	ECL	ECL in most cases
Gastric mucosa	Atrophic ECL hyperplasia	Hypertrophic ECL hyperplasia	Normal
Endoscopic appearance	Polypoid/subepithelial	Polypoid/subepithelial	Polypoid/subepithelial
Location	Body and fundus	Body and fundus	Any region
Number	Multiple	Multiple	Single
Size (mm)	≤10	≤10	Often >20
Differentiation	Well differentiated	Well differentiated	Well differentiated
Grading	G1/G2	G1/G2	G1/G2/G3
Depth of invasion	Mucosa/submucosa	Mucosa/submucosa	Any depth
Angioinvasion (%)	Rare	<10	> 50

ECL enterochromaffin-like cells

(gastrinoma) in the context of a Zollinger–Ellison syndrome (ZES), almost exclusively associated with a multiple endocrine neoplasia type 1 (MEN-1) [21–24].

Although proton pump inhibitors (PPIs) can induce ECL cell hyperplasia, only rare cases of well-differentiated g-NETs developing after long-term PPI use are reported in the literature [25].

Type III g-NETs are not associated with any background gastric pathology, and serum fast gastrin levels are normal. These neoplasms have a more aggressive clinical behavior mimicking that of gastric adenocarcinoma [11, 26]. Occasionally, they are associated with an atypical carcinoid syndrome [4, 27, 28].

Gastric NECs are highly aggressive and, usually, at an advanced stage at the time of presentation. They are rare and solitary, mainly diagnosed in men over 60 years of age. NECs are high-grade and poorly differentiated epithelial neoplasms showing neuroendocrine differentiation by morphology and immunohistochemistry. Genomic evidence suggest that NETs and NECs are unrelated neoplasms. They have the worst prognosis among all g-NENs with 50% of the patients dying within 12 months [13, 29–32].

13.2 Clinical Presentation and Prognosis

13.2.1 Type I Gastric Neuroendocrine Tumors

Type I g-NETs are the most common, accounting for 75–80% of cases. They develop in response to hypergastrinemia because of achlorhydria

secondary to autoimmune CAG where gastric acid-producing parietal cells are destroyed by an autoimmune process [19]. Less frequently, they can also arise in the setting of *Helicobacter pylori*-induced CAG [33].

Type I g-NETs mostly occur in women in the fifth and seventh decades, although with the more extensive use of endoscopy, they are increasingly diagnosed at younger age, mainly in patients with multiple autoimmune disease (most frequently autoimmune thyroid disease and type I diabetes) [34, 35].

Most of the time, type I g-NETs are incidentally observed during endoscopic procedure in patients with macrocytic or iron deficiency anemia. In fact, gastric parietal cell loss in CAG impairs iron and vitamin B_{12} absorption through a reduced acid output and intrinsic factor availability. Moreover, patients may complain of dysmotility-like dyspepsia (due to slow gastric emptying associated with CAG) or other gastrointestinal symptoms [36–39].

Endoscopically, they generally present as smooth, rounded, subepithelial, or polypoid multiple lesions in the gastric fundus or gastric body with or without central depression and ulceration [40] (Figs. 13.1 and 13.2). Gastric folds are reduced, the mucosa is atrophic, and the NETs are usually less than 10 mm in size although they can be identified only in biopsies in 22.2% of patients [41]. At endoscopic ultrasonography (EUS) g-NETs appear as hypoechoic homogeneous lesions with clear and regular margins, usually placed in the first three echo layers of the gastric wall (the mucosa and the submucosa) (Fig. 13.3) [42].

Type I g-NETs are well-differentiated NENs, they have a low to moderate proliferation grade and show a very low malignant potential with an excellent prognosis and a 5-year survival rate of almost 100% [43]. However, rare cases of metastatic spread and

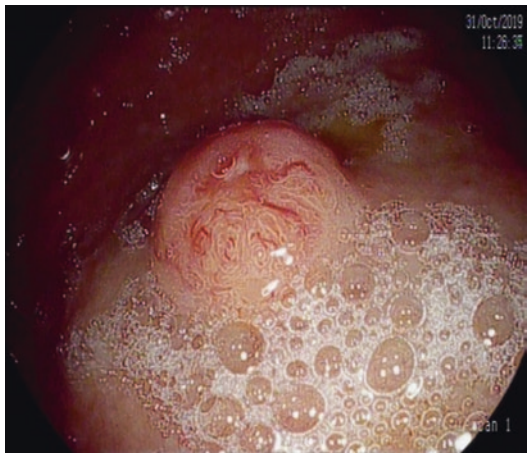

Fig. 13.1 A typical endoscopic appearance of type I g-NET with a rich superficial vascular supply

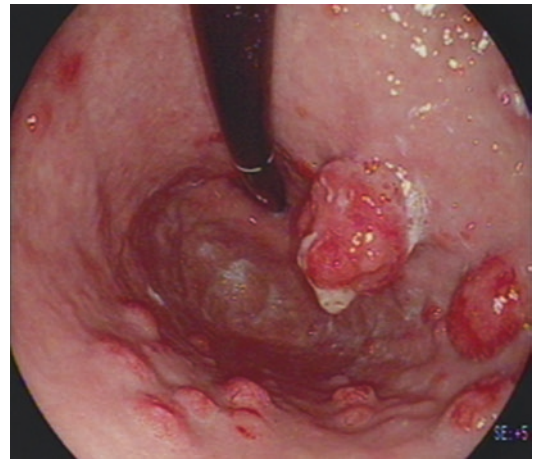

Fig. 13.2 Multiple type I g-NETs with marked atrophy of the surrounding mucosa

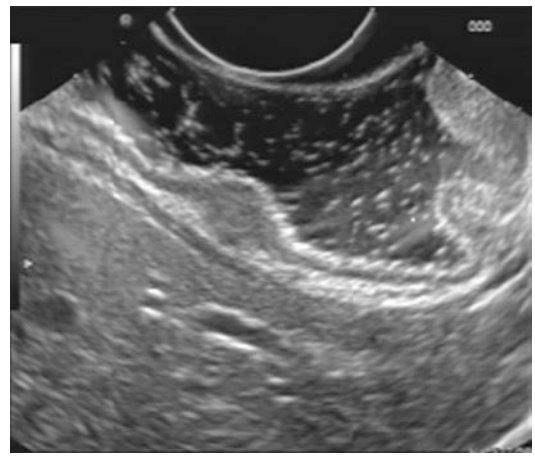

Fig. 13.3 Type I g-NET at endoscopic ultrasonography. A well-demarcated hypoechoic lesion with regular borders, placed in the first three echo layers of the gastric wall (the mucosa and the submucosa)

extraordinary tumor-related death at follow-up have been described [11, 14–16].

13.2.2 Type II Gastric Neuroendocrine Tumors

Type II g-NETs are the least common, accounting for 5–6% of cases. They develop in response to hypergastrinemia in the setting of hyperchlorhydria due to neoplastic secretion from gastrinomas, mostly in ZES-MEN1 patients, rarely in sporadic ZES [21–24]. For this reason, in type II g-NET patients, a screening for other associated tumors in the pituitary and parathyroid is required. Germline testing for MEN-1 should be considered. Type II g-NETs are equally frequent in men and women, with a clinical presentation characterized by severe peptic disease and diarrhea, both caused by an excessive gastric acid production [4, 44]. Endoscopically, they have the same presentation of type I g-NETs but with a hypertrophic background gastric mucosa (Fig. 13.4).

Type II g-NETs are well-differentiated NENs with a low to moderate proliferation grade, but unlike type I, they show a more aggressive behavior, with an increased metastatic potential (10–30% of cases) [4]. The 5-year survival rate of these patients is good (70–90%) although their prognosis is dominated by the behavior of the concomitant gastrinoma [45].

13.2.3 Type III Gastric Neuroendocrine Tumors

Type III g-NETs account for 15–20% of cases. They are generally observed in male patients over the fifth decade and are not associated with hypergastrinemia or any background gastric mucosa pathology. These NETs develop from ECL cells in most cases, in the absence of gastric mucosa ECL cells hyperplasia.

It is not uncommon that type III g-NETs diagnosis is made in asymptomatic patients when searching for a primary tumor in the setting of liver metastases of unknown origin. However, patients usually complain of pain, weight loss, and iron deficiency anemia as seen in adenocarcinoma of the stomach [29].

Mostly non-functioning, type III g-NETs are infrequently associated with an atypical carcinoid syndrome due to histamine production [4, 27, 28].

Endoscopically, they are generally larger than 2 cm and solitary with an infiltrative growth pattern, arising everywhere in the stomach on a normal-looking gastric mucosa (Fig. 13.5).

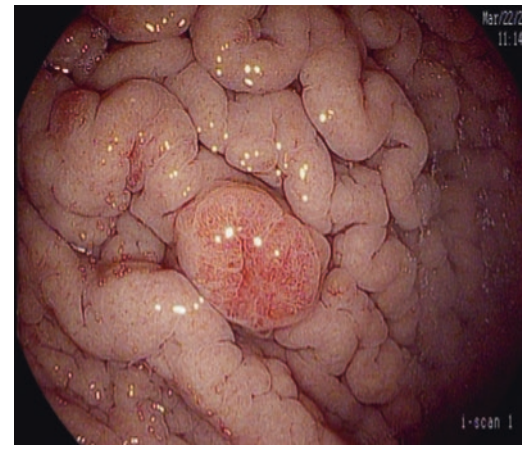

Fig. 13.4 A type II g-NET with significantly hypertrophic adjacent gastric folds in a patient with Zollinger–Ellison syndrome and multiple endocrine neoplasia type 1

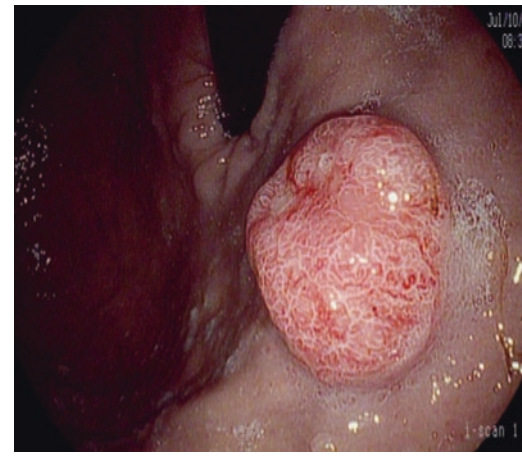

Fig. 13.5 A type III g-NET of the proximal gastric body. The lesion is larger than 25 mm, sessile, with a broad base and central depressed region

Type III g-NETs are well-differentiated NENs with a low to high proliferation grade. Frequently, at diagnosis local and distant metastases are observed (>50%). Type III g-NETs show the worst prognosis among all g-NETs with a 5-year survival rate of less than 35% [11, 17, 26, 30, 34, 46].

13.3 Diagnosis and Tumor Staging

Upper GI endoscopy with careful evaluation of the tumors is the gold standard in diagnosing g-NETs. In addition to assess site, number, and size of the lesions, it allows their adequate pathological diagnosis and characterization by the biotic sampling. Multiple random antrum, corpus, and fundus biopsies should also be taken to search for etiologic orientation, such as the presence of CAG (whose diagnosis is essential to define type I g-NETs), and to assess the presence of ECL cell hyperplasia and *Helicobacter pylori* infection. In type II g-NETs, upper GI endoscopy is also necessary to search for duodenal gastrinomas and to verify adequate control of gastric hypersecretion (healing of peptic disease) [47–49].

Endoscopic ultrasonography is recommended in g-NETs that appear resectable, except for lesions <10 mm in size, to define parietal invasion and regional lymph nodes status. Furthermore, it allows lymph node cytological assessment by fine needle aspiration. Moreover, in ZES-MEN1 patients with normal conventional imaging studies, EUS has a pivotal role to search for small pancreatic gastrinomas [47–50].

Contrast-enhanced abdominopelvic computerized tomography (CT) scan and magnetic resonance imaging (MRI) with gadolinium-enhanced and diffusion-weighted sequences are of very limited value for small type I and II g-NETs. However, they are mandatory in all patients with an increased risk of regional/distant tumor spreading such as type I and II g-NET patients with a tumor size ≥10 mm and/or muscularis propria invasion and type III g-NET patients [15, 35, 49]. Transabdominal ultrasonography can be used in situations with a very low risk of local or distant metastases. Somatostatin-receptor imaging [Somatostatin-receptor scintigraphy and 68Ga-DOTA positron-emitting tomography (PET)] should be performed in all g-NETs associated with liver metastases or if there is concern for metastatic disease or lymph node involvement [35, 49]. 18Fluorodeoxyglucose-PET is helpful in higher grade g-NETs, and its positivity is an independent poor prognostic factor [49, 51].

Laboratory tests should be performed for diagnosis and during follow-up. The measurement of gastrin values is crucial for diagnostic purposes. In patients with type I and II g-NETs, serum gastrin levels are always elevated differently from patients with type III who have normal serum gastrin levels. Hypergastrinemia is also observed in approximately one third of patients with NECs. Gastrin measurement during follow-up is not necessary. It is worth to keep in mind that PPIs alter serum gastrin levels whose dosage should be preferably performed 14 days after the interruption of these drugs (except in ZES patients, in whom PPIs must not be stopped to prevent rebound acid secretion, possibly leading to peptic ulceration and GI bleeding) [35, 52, 53].

Serum CgA levels are always elevated in type I and II g-NETs because of the hypergastrinemia-induced ECL cells hypertrophy/hyperplasia. For this reason, the measurement of this biochemical marker is not necessary neither for the diagnosis nor during the follow-up of these patients. However, in patients with type III g-NETs in which serum gastrin levels are normal and liver metastases are frequently observed, plasma CgA may be useful [35]. In fact, it is well known that CgA has a higher sensitivity for metastatic NETs in comparison with localized NETs [54]. CgA false-positive results may be observed during treatment with PPIs or in patients with heart disease and severe kidney failure [55]. As well as serum gastrin levels, serum CgA evaluation should be preferably performed 14 days after PPI interruption (see the above comment about PPI withdrawal) [54, 56].

Urinary 5-hydroxy-indolacetic acid dosage should also be considered in type III g-NET

patients in the rare cases with associated symptoms suggestive of the carcinoid syndrome.

In patients with type I g-NETs anti-parietal cell and anti-intrinsic factor antibodies should be evaluated in the context of autoimmune CAG. *Helicobacter pylori* should be searched because its eradication may modify the natural history of gastric atrophy [17, 57].

It must be highlighted that is of paramount importance that patients with type I g-NETs, particularly if elderly, are screened for iron and vitamin B_{12} deficiency at diagnosis and mainly during follow-up. In fact, iron deficiency anemia has been found to be the presenting feature in more the 50% of CAG patients, whereas vitamin B_{12} deficiency is frequently observed in these patients and can be responsible of significant health consequences (neurological, cognitive, psychotic, and mood impairment) [57].

Thyroid function, thyroid peroxidase antibodies, and thyroglobulin antibodies should be assessed in type I g-NETs because of the possible association of autoimmune CAG with autoimmune thyroiditis [41, 57].

13.4 Treatment and Follow-Up

An expert NEN-dedicated multidisciplinary team should be involved to individualize treatment.

13.4.1 Localized Disease

13.4.1.1 Type I Gastric Neuroendocrine Tumors

Due to the indolent course of type I g-NETs, a conservative management is to be preferred over surgery [48]. In these patients, tumor size ≥1 cm is a potential predictor of lymph nodal metastases and should be the lesion characteristic considered first when their management is planned [14, 15].

Lesions <1 cm should be removed without any additional evaluation, although nothing suggests a less favorable evolution if they are left in place and followed up [58]. Endoscopic resection is the treatment of choice for these tumors, ranging from polypectomy and endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD) [48].

Complete resection of g-NETs is difficult with conventional polypectomy because most of them are not confined to the mucosa but, rather, they invade the submucosa, resulting in frequent involvement of the resection margins. This might account for the high recurrence rates observed in some series [41]. EMR and ESD can satisfactorily achieve the en bloc resection of these lesions without any difference in complication (bleeding and perforation) incidence, although ESD is more time-consuming than EMR [59–62]. However, the rate of vertical resection margin involvement has been observed to be significantly lower in the ESD-treated lesions than in those treated with EMR [61, 62]. Moreover, EMR and ESD might be used to resect remnant tumor after an initial incomplete endoscopic resection as observed in incompletely resected rectal NETs [63, 64].

Recently, a novel endoscopic therapeutic technique, the endoscopic full-thickness resection (EFTR), has been used for the treatment of gastric subepithelial tumors. ETFR allows a full-thickness resection of the gastric wall showing interesting results for the treatment g-NETs [65].

In the case of type I g-NETs ≥1 cm, CT scan or MRI is necessary to rule out lymph nodal and/or distant metastases. EUS evaluation is mandatory to exclude invasion beyond the submucosal layer or regional lymph nodal invasion. If the lesions do not reach the muscularis propria layer, then endoscopic resection, preferably using the ESD technique, should be performed [48].

After endoscopic resection, an endoscopic surveillance is required. First, because type I g-NETs are recurring disease. Second, because of the underlying CAG, to monitor the risk of development of intestinal metaplasia, dysplasia, and adenocarcinoma [66, 67]. Endoscopic surveillance is suggested every 12 months for patients with recurring neoplasms and every 24 months for those with non-recurring lesions [35, 41].

Surgery (wedge resection or total gastrectomy with lymphadenectomy) should be considered for lesions not amenable to endoscopic resection

(lymph nodal and/or distant spread, extensive multifocal diffusion), in case of involvement beyond the submucosa (at EUS or at pathological examination of an endoscopically resected tumor), in the presence of positive margins after endoscopic resection and if vascular and/or lymphatic invasion are observed [48]. Any surgical treatment should be planned considering patient-related parameters (age, comorbidity) and the well-known usually indolent course of type I g-NETs also in the presence of recurrence and local or distant spread [14, 41, 59].

Antrectomy is a further surgical option for the treatment of type I g-NETs. It can be considered for extensive recurrent or multifocal lesions not amenable of less invasive treatment [48]. Antrectomy removes the source of the hypergastrinemia which is the cause of ECL cell hypertrophy/hyperplasia and, ultimately, ECL cell NET development [28]. Patients treated with antrectomy have a lower risk of recurrence and need fewer follow-up endoscopies than those treated with endoscopic resection [68]. However, given the evidence that some lesions recur after hypergastrinemia interruption, the improvement in endoscopic techniques, the complications and side effects of surgery, and the possibility of medical treatment, its use is debated and rarely practiced [48, 69].

Long acting somatostatin analogs (SSAs), because of their antiproliferative, antiangiogenetic, and antisecretive effects, are widely used as a medical treatment of both functioning and non-functioning NENs [70]. They inhibit gastrin release from antral G cells suppressing hypergastrinemia, the leading cause of ECL cell NET development, and directly inhibit endocrine cells proliferation. When administered continuously, SSAs have been demonstrated to reduce the number and size of type I g-NETs. However, after their withdrawal, lesions recur early and increase in size [71–76]. SSAs must be given by injection and are generally well tolerated, although some adverse drug reaction (ADR) such as diarrhea, headache, gallstones development, and hyperglycemia are non-infrequently observed [70]. Because of the high costs of SSAs, their ADR profile and the usually excellent prognosis of most type I g-NET patients, these drugs might be proposed in selected cases, as for recurrent or multifocal lesions and when endoscopic resection is not feasible or radical. Randomized controlled trials comparing SSA treatment efficacy to endoscopic management are needed. ENET guidelines suggest their use only according to expert opinion [35, 48].

Another potential medical option in type I g-NET treatment is Netazepide, an orally active, highly selective, competitive gastrin/cholecystokinin 2 receptor antagonist. In 16 patients treated once daily for 12 weeks, it significantly reduced the number of tumors, the size of the largest tumors, and the circulating CgA within the normal range. Serum gastrin values were unaffected. Netazepide is safe and well tolerated; however, the tumors regrow quickly after the drug is discontinued [77, 78]. The same results in terms of efficacy, safety, and tolerability were observed in 13 patients treated with netazepide daily for 52 weeks. It is interesting to note that also circulating CgA increased again after netazepide was stopped. ECL cells, both in g-NETs and in CAG, are the source of CgA, and its normalization is consistent with netazepide inhibiting ECL cell growth. Thus, CgA might be used to monitor treatment [79].

Despite these initial favorable experiences, placebo-controlled studies in a larger number of patients and for a longer time are needed to confirm the use of netazepide for the treatment of type I g-NETs.

13.4.1.2 Type II Gastric Neuroendocrine Tumors

Even more than in type I g-NETs, treatment strategy of type II g-NET patients should be planned in a NEN-dedicated multidisciplinary team. Their management needs to be individualized and to be approached in the context of MEN-1 syndrome whose treatment is first influenced by the presence of duodenal or pancreatic gastrinomas for whom surgical resection is recommended whenever it is possible.

Because of the more aggressive clinical behavior than type I g-NETs, type II should always be treated, and local or limited excision

are recommended. Endoscopic resection is reserved for lesions limited to the gastric wall and without invasion beyond the submucosa otherwise surgery is recommended. As in type I g-NETs, further treatments will be evaluated in relation to the pathological examination of the resected lesions. For the endoscopically successfully managed patients, endoscopic surveillance is suggested yearly [18, 35, 48].

Some case series have shown that SSA treatment resulted in reduction in size and number of type II g-NETs [80].

In type II g-NET patients, high-dose PPI therapy is mandatory to control acid hypersecretion and to prevent life-threatening complications from peptic ulceration [81].

13.4.1.3 Type III Gastric Neuroendocrine Tumors

At diagnosis, most of type III g-NETs show invasion beyond the submucosa, lymphoinvasion, angioinvasion, and local or distant spread. They should be managed aggressively following the same guidelines for gastric adenocarcinomas. Resectable disease often undergoes partial or total gastrectomy with lymphadenectomy [48].

Endoscopic management by means of EMR or better with ESD for small (generally ≤2 cm) type III g-NETs might be considered as initial treatment if an appropriate and careful preoperative staging is unremarkable. The pathological examination of the resected lesion will dictate the need for further treatments [60, 82, 83]. A close endoscopic and radiological (CT scan or MRI) follow-up is then mandatory for these patients.

13.4.2 Advanced Disease

Treatment options for advanced g-NETs, include SSAs, systemic chemotherapy and molecular targeted agents. Liver metastases can be treated also with locoregional therapies (transarterial chemoembolization and radiofrequency ablation), peptide-receptor radionuclide therapy, and surgery [84].

The treatment strategy should be planned on a case-by-case basis and discussed by an expert NEN-dedicated multidisciplinary team. Previous treatment, cumulative toxicity, the impact of treatment on patient's quality of life and the long survival of g-NETs must properly weighted.

13.5 Conclusions

Gastric neuroendocrine tumor diagnosis is on the rise, and they are more frequently diagnosed at an early stage, allowing a conservative approach for most of them. Based on pathophysiology, three types of g-NETs are recognized. Type I are the most frequent and associated with CAG. They are slow-growing neoplasms with an excellent prognosis also in the presence of local or distant spread which is infrequently observed. Endoscopy is a powerful and suitable technique to manage most of them in terms of both diagnosis/staging and treatment. Because of CAG, it is of paramount clinical relevance to screen type I g-NET patients for micronutrients deficiency and gastric adenocarcinoma development.

Types II and III g-NETS are less frequently observed, but they behave more aggressively. The former, usually managed as type I, should be approached in the context of MEN-1 syndrome. The latter have the worst prognosis among all g-NETs. They are surgically managed although the endoscopic resection may be adequate in selected cases.

References

1. WHO Classification of Tumours. Digestive system tumours, vol. 1. 5th ed. Lyon: IARC; 2019.
2. Bierley J, Gospodarowicz MK, Wittekind C, International Union Against Cancer. TNM classification of malignant tumours. 8th ed. Oxford; Hoboken, NJ: Wiley-Blackwell; 2017.
3. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP, Moss SF, Nilsson O, Rindi G, Salazar R, Ruszniewski P, Sundin A. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9(1):61–72. https://doi.org/10.1016/S1470-2045(07)70410-2.
4. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine

tumors. Endocr Rev. 2004;25(3):458–511. https://doi.org/10.1210/er.2003-0014.
5. Kidd M, Gustafsson B, Modlin IM. Gastric carcinoids (neuroendocrine neoplasms). Gastroenterol Clin North Am. 2013;42(2):381–97. https://doi.org/10.1016/j.gtc.2013.01.009.
6. Kaltsas G, Grozinsky-Glasberg S, Alexandraki KI, Thomas D, Tsolakis AV, Gross D, Grossman AB. Current concepts in the diagnosis and management of type 1 gastric neuroendocrine neoplasms. Clin Endocrinol (Oxf). 2014;81(2):157–68. https://doi.org/10.1111/cen.12476.
7. O'Connor JM, Marmissolle F, Bestani C, Pesce V, Belli S, Dominichini E, Mendez G, Price P, Giacomi N, Pairola A, Loria FS, Huertas E, Martin C, Patane K, Poleri C, Rosenberg M, Cabanne A, Kujaruk M, Caino A, Zamora V, Mariani J, Dioca M, Parma P, Podesta G, Andriani O, Gondolesi G, Roca E. Observational study of patients with gastroenteropancreatic and bronchial neuroendocrine tumors in Argentina: Results from the large database of a multidisciplinary group clinical multicenter study. Mol Clin Oncol. 2014;2(5):673–84. https://doi.org/10.3892/mco.2014.332.
8. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121(4):589–97. https://doi.org/10.1002/cncr.29099.
9. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063–72. https://doi.org/10.1200/JCO.2007.15.4377.
10. Niederle MB, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine tumour society classification: an analysis based on prospectively collected parameters. Endocr Relat Cancer. 2010;17(4):909–18. https://doi.org/10.1677/ERC-10-0152.
11. Modlin IM, Lye KD, Kidd M. A 50-year analysis of 562 gastric carcinoids: small tumor or larger problem? Am J Gastroenterol. 2004;99(1):23–32. https://doi.org/10.1046/j.1572-0241.2003.04027.x.
12. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the incidence, prevalence, and survival outcomes in patients with Neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335–42. https://doi.org/10.1001/jamaoncol.2017.0589.
13. Assarzadegan N, Montgomery E. What is new in 2019 World Health Organization (WHO) classification of tumors of the digestive system: review of selected updates on neuroendocrine neoplasms, appendiceal tumors, and molecular testing. Arch Pathol Lab Med. 2020. https://doi.org/10.5858/arpa.2019-0665-RA.
14. Grozinsky-Glasberg S, Thomas D, Strosberg JR, Pape UF, Felder S, Tsolakis AV, Alexandraki KI, Fraenkel M, Saiegh L, Reissman P, Kaltsas G, Gross DJ. Metastatic type 1 gastric carcinoid: a real threat or just a myth? World J Gastroenterol. 2013;19(46):8687–95. https://doi.org/10.3748/wjg.v19.i46.8687.
15. Tsolakis AV, Ragkousi A, Vujasinovic M, Kaltsas G, Daskalakis K. Gastric neuroendocrine neoplasms type 1: a systematic review and meta-analysis. World J Gastroenterol. 2019;25(35):5376–87. https://doi.org/10.3748/wjg.v25.i35.5376.
16. Spampatti MP, Massironi S, Rossi RE, Conte D, Sciola V, Ciafardini C, Ferrero S, Lodi L, Peracchi M. Unusually aggressive type 1 gastric carcinoid: a case report with a review of the literature. Eur J Gastroenterol Hepatol. 2012;24(5):589–93. https://doi.org/10.1097/MEG.0b013e328350fae8.
17. Rindi G, Luinetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology. 1993;104(4):994–1006. https://doi.org/10.1016/0016-5085(93)90266-f.
18. Grozinsky-Glasberg S, Alexandraki KI, Angelousi A, Chatzellis E, Sougioultzis S, Kaltsas G. Gastric carcinoids. Endocrinol Metab Clin North Am. 2018;47(3):645–60. https://doi.org/10.1016/j.ecl.2018.04.013.
19. Vannella L, Sbrozzi-Vanni A, Lahner E, Bordi C, Pilozzi E, Corleto VD, Osborn JF, Delle Fave G, Annibale B. Development of type I gastric carcinoid in patients with chronic atrophic gastritis. Aliment Pharmacol Ther. 2011;33(12):1361–9. https://doi.org/10.1111/j.1365-2036.2011.04659.x.
20. Dias AR, Azevedo BC, Alban LBV, Yagi OK, Ramos MFKP, Jacob CE, Barchi LC, Cecconello I, Ribeiro U Jr, Zilberstein B. Gastric neuroendocrine tumor: review and update. Arq Bras Cir Dig. 2017;30(2):150–4. https://doi.org/10.1590/0102-6720201700020016.
21. Cadiot G, Lehy T, Mignon M. Gastric endocrine cell proliferation and fundic argyrophil carcinoid tumors in patients with the Zollinger-Ellison syndrome. Acta Oncol. 1993;32(2):135–40. https://doi.org/10.3109/02841869309083902.
22. Norton JA, Melcher ML, Gibril F, Jensen RT. Gastric carcinoid tumors in multiple endocrine neoplasia-1 patients with Zollinger-Ellison syndrome can be symptomatic, demonstrate aggressive growth, and require surgical treatment. Surgery. 2004;136(6):1267–74. https://doi.org/10.1016/j.surg.2004.06.057.
23. Gibril F, Schumann M, Pace A, Jensen RT. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. Medicine (Baltimore). 2004;83(1):43–83. Erratum in: Medicine (Baltimore). 2004 May;83(3):175. https://doi.org/10.1097/01.md.0000112297.72510.32.
24. Cadiot G, Vissuzaine C, Potet F, Mignon M. Fundic argyrophil carcinoid tumor in a patient with sporadic-type Zollinger-Ellison syndrome. Dig Dis

Sci. 1995;40(6):1275–8. https://doi.org/10.1007/BF02065537.
25. Cavalcoli F, Zilli A, Conte D, Ciafardini C, Massironi S. Gastric neuroendocrine neoplasms and proton pump inhibitors: fact or coincidence? Scand J Gastroenterol. 2015;50(11):1397–403. https://doi.org/10.3109/00365521.2015.1054426.
26. Rindi G, Bordi C, Rappel S, La Rosa S, Stolte M, Solcia E. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. World J Surg. 1996;20(2):168–72. https://doi.org/10.1007/s002689900026.
27. Bordi C, D'Adda T, Azzoni C, Canavese G, Brandi ML. Gastrointestinal endocrine tumors: recent developments. Endocr Pathol. 1998;9:99–115. https://doi.org/10.1007/BF02782603.
28. Basuroy R, Srirajaskanthan R, Prachalias A, Quaglia A, Ramage JK. Review article: the investigation and management of gastric neuroendocrine tumours. Aliment Pharmacol Ther. 2014;39(10):1071–84. https://doi.org/10.1111/apt.12698.
29. Scherübl H, Cadiot G, Jensen RT, Rösch T, Stölzel U, Klöppel G. Neuroendocrine tumors of the stomach (gastric carcinoids) are on the rise: small tumors, small problems? Endoscopy. 2010;42(8):664–71. https://doi.org/10.1055/s-0030-1255564.
30. Rindi G, Azzoni C, La Rosa S, Klersy C, Paolotti D, Rappel S, Stolte M, Capella C, Bordi C, Solcia E. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. Gastroenterology. 1999;116(3):532–42. https://doi.org/10.1016/s0016-5085(99)70174-5.
31. La Rosa S, Vanoli A. Gastric neuroendocrine neoplasms and related precursor lesions. J Clin Pathol. 2014;67(11):938–48. https://doi.org/10.1136/jclinpath-2014-202515.
32. Li TT, Qiu F, Qian ZR, Wan J, Qi XK, Wu BY. Classification, clinicopathologic features and treatment of gastric neuroendocrine tumors. World J Gastroenterol. 2014;20(1):118–25. https://doi.org/10.3748/wjg.v20.i1.118.
33. Sato Y, Iwafuchi M, Ueki J, Yoshimura A, Mochizuki T, Motoyama H, Sugimura K, Honma T, Narisawa R, Ichida T, Asakura H, Van Thiel DH. Gastric carcinoid tumors without autoimmune gastritis in Japan: a relationship with helicobacter pylori infection. Dig Dis Sci. 2002;47(3):579–85. https://doi.org/10.1023/a:1017972204219.
34. Modlin IM, Lye KD, Kidd M. Carcinoid tumors of the stomach. Surg Oncol. 2003;12(2):153–72. https://doi.org/10.1016/s0960-7404(03)00034-3.
35. Delle Fave G, Kwekkeboom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, Sasano H, Tomassetti P, Salazar R, Ruszniewski P, Barcelona Consensus Conference Participants. ENETS consensus guidelines for the management of patients with gastroduodenal neoplasms. Neuroendocrinology. 2012;95(2):74–87. https://doi.org/10.1159/000335595.
36. Borch K, Renvall H, Liedberg G. Gastric endocrine cell hyperplasia and carcinoid tumors in pernicious anemia. Gastroenterology. 1985;88(3):638–48. https://doi.org/10.1016/0016-5085(85)90131-3.
37. Stockbrügger RW, Menon GG, Beilby JO, Mason RR, Cotton PB. Gastroscopic screening in 80 patients with pernicious anaemia. Gut. 1983;24(12):1141–7. https://doi.org/10.1136/gut.24.12.1141.
38. Thomas RM, Baybick JH, Elsayed AM, Sobin LH. Gastric carcinoids. An immunohistochemical and clinicopathologic study of 104 patients. Cancer. 1994;73(8):2053–8. https://doi.org/10.1002/1097-0142(19940415)73:8<2053::aid-cncr2820730807>3.0.co;2-0.
39. Marignani M, Delle Fave G, Mecarocci S, Bordi C, Angeletti S, D'Ambra G, Aprile MR, Corleto VD, Monarca B, Annibale B. High prevalence of atrophic body gastritis in patients with unexplained microcytic and macrocytic anemia: a prospective screening study. Am J Gastroenterol. 1999;94(3):766–72. https://doi.org/10.1111/j.1572-0241.1999.00949.x.
40. Sato Y. Endoscopic diagnosis and management of type I neuroendocrine tumors. World J Gastrointest Endosc. 2015;7(4):346–53. https://doi.org/10.4253/wjge.v7.i4.346.
41. Merola E, Sbrozzi-Vanni A, Panzuto F, D'Ambra G, Di Giulio E, Pilozzi E, Capurso G, Lahner E, Bordi C, Annibale B, Delle FG. Type I gastric carcinoids: a prospective study on endoscopic management and recurrence rate. Neuroendocrinology. 2012;95(3):207–13. https://doi.org/10.1159/000329043.
42. Chin JL, O'Toole D. Diagnosis and management of upper gastrointestinal neuroendocrine tumors. Clin Endosc. 2017;50(6):520–9. https://doi.org/10.5946/ce.2017.181.
43. Crosby DA, Donohoe CL, Fitzgerald L, Muldoon C, Hayes B, O'Toole D, Reynolds JV. Gastric neuroendocrine tumours. Dig Surg. 2012;29(4):331–48. https://doi.org/10.1159/000342988.
44. Ito T, Igarashi H, Jensen RT. Zollinger-Ellison syndrome: recent advances and controversies. Curr Opin Gastroenterol. 2013;29(6):650–61. https://doi.org/10.1097/MOG.0b013e328365efb1.
45. O'Toole D, Delle Fave G, Jensen RT. Gastric and duodenal neuroendocrine tumours. Best Pract Res Clin Gastroenterol. 2012;26(6):719–35. https://doi.org/10.1016/j.bpg.2013.01.002.
46. Borch K, Ahrén B, Ahlman H, Falkmer S, Granérus G, Grimelius L. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. Ann Surg. 2005;242(1):64–73. https://doi.org/10.1097/01.sla.0000167862.52309.7d.
47. Attili F, Capurso G, Vanella G, Fuccio L, Delle Fave G, Costamagna G, Larghi A. Diagnostic and therapeutic role of endoscopy in gastroenteropancreatic neuroendocrine neoplasms. Dig Liver Dis. 2014;46(1):9–17. https://doi.org/10.1016/j.dld.2013.04.007.
48. 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 gastroduodenal neuroendocrine neoplasms. Neuroendocrinology. 2016;103(2):119–24. https://doi.org/10.1159/000443168.

49. de Mestier L, Lepage C, Baudin E, Coriat R, Courbon F, Couvelard A, Do Cao C, Frampas E, Gaujoux S, Gincul R, Goudet P, Lombard-Bohas C, Poncet G, Smith D, Ruszniewski P, Lecomte T, Bouché O, Walter T, Cadiot G, Thésaurus National de Cancérologie Digestive (TNCD). Digestive Neuroendocrine Neoplasms (NEN): French Intergroup clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, GTE, RENATEN, TENPATH, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR). Dig Liver Dis. 2020;52(5):473–92. https://doi.org/10.1016/j.dld.2020.02.011.
50. Zilli A, Arcidiacono PG, Conte D, Massironi S. Clinical impact of endoscopic ultrasonography on the management of neuroendocrine tumors: lights and shadows. Dig Liver Dis. 2018;50(1):6–14. https://doi.org/10.1016/j.dld.2017.10.007.
51. Bahri H, Laurence L, Edeline J, Leghzali H, Devillers A, Raoul JL, Cuggia M, Mesbah H, Clement B, Boucher E, Garin E. High prognostic value of 18F-FDG PET for metastatic gastroenteropancreatic neuroendocrine tumors: a long-term evaluation. J Nucl Med. 2014;55(11):1786–90. https://doi.org/10.2967/jnumed.114.144386.
52. Singh Ospina N, Donegan D, Rodriguez-Gutierrez R, Al-Hilli Z, Young WF Jr. Assessing for multiple endocrine Neoplasia type 1 in patients evaluated for Zollinger-Ellison syndrome-clues to a safer diagnostic process. Am J Med. 2017;130(5):603–5. https://doi.org/10.1016/j.amjmed.2016.11.035.
53. Poitras P, Gingras MH, Rehfeld JF. The Zollinger-Ellison syndrome: dangers and consequences of interrupting antisecretory treatment. Clin Gastroenterol Hepatol. 2012;10(2):199–202. https://doi.org/10.1016/j.cgh.2011.08.012.
54. Oberg K, Couvelard A, Delle Fave G, Gross D, Grossman A, Jensen RT, Pape UF, Perren A, Rindi G, Ruszniewski P, Scoazec JY, Welin S, Wiedenmann B, Ferone D, Antibes Consensus Conference Participants. ENETS consensus guidelines for standard of care in neuroendocrine tumours: biochemical markers. Neuroendocrinology. 2017;105(3):201–11. https://doi.org/10.1159/000472254.
55. Vezzosi D, Walter T, Laplanche A, Raoul JL, Dromain C, Ruszniewski P, d'Herbomez M, Guigay J, Mitry E, Cadiot G, Leboulleux S, Lombard-Bohas C, Borson-Chazot F, Ducreux M, Baudin E. Chromogranin a measurement in metastatic well-differentiated gastroenteropancreatic neuroendocrine carcinoma: screening for false positives and a prospective follow-up study. Int J Biol Markers. 2011;26(2):94–101. https://doi.org/10.5301/JBM.2011.8327.
56. Korse CM, Muller M, Taal BG. Discontinuation of proton pump inhibitors during assessment of chromogranin a levels in patients with neuroendocrine tumours. Br J Cancer. 2011;105(8):1173–5. https://doi.org/10.1038/bjc.2011.380.
57. Lahner E, Zagari RM, Zullo A, Di Sabatino A, Meggio A, Cesaro P, Lenti MV, Annibale B, Corazza GR. Chronic atrophic gastritis: natural history, diagnosis and therapeutic management. A position paper by the Italian Society of Hospital Gastroenterologists and Digestive Endoscopists [AIGO], the Italian Society of Digestive Endoscopy [SIED], the Italian Society of Gastroenterology [SIGE], and the Italian Society of Internal Medicine [SIMI]. Dig Liver Dis. 2019;51(12):1621–32. https://doi.org/10.1016/j.dld.2019.09.016.
58. Ravizza D, Fiori G, Trovato C, Fazio N, Bonomo G, Luca F, Bodei L, Pelosi G, Tamayo D, Crosta C. Long-term endoscopic and clinical follow-up of untreated type 1 gastric neuroendocrine tumours. Dig Liver Dis. 2007;39(6):537–43. https://doi.org/10.1016/j.dld.2007.01.018.
59. Uygun A, Kadayifci A, Polat Z, Yilmaz K, Gunal A, Demir H, Bagci S. Long-term results of endoscopic resection for type I gastric neuroendocrine tumors. J Surg Oncol. 2014;109(2):71–4. https://doi.org/10.1002/jso.23477.
60. Chen WF, Zhou PH, Li QL, Xu MD, Yao LQ. Clinical impact of endoscopic submucosal dissection for gastric neuroendocrine tumors: a retrospective study from mainland China. Sci World J. 2012;2012:869769. https://doi.org/10.1100/2012/869769.
61. Kim HH, Kim GH, Kim JH, Choi MG, Song GA, Kim SE. The efficacy of endoscopic submucosal dissection of type I gastric carcinoid tumors compared with conventional endoscopic mucosal resection. Gastroenterol Res Pract. 2014;2014:253860. https://doi.org/10.1155/2014/253860.
62. Sato Y, Takeuchi M, Hashimoto S, Mizuno K, Kobayashi M, Iwafuchi M, Narisawa R, Aoyagi Y. Usefulness of endoscopic submucosal dissection for type I gastric carcinoid tumors compared with endoscopic mucosal resection. Hepatogastroenterology. 2013;60(126):1524–9. https://doi.org/10.5754/hge121185.
63. Zhou X, Xie H, Xie L, Li J, Cao W, Fu W. Endoscopic resection therapies for rectal neuroendocrine tumors: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2014;29(2):259–68. https://doi.org/10.1111/jgh.12395.
64. Jeon SM, Lee JH, Hong SP, Kim TI, Kim WH, Cheon JH. Feasibility of salvage endoscopic mucosal resection by using a cap for remnant rectal carcinoids after primary EMR. Gastrointest Endosc. 2011;73(5):1009–14. https://doi.org/10.1016/j.gie.2010.12.029.
65. Meier B, Schmidt A, Glaser N, Meining A, Walter B, Wannhoff A, Riecken B, Caca K. Endoscopic full-thickness resection of gastric subepithelial tumors with the gFTRD-system: a prospective pilot study (RESET trial). Surg Endosc. 2020;34(2):853–60. https://doi.org/10.1007/s00464-019-06839-2.

66. Chen WC, Warner RR, Ward SC, Harpaz N, Divino CM, Itzkowitz SH, Kim MK. Management and disease outcome of type I gastric neuroendocrine tumors: the Mount Sinai experience. Dig Dis Sci. 2015;60(4):996–1003. https://doi.org/10.1007/s10620-014-3410-1.
67. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, Garrido M, Kikuste I, Megraud F, Matysiak-Budnik T, Annibale B, Dumonceau JM, Barros R, Fléjou JF, Carneiro F, van Hooft JE, Kuipers EJ, Dinis-Ribeiro M. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy. 2019;51(4):365–88. https://doi.org/10.1055/a-0859-1883.
68. Jenny HE, Ogando PA, Fujitani K, Warner RR, Divino CM. Laparoscopic antrectomy: a safe and definitive treatment in managing type 1 gastric carcinoids. Am J Surg. 2016;211(4):778–82. https://doi.org/10.1016/j.amjsurg.2015.08.040.
69. Gladdy 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(11):3154–60. https://doi.org/10.1245/s10434-009-0687-y.
70. Eriksson B, Oberg K. Summing up 15 years of somatostatin analog therapy in neuroendocrine tumors: future outlook. Ann Oncol. 1999;10(Suppl 2):S31–8. https://doi.org/10.1093/annonc/10.suppl_2.s31.
71. Massironi S, Zilli A, Fanetti I, Ciafardini C, Conte D, Peracchi M. Intermittent treatment of recurrent type-1 gastric carcinoids with somatostatin analogues in patients with chronic autoimmune atrophic gastritis. Dig Liver Dis. 2015;47(11):978–83. https://doi.org/10.1016/j.dld.2015.07.155.
72. Grozinsky-Glasberg S, Kaltsas G, Gur C, Gal E, Thomas D, Fichman S, Alexandraki K, Barak D, Glaser B, Shimon I, Gross DJ. Long-acting somatostatin analogues are an effective treatment for type 1 gastric carcinoid tumours. Eur J Endocrinol. 2008;159(4):475–82. https://doi.org/10.1530/EJE-08-0420.
73. Campana D, Nori F, Pezzilli 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(1):337–42. https://doi.org/10.1677/ERC-07-0251.
74. Jianu CS, Fossmark R, Syversen U, Hauso Ø, 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(4):456–63. https://doi.org/10.3109/00365521.2010.539255.
75. Khuroo MS, Khuroo MS, Khuroo NS. Treatment of type I gastric neuroendocrine tumors with somatostatin analogs. J Gastroenterol Hepatol. 2010;25(3):548–54. https://doi.org/10.1111/j.1440-1746.2009.06131.x.
76. Thomas D, Tsolakis AV, Grozinsky-Glasberg S, Fraenkel M, Alexandraki K, Sougioultzis S, Gross DJ, Kaltsas G. Long-term follow-up of a large series of patients with type 1 gastric carcinoid tumors: data from a multicenter study. Eur J Endocrinol. 2013;168(2):185–93. https://doi.org/10.1530/EJE-12-0836.
77. Fossmark R, Sørdal Ø, Jianu CS, Qvigstad G, Nordrum IS, Boyce M, Waldum HL. Treatment of gastric carcinoids type 1 with the gastrin receptor antagonist netazepide (YF476) results in regression of tumours and normalisation of serum chromogranin a. Aliment Pharmacol Ther. 2012;36(11–12):1067–75. https://doi.org/10.1111/apt.12090.
78. Moore AR, Boyce M, Steele IA, Campbell F, Varro A, Pritchard DM. Netazepide, a gastrin receptor antagonist, normalises tumour biomarkers and causes regression of type 1 gastric neuroendocrine tumours in a nonrandomised trial of patients with chronic atrophic gastritis. PLoS One. 2013;8(10):e76462. https://doi.org/10.1371/journal.pone.0076462.
79. Boyce M, Moore AR, Sagatun L, Parsons BN, Varro A, Campbell F, Fossmark R, Waldum HL, Pritchard DM. Netazepide, a gastrin/cholecystokinin-2 receptor antagonist, can eradicate gastric neuroendocrine tumours in patients with autoimmune chronic atrophic gastritis. Br J Clin Pharmacol. 2017;83(3):466–75. https://doi.org/10.1111/bcp.13146.
80. Tomassetti P, Migliori M, Caletti GC, Fusaroli P, Corinaldesi R, Gullo L. Treatment of type II gastric carcinoid tumors with somatostatin analogues. N Engl J Med. 2000;343(8):551–4. https://doi.org/10.1056/NEJM200008243430805.
81. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, Scoazec JY, Salazar R, Sauvanet A, Kianmanesh R, Barcelona Consensus Conference Participants. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology. 2012;95(2):98–119. https://doi.org/10.1159/000335591.
82. Kwon YH, Jeon SW, Kim GH, Kim JI, Chung IK, Jee SR, Kim HU, Seo GS, Baik GH, Choi KD, Moon JS. Long-term follow up of endoscopic resection for type 3 gastric NET. World J Gastroenterol. 2013;19(46):8703–8. https://doi.org/10.3748/wjg.v19.i46.8703.
83. Hirasawa T, Yamamoto N, Sano T. Is endoscopic resection appropriate for type 3 gastric neuroendocrine tumors? Retrospective multicenter study. Dig Endosc. 2020. https://doi.org/10.1111/den.13778.
84. Ahmed M. Gastrointestinal neuroendocrine tumors in 2020. World J Gastrointest Oncol. 2020;12(8):791–807. https://doi.org/10.4251/wjgo.v12.i8.791.