Clinical features and management of type I gastric carcinoids

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Abstract Type I gastric carcinoids (TIGCs) are related to chronic atrophic gastritis and are characterized by hypergastrinemia and hyperplasia of enterochromaffin-like cells. TIGCs are the most frequently diagnosed of all gastric carcinoids, accounting for about 70–80 %. Endoscopically, TIGCs are present as small (<10 mm), polypoid lesions or, more frequently, as smooth, rounded submucosal lesions. Histologically, TIGCs arise in the deep mucosa, with some invading the submucosa. Most TIGCs are well-differentiated tumors, with metastasis being rare. Therefore, patients with TIGCs generally have an excellent prognosis. Among the currently available treatment options are total gastrectomy, partial resection, antrectomy, endoscopic resection, and endoscopic surveillance, although no consensus has been reached on their optimal management. Further studies are needed to develop better management options for patients with TIGC.

Keywords Gastric carcinoid · Gastric neuroendocrine tumor · Type-A gastritis · *Helicobacter pylori*

Introduction

Carcinoids arise from cells of the diffuse neuroendocrine system and are, therefore, also called neuroendocrine

tumors [1]. The incidence of gastric carcinoids (GC) among all gastrointestinal carcinoids (GICs) has gradually increased [2–4], making it important to understand the clinical features and management of GCs. GCs can be classified into three distinct subgroups, with Table 1 showing the clinical characteristics of these three types [5–11].

Type I GCs (TIGCs) arise in patients with chronic atrophic gastritis (CAG), including autoimmune gastritis (AIG; i.e. type A gastritis) and *Helicobacter pylori*-associated atrophic gastritis [12, 13]. TIGCs are associated with hypergastrinemia and hyperplasia of enterochromaffin-like (ECL) cells. TIGCs are often small (<10 mm), occurring as multiple tumors in individual patients, and are located in the gastric fundus or corpus. Most tumors are limited to the mucosa or submucosa. TIGCs are the most frequently diagnosed of all GCs, accounting for about 70–80 %. TIGCs tend to display a nearly benign behavior with a low risk for progression or metastasis.

Type II GCs are rare and account for 5–6 % of all GCs. They are associated with gastrin-producing neoplasms in patients with multiple endocrine neoplasia/Zollinger–Ellison syndrome. Similar to TIGCs, type II GCs are small and multiple, associated with hypergastrinemia and hyperplasia of ECL cells, and considered benign.

In contrast, type III GCs are sporadic carcinoids without specific background factors, therefore, occurring under normogastrinemic conditions. Type III GCs are often single and large tumors, accounting for 10–15 % of all GCs. These tumors behave more aggressively, with higher rates of metastasis and regional lymph node involvement.

In Japan, TIGCs constitute 87.1 % of all GCs [14]. This review focuses on the epidemiology, pathogenesis, diagnosis, and management of TIGCs.

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Table 1 Characteristics of gastric carcinoid tumors

Characteristic	Type I GCs	Type II GCs	Type III GCs
Proportion of GCs (%)	70–80	5–10	10–15
Associated disease	Chronic atrophic gastritis (type A gastritis, <i>H. pylori</i>)	Multiple endocrine neoplasia (MEN) type 1/gastrinoma	None
Gender	Females > males	Females = males	Females < males
Number of tumors	Multiple	Multiple	Solitary
Size of tumors	Often small (<10 mm)	Often small (<10 mm)	Often >20 mm
Histology	Well-differentiated	Well-differentiated	From well- to poorly differentiated
WHO grading	G1 tumor	G1 tumor	G1/G2/G3 (NEC) tumor
Depth of invasion	Mucosa or submucosa	Mucosa or submucosa	Any depth
Serum gastrin	Increased	Increased	Normal
Gastric pH	Low	High	Normal
Risk of metastasis	2–5 %	10–20 %	>50 %
Prognosis	Excellent	Good	Poor

GC gastric carcinoid

Epidemiology

GCs are rare tumors, although their incident rates have gradually increased. For example, over a 35-year period, the incidence of GC in the United States has increased nearly tenfold [2], while the incidence of GC in the UK has increased 23-fold in men and 47-fold in women [3]. As of 1999, the percentage of GCs among all gastric malignancies in the United States increased from 0.3 to 1.77 % over 50 years, and the percentage of GCs among all GICs increased from 2.4 to 8.7 % over 30 years [4]. More recent reports have revealed that the ratio of GCs to all GICs has increased further, at rates of 12 % in the UK [3], 23 % in Austria [15], 14.6 % in Korea [16], 11.9 % in the United States [17], and 15.1 % in Japan [14]. Although these increases in the incidence of GCs may be due in part to a true increase in the incidence, they may also be due to improvements in diagnostic technology, including endoscopy, and an increased awareness of GCs.

Since no specific symptoms are associated with TIGC, most TIGCs are detected incidentally during endoscopy. TIGCs are more prevalent in women than in men [9, 12], owing to the greater incidence of AIG in women [18]. In Japan, however, TIGC is more common in men than in women [19], perhaps owing to the lower rates of co-occurrence of TIGC and AIG.

Pathophysiology

On ingestion of food, antral G cells in the stomach secrete gastrin, which binds to cholecystokinin-2 (CCK-2) receptors located on the membranes of ECL cells, leading to histamine release. Histamine binds to H₂ receptors on gastric parietal cells to produce hydrochloric acid. In the AIG, anti-parietal cell antibodies act on gastric parietal cells, leading to achlorhydria, which induces G cell hyperplasia and their secretion of additional gastrin, resulting in hypergastrinemia.

Gastrin stimulates gastric epithelial cell proliferation and acts as a trophic factor for ECL cells, leading to ECL cell hyperplasia. Therefore, in some patients, hypergastrinemia can lead to TIGC development. Since only some patients with AIG develop TIGC, other cofactors, such as Reg [20], mcl-1 [21], and MEN-1 gene mutation [22], may play a role in the development of TIGC.

In *H. pylori* associated gastritis, *H. pylori* induces hypergastrinemia [23, 24]. *H. pylori* infection is a risk factor for the development of gastric mucosal atrophy, resulting in low acid output [25]. Antibodies against *H. pylori* may act as autoantibodies to parietal cells [26–28]. Additionally, hypergastrinemia related to *H. pylori* infection would be due to up-regulation of tumor necrosis factor- α and interleukin- β and down-regulation of somatostatin [29]. Furthermore, *H. pylori* lipopolysaccharide stimulates DNA

synthesis in ECL cells, suggesting that it may act on ECL cell hyperplasia [30]. *H. pylori* infection may, therefore, be a risk factor for TIGC by inducing hypergastrinemia [13, 31]. In either AIG or *H. pylori*-associated gastritis, under the condition of CAG, a lack of gastric acid production results in hyperplasia of G cells and hypergastrinemia, leading to TIGC development.

Diagnosis

Most patients with TIGCs do not complain of flushing or any other symptoms related to carcinoid syndrome [32, 33]. However, patients with TIGC have nonspecific symptoms, such as nausea, abdominal pain, and/or dyspepsia [34], or pernicious anemia complicated by AIG. Therefore, TIGCs are detected incidentally during screening by esophagogastroduodenal endoscopy.

Endoscopically, TIGC is present as polypoid lesions or, more frequently, as smooth and rounded submucosal lesions [35]. TIGCs are often found in the gastric corpus or fundus, are small in size (<10 mm), and multiple. Narrow band imaging and high resolution magnification endoscopy may be helpful for the endoscopic diagnosis of TIGC [36].

Histologically, TIGCs are composed of small uniform cells in nests and infiltrating strands, or with an anastomosing ribbon-like, tubular, or acinar pattern. These tumors arise in the deep mucosa, in some cases invading the submucosa. Moreover, these tumors are covered by normal mucosa, requiring deeper biopsy to remove specimens adequate for diagnosis. Sampling biopsy should not include only the TIGC lesion, but also both the antrum and the corpus/fundus to assess for the presence of atrophic gastritis and precursor lesions of TIGCs [37].

Hyperplastic and dysplastic ECL cells are considered precursors of ECL cell carcinoids [38] and are often detected in biopsy specimens from non-tumor mucosa adjacent to tumors. The 2010 World Health Organization (WHO) classification system has defined ECL cell hyperplasia as diffuse, linear, micronodular, or adenomatoid hyperplasia, whereas ECL cell dysplasia is characterized by enlarged or fused micronodules, microinvasion, or newly formed stroma [1, 39]. Nodules that increase in size to >0.5 mm or invade the submucosa are classified as microcarcinoids (<0.5 cm) or plain carcinoids (≥ 0.5 cm) [1].

GCs are classified histologically by grade and differentiation. The 2010 WHO classification system grades GCs by counting mitoses and by the Ki67 index: G1, <2 mitoses per 10 high power fields (HPF) ($=2 \text{ mm}^2$) and/or a Ki67 index $\leq 2\%$; G2, 2–20 mitoses per 10 HPF and/or a Ki67 index of 2–20%; or G3, >20 mitoses per 10 HPF and/or a

Ki67 index >20% [40]. Most TIGCs are classified as G1 tumors.

Endoscopic ultrasonography is useful for assessing the depth of gastric wall invasion of tumors >1 cm in size [41]. CT or MRI scan can provide useful information in patients with metastatic disease. The role of fluorodeoxyglucose positron emission tomography in assessing TIGCs is unclear [42]. Octreoscan can be used to assess metastases and somatostatin receptor status if treatment with somatostatin receptor antagonist is being considered [43]. However, Octreoscan is generally unavailable in Japan.

Prognosis

Since most TIGCs are G1 tumors and are limited to the mucosa or submucosa, patients with TIGCs generally have an excellent prognosis. Endoscopic resection of localized T1 lesions can achieve a close to 100% survival rate [44]. A recent report of a large series of patients with TIGC found that the rate of lymph node metastases was 5.3% and the rate of tumor-associated death was 1.07% [45]. Tumor size and depth predict lymph node metastasis [46]. Although most patients with TIGCs classified as G1 had an excellent prognosis, those with TIGCs classified as G2 and G3 had poorer or very severe prognosis, respectively [45]. Metastatic TIGC is related to be a tumor size ≥ 1 cm, an elevated Ki-67 index and high serum gastrin levels [47]. Therefore, assessment of tumor size, depth, and histological stage may be predictive of patient prognosis.

Management

The clinical management and treatment of patients with TIGC depend on tumor size and the presence of risk factors, including muscle wall infiltration, increased proliferation, and/or metastasis. Hitherto, endoscopic resection has been recommended for patients with a few (<3–5 lesions) small (<1 cm) TIGCs, whereas antrectomy or local resection is recommended for patients with many (>3–5 lesions) or large (>1 cm) TIGCs [48]. However, recent studies revealing the generally indolent nature of TIGCs led to a shift in management and treatment. Patients with small tumors and lacking risk factors have been managed by simple observation, without endoscopic or surgical resection [12, 19, 32, 37, 49, 50]. In contrast, the ENETS guidelines have recommended that all TIGCs should be removed whenever possible, although tumor development has not been found to be less favorable in patients with tumors <10 mm left in place [37]. NCCN guidelines [50] have recommended that patients with locoregional

TIGC ≤ 20 mm in size undergo (a) endoscopic surveillance every 6–12 months, and (b) endoscopic resection, if feasible, with biopsy of the tumor and adjacent mucosa.

The treatment of TIGCs 10–20 mm in size is unclear. In the WHO classification, GCs 1 cm in size is the cut-off defining T1 and T2 tumors. ENETS guidelines have suggested endoscopic removal of TIGCs larger than 10 mm in size without invasion of the muscularis propria and lymph nodes, and surgical resection of tumors with involvement beyond the submucosa or lymph nodes or with distant disease [37]. However, NCCN guidelines have recommended either endoscopic resection or observation of local TIGCs 10–20 mm in diameter.

ENETS guidelines recommend endoscopic mucosal resection (EMR) of TIGCs that have not invaded the muscularis propria. However, TIGCs frequently invade the submucosa [19], making it difficult to remove TIGCs completely, even small ones, by snare polypectomy or conventional EMR. In contrast, endoscopic submucosal dissection (ESD) is a feasible technique for the removal of tumors present in the submucosal layer, such as TIGCs. Recent reports have revealed that the complete resection rate of GC tumors was higher with ESD than with EMR [51, 52].

Surgical resection is generally recommended for TIGCs larger than 20 mm in diameter or those that extend deeper than the submucosa [37, 50]. Moreover, the latest ENETS guidelines endorsed the use of surgery in patients with lymph node or distant disease spread, and in those with poorly differentiated neoplasms [37]. Surgery should include local resection and antrectomy to reduce gastrin levels. However, antrectomy may not be effective in preventing recurrence and/or metastasis [53].

Patients with locoregionally unresectable and/or metastatic TIGCs should be treated with somatostatin analogs (SSAs) and/or undergo complete resection of the primary tumor and metastases. Treatment with SSAs has been shown effective in reducing the number and size of TIGCs [54–56]. SSAs act on G cells to inhibit gastrin secretion and have a role in reducing ECL cell hyperplasia. However, use of SSAs cannot be recommended, because their effects are short-term, with tumor progression occurring after the completion of SSA treatment [57]. Recently, natazepide (YF476), a peripheral gastrin (CCK-B) receptor antagonist, has been reported to inhibit acid secretion and ECL cell proliferation and to reduce the size and number of TIGCs [58]. Large, long-term, follow-up studies are needed to determine the efficacy of this CCK-B receptor antagonist in the treatment of TIGCs.

After treatment, the ENETS guidelines recommend endoscopic surveillance every 12 months in patients with tumor recurrence, and every 24 months in patients without tumor recurrence [37]. NCCN guidelines have recommended that patients with small (≤ 20 mm) TIGCs who did

not require endoscopic resection or treatment should be evaluated by patient history and physical examination every 6–12 months [50]. Moreover, in the absence of tumor recurrence or progression, follow-up endoscopies should be performed every 6–12 months for the first 3 years and annually thereafter [50]. However, an optimal follow-up schedule has not yet been established as a clinical standard.

Conclusion

TIGCs are related to CAG with hypergastrinemia and hyperplasia of ECL cells. The incidence of GCs has significantly increased, with the great majority of GCs being TIGCs. TIGCs are present as small (<10 mm) and multiple lesions endoscopically, and are generally limited to the mucosa or submucosa. TIGCs tend to display a nearly benign behavior with a low risk for progression or metastasis. Several treatment options are currently available for TIGCs, but their optimal management has not been established. Further studies on TIGCs are needed to develop new promising management for patients with these tumors.

Disclosures

Conflict of Interest: Yuichi Sato declare that he has no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent: This study does not apply to giving Informed Consent because the present manuscript is a review article.

References

1. Solcia E, Arnold R, Capella C, et al. Neuroendocrine neoplasms of the stomach. In: Bosman FT, Carneiro F, Hruban RH, Theise ND editors WHO classification of tumours of the digestive system. Lyon: IARC, 2010. p. 64–68.
2. Yao JC, Hassan M, Phan A, et al. 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;26:3063–72.
3. Ellis L, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *Am J Gastroenterol*. 2010;105:2563–9.
4. Modlin IM, Lye KD, Kidd M. A 50-year analysis of 562 gastric carcinoids: small tumor or larger problem? *Am J Gastroenterol*. 2004;99:23–32.
5. Rindi G, Luinetti O, Cornaggia M, et al. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathological study. *Gastroenterology*. 1993; 104:994–1006.

6. Nikou GC, Angelopoulos TP. Current concepts on gastric carcinoid tumors. *Gastroenterol Res Pract*. 2012; Article ID 287825.
7. Basuroy R, Srirajskanthan R, Prachalias A, et al. Review article: the investigation and management of gastric neuroendocrine tumours. *Aliment Pharmacol Ther*. 2014;39:1071–84.
8. Li TT, Qiu F, Qian ZR, et al. Classification, clinicopathologic features and treatment of gastric neuroendocrine tumors. *World J Gastroenterol*. 2014;20:118–25.
9. Massironi S, Sciola V, Spampatti MP, et al. Gastric carcinoids: between underestimation and overtreatment. *World J Gastroenterol*. 2009;15:2177–83.
10. Zhang L, Ozao J, Warner R, Divino C. Review of the pathogenesis, diagnosis, and management of type I gastric carcinoid tumor. *World J Surg*. 2011;35:1879–86.
11. Kaltsas G, Grozinsky-Glasberg S, Alexandraki KI, et al. Current concepts in the diagnosis and management of type I gastric neuroendocrine neoplasms. *Clin Endocrinol (Oxf)*. 2014;81:157–68.
12. Scherübl H, Cadiot G, Jensen RT, et al. Neuroendocrine tumors of the stomach (gastric carcinoids) are on the rise: small tumors, small problems? *Endoscopy*. 2010;42:664–71.
13. Sato Y, Iwafuchi M, Ueki J, et al. Gastric carcinoid tumors without autoimmune gastritis in Japan: a relationship with *Helicobacter pylori* infection. *Dig Dis Sci*. 2002;47:579–85.
14. Ito T, Sasano H, Tanaka M, et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. *J Gastroenterol*. 2010;45:234–43.
15. 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;17:909–18.
16. Cho MY, Kim JM, Sohn JH, et al. Current trends of the incidence and pathological diagnosis of gastroenteropancreatic neuroendocrine tumors (gep-nets) in Korea 2000–2009: multicenter study. *Cancer Res Treat*. 2012;44:157–65.
17. Lawrence B, Gustafsson BI, Chan A, et al. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am*. 2011;40:1–18.
18. Soykan I, Yakut M, Keskin O, et al. Clinical profiles, endoscopic and laboratory features and associated factors in patients with autoimmune gastritis. *Digestion*. 2012;86:20–6.
19. Sato Y, Inamura H, Kaizaki Y, et al. Management and clinical outcomes of type I gastric carcinoid patients: retrospective, multicenter study in Japan. *Dig Endosc*. 2014;26:377–84.
20. Higham AD, Bishop LA, Dimaline R, et al. Mutations of *RegI* alpha are associated with enterochromaffin-like cell tumor development in patients with hypergastrinemia. *Gastroenterology*. 1999;116:1310–8.
21. Pritchard DM, Berry D, Przemeck SM, et al. Gastrin increases mcl-1 expression in type I gastric carcinoid tumors and a gastric epithelial cell line that expresses the CCK-2 receptor. *Am J Physiol Gastrointest Liver Physiol*. 2008;295:G798–805.
22. D'Adda T, Keller G, Bordi C, Höfler H. Loss of heterozygosity in 11q13-14 regions in gastric neuroendocrine tumors not associated with multiple endocrine neoplasia type 1 syndrome. *Lab Invest*. 1999;79:671–7.
23. Chittajalla RS, Ardill JES, McColl KEL. The degree of hypergastrinemia induced by *Helicobacter pylori* is the same in duodenal ulcer patients and asymptomatic volunteers. *Eur J Gastroenterol*. 1992;4:49–53.
24. Smith JTL, Pounder RE, Nwokolo CU. Inappropriate hypergastrinemia in asymptomatic healthy subjects infected with *Helicobacter pylori*. *Gut*. 1990;31:522.
25. El-Omar EM, Oien K, El-Nujumi A, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. *Gastroenterology*. 1997;113:15–24.
26. Faller G, Steininger H, Kränzlein J, et al. Antigastric autoantibodies in *Helicobacter pylori* infection: implications of histological and clinical parameters of gastritis. *Gut*. 1997;41:619–23.
27. Claeys D, Faller G, Appelmek BJ, et al. The gastric H, K⁺-ATPase is a major autoantigen in chronic *Helicobacter pylori* gastritis with body mucosa atrophy. *Gastroenterology*. 1998;115:340–7.
28. Negrini R, Savio A, Poiesi C, et al. Antigenic mimicry between *Helicobacter pylori* and gastric mucosa in the pathogenesis of body atrophic gastritis. *Gastroenterology*. 1996;111:655–65.
29. Calam J, Gibbons A, Healey ZV, et al. How does *Helicobacter pylori* cause mucosal damage? Its effect on acid and gastrin physiology. *Gastroenterology*. 1997;113:S43–9.
30. Kidd M, Miu K, Tang LH, et al. *Helicobacter pylori* lipopolysaccharide stimulates histamine release and DNA synthesis in rat enterochromaffin-like cells. *Gastroenterology*. 1997;113:1110–7.
31. Solcia E, Rindi G, Fiocca R, et al. Distinct patterns of chronic gastritis associated with carcinoid and cancer and their role in tumorigenesis. *Yale J Biol Med*. 1992;65:793–804.
32. Ravizza D, Fiori G, Trovato C, et al. Long-term endoscopic and clinical follow-up of untreated type I gastric neuroendocrine tumours. *Dig Liver Dis*. 2007;39:537–43.
33. Borch K, Åhrén B, Ahlman H, et al. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. *Ann Surg*. 2005;242:64–73.
34. Granberg D, Wilander E, Stridsberg M, et al. Clinical symptoms, hormone profiles, treatment, and prognosis in patients with gastric carcinoids. *Gut*. 1998;43:223–8.
35. Ichikawa J, Tanabe S, Koizumi W, et al. Endoscopic mucosal resection in the management of gastric carcinoid tumors. *Endoscopy*. 2003;35:203–6.
36. Singh R, Yao K, Anagnostopoulos G, et al. Microcarcinoid tumor diagnosed with high-resolution magnification endoscopy and narrow band imaging. *Endoscopy*. 2008;40(Suppl 2):E12.
37. Delle Fave G, Kwekkeboom DJ, Van Cutsem E, et al. ENETS Consensus Guidelines for the management of patients with gastroenteropancreatic neuroendocrine neoplasms. *Neuroendocrinology*. 2012;95:74–87.
38. La Rosa S, Vanoli A. Gastric neuroendocrine neoplasms and related precursor lesions. *J Clin Pathol*. 2014; 22 Jul. doi:10.1136/jclinpath-2014-202515.
39. Solcia E, Bordi C, Creutzfeldt W, et al. Histopathological classification of nonantral gastric endocrine growths in man. *Digestion*. 1988;41:185–200.
40. Rindi G, Arnold R, Bosman FT, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban R, Theise ND, editors. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on cancer (IARC); 2010. p. 13–14.
41. Karaca C, Turner BG, Cizginer S, Forcione D, Brugge W. Accuracy of EUS in the evaluation of small gastric subepithelial lesions. *Gastrointest Endosc*. 2010;71:722–7.
42. Bushnell DL, Baum RP. Standard imaging techniques for neuroendocrine tumors. *Endocrinol Metab Clin North Am*. 2011;40:153–62.
43. Gibril F, Reynolds JC, Lubensky IA, et al. Ability of somatostatin receptor scintigraphy to identify patients with gastric carcinoids: a prospective study. *J Nucl Med*. 2000;41:1646–56.
44. O'Toole D, Delle Fave G, Jensen RT. Gastric and duodenal neuroendocrine tumours. *Best Pract Res Clin Gastroenterol*. 2012;26:719–35.
45. La Rosa S, Inzani F, Vanoli A, et al. Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. *Hum Pathol*. 2011;42:1373–84.
46. Saund MS, Al Natour RH, Sharma AM, et al. Tumor size and depth predict rate of lymph node metastasis and utilization of

- lymph node sampling in surgically managed gastric carcinoids. *Ann Surg Oncol*. 2011;18:2826–32.
47. Grozinsky-Glasberg S, Thomas D, Strosberg JR, et al. Metastatic type 1 gastric carcinoid: a real threat or just a myth? *World J Gastroenterol*. 2013;19:8687–95.
48. Gilligan CJ, Lawton GP, Tang LH, et al. Gastric carcinoid tumors: the biology and therapy of an enigmatic and controversial lesion. *Am J Gastroenterol*. 1995;90:338–52.
49. Hosokawa O, Kaizaki Y, Hattori M, et al. Long-term follow up of patients with multiple gastric carcinoids associated with type A gastritis. *Gastric Cancer*. 2005;8:42–6.
50. Kulke MH, Benson AB 3rd, Bergsland E, et al. National comprehensive cancer networks. neuroendocrine tumors. *J Natl Compr Canc Netw*. 2012;10:724–64.
51. Sato Y, Takeuchi M, Hashimoto S, et al. Usefulness of endoscopic submucosal dissection for type I gastric carcinoid tumors compared with endoscopic mucosal resection. *Hepatogastroenterology*. 2013;60:1524–7.
52. 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; 253860. doi:[10.1155/2014/253860](https://doi.org/10.1155/2014/253860). Epub 17 Feb 2014.
53. Gladdy RA, Strong VE, Coit D, Allen PJ, et al. Defining surgical indications for type I gastric carcinoid tumor. *Ann Surg Oncol*. 2009;16:3154–60.
54. Thomas D, Tsolakis AV, Grozinsky-Glasberg S, et al. 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;168:185–93.
55. Grozinsky-Glasberg S, Kaltsas G, Gur C, et al. Long-acting somatostatin analogues are an effective treatment for type 1 gastric carcinoid tumours. *Eur J Endocrinol*. 2008;159:475–82.
56. Campana D, Nori F, Pezzilli R, et al. Gastric endocrine tumors type I: treatment with long-acting somatostatin analogs. *Endocr Relat Cancer*. 2008;15:337–42.
57. Jianu CS, Fossmark R, Syversen U, et al. Five-year follow-up of patients treated for 1 year with octreotide long-acting release for enterochromaffin-like cell carcinoids. *Scand J Gastroenterol*. 2011;46:456–63.
58. Fossmark R, Sørđal Ø, Jianu CS, et al. 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;36:1067–75.