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EDITORIAL

Somatostatin analogs for gastric carcinoids: For many, but not all

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Abstract

Gastric carcinoids (GCs) are classified as: type Ⅰ, related to hypergastrinemia due to chronic atrophic gastritis (CAG), type Ⅱ, associated with Zollinger-Ellison syndrome in multiple endocrine neoplasia type 1, and type Ⅲ, which is normogastrinemic. The management of type-Ⅰ gastric carcinoids (GC1s) is still debated, because of their relatively benign course. According to the European Neuroendocrine Tumor Society guidelines endoscopic resection is indicated whenever possible; however, it is not often feasible because of the presence of a multifocal disease, large lesions, submucosal invasion or, rarely, lymph node involvement. Therefore, somatostatin analogs (SSAs) have been proposed as treatment for GC1s in view of their antisecretive, antiproliferative and antiangiogenic effects. However, in view of the high cost of this therapy, its possible side effects and the relatively benign course of the disease, SSAs should be reserved to specific subsets of "high risk patients", *i.e.*, those patients with multifocal or recurrent GCs. Indeed, it is reasonable that, after the development of a gastric neuroendocrine neoplasm in patients with a chronic predisposing condition (such as CAG), other enterochromaffin-like cells can undergo neoplastic proliferation, being chronically stimulated by hypergastrinemia. Therefore, definite indications to SSAs treatment should be established in order to avoid the undertreatment or overtreatment of GCs.

Key words: Neuroendocrine tumors; Atrophic gastritis; Octreotide; Lanreotide; Enterochromaffin-like cells; Carcinoid tumors

Core tip: The management of type-Ⅰ gastric carcinoids is still debated because of their relatively benign course against the fact that they can have a heterogeneous

unpredictable biological behavior. Even if in most cases their endoscopic treatment is effective, in some particular cases it may not be sufficient. The potential role of somatostatin analogs (SSAs) has been reported in several recent studies. However, neither a standard indication nor a specific schedule of treatment with defined dosage and duration have been adopted to date. Because of the high cost of SSAs, clear-cut indications for this therapy are required in order to avoid any overtreatment.

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INTRODUCTION

Gastric carcinoids - clinical features

Epidemiology: Gastric carcinoids (GCs) represent up to 23% of all digestive neuroendocrine neoplasms (NENs). Their annual incidence is of about 0.2/100000, with a marked increase in the last few decades, also owing to the expanding indications for upper gastrointestinal tract endoscopy (UGE) and improved immunohistological identification techniques[1-4]. Over the last 35 years a 10 to 15-fold increase has been reported in the United States[5] and in the United Kingdom[6] respectively.

Modlin reported that the percentage of GCs among all gastric tumors has increased from 0.3% to 1.77%. Notably, the 5-year survival rate for GCs has risen from 51% to 63%[7].

Classification: GCs include three different types of gastric neuroendocrine tumors[8]: types Ⅰ (GC1s) and Ⅱ (GC2s) are related to hypergastrinemia, due to chronic atrophic autoimmune gastritis[9] and gastrinoma-related Zollinger-Ellison syndrome (ZES) respectively, while type Ⅲ (GC3s) are generally sporadic tumors, associated with normal gastrin levels and a worse prognosis[10] (Table 1).

GC1s account for 75%-80% of all GCs. They usually occur in women in their 50s and 70s and are usually asymptomatic and non-functioning, thus they are incidentally detected during UGE performed for other reasons, *e.g.,* anemia or dyspepsia[11,12]. Most GC1 cases are polypoid with a median diameter of 5 mm ø, generally confined to the mucosa-submucosa of the gastric fundus or body and, less frequently, antrum. They are usually well differentiated (*i.e.,* with Ki-67 index < 2%), multiple in 65% of all cases and sometimes present as microcarcinoids, macroscopically undetectable at UGE. Noteworthy, 8%-23% of GC1s may metastasize to regional lymph nodes and seldom even to the liver, mainly when facing with lesions extended to the deep submucosa or presenting lymph node involvement[13,14]. Moreover, the evolution to neuroendocrine carcinoma may occur in 3% of patients[15]. Nevertheless, local or distant metastases have been reported also in patients affected by GC1s with low proliferation index (< 2%), small size and exclusive intramucosal invasion[16-19]. In addition, GC1s frequently recur (5%-67% of cases after endoscopic treatment)[20,21], with a median recurrence-free time interval of 24 mo after endoscopic resection. Notably, recurrences are independent of polyp diameter, number of polyps or serum gastrin levels.

Table 1 Characteristics of gastric carcinoids according to the European Neuroendocrine Tumor Society guidelines[8]

	GC1	GC2	GC3
Proportion among g-NEN	70%-80%	5%-6%	14%-25%
Grading	NET G1	NET G1-G2	NEC G3
Associated conditions	CAG	Gastrinoma/ MEN-1	None
Serum gastrin values	Elevated	Elevated	Normal
Metastases	2%-5%	10%-30%	50%-100%
Mortality rate	0%	< 10%	25%-30%

GC 1, 2 and 3: Type Ⅰ, Ⅱ and Ⅲ gastric carcinoids; NENs: Neuroendocrine neoplasms; CAG: Chronic atrophic gastritis; MEN-1: Multiple endocrine neoplasia type Ⅰ.

GC2s generally develop in patients with duodenal or pancreatic gastrinoma causing ZES syndrome in the context of a multiple endocrine neoplasia type Ⅰ (MEN-1)[22]. These are usually small multiple polyps (diameter of 1-2 cm ø), localized in the fundic mucosa, with a low or moderate proliferation grade, but may also exhibit angioinvasion, invasion of muscularis propria and metastases at regional lymph nodes or, less frequently, at distant sites. Unlike GC1s, GC2s are equally frequent in male and female patients. Their local excision is generally recommended, even in the presence of multiple lesions. In addition, in view of their antiproliferative effects, SSAs may be useful in those subgroups of patients presenting slowly progressive carcinoids. Tomassetti *et al*[23] observed GC2 regression in three patients with ZES/MEN-1 after a long-term therapy with SSAs. However, the management of GC2s is complicated by the controversies regarding the treatment of gastrinoma in MEN-1. Indeed, the indication for extensive duodenal-pancreatic surgery in patients with MEN-1, who present pharmacologically controllable ZES and no other clinically symptomatic hormonal excess syndrome, remains debatable, also because SSAs play a role in reducing tumor growth[24].

GC3s are generally large (> 2 cm ø), solitary, ulcerated neoplasms, with infiltrative growth, elevated Ki-67 index and a higher risk of metastatic spreading when compared to GC1s and GC2s (metastatic rate of 50%-100%). GC3s occur mostly in men older than 50 years, presenting pain, anemia and weight

Table 2 Grading of neuroendocrine neoplasms according to the World Health Organization 2010 classification[8]

Histological classification	G1 (low grade)	G2 (intermediate grade)	G3 (high grade)
Mitotic rate (*n*/10 HPF)	< 2	2–20	> 20
Ki-67 index	< 3%	3%–20%	> 20%

loss. Unlike GC1s and GC2s, GC3s may be associated with an atypical carcinoid syndrome, characterized by itching, bronchospasm and flushing, mediated by histamine released from enterochromaffin-like (ECL) cells. The management of GC3s is fairly clear and similar to that of gastric adenocarcinoma; it is based on surgery (partial or total gastrectomy with lymph node dissection) and chemotherapy if surgery is not feasible[8].

The treatment of metastatic liver disease includes hepatic resection, embolization of the hepatic artery, radiofrequency ablation and cryoablation.

Grading and staging: The histological classification of NENs includes grade (G) and differentiation. The grading system (Table 2) is based on the rate of proliferation, defined by the number of mitoses per 10 high-power microscopic fields or per 2 mm^2 (mitotic rate) and as the percentage of tumor cells positively immuno-labelling for the Ki-67 antigen (Ki-67 index). Differentiation refers to the extent to which neoplastic cells resemble normal cells. Generally, well-differentiated NENs are of low or intermediate grade, whereas poorly differentiated NENs are usually of high grade[25].

The tumor-node-metastasis (TNM) staging system is based on the size and/or extent (reach) of the primary tumor (T), whether cancer cells have spread to nearby (regional) lymph nodes (N), and whether any metastasis (M), or the spread of the cancer to other parts of the body, has occurred. According to the TNM staging, five stages can be considered: 0 for tumors in situ < 0.5 mm ø, Ⅰ for small NENs invading submucosa or lamina propria, Ⅱ for larger or more invasive neoplasms without metastases, Ⅲ for tumors invading surrounding structures or spreading to regional node metastases, and Ⅳ for NENs with distant metastases (Table 3)[26].

Table 3 Scoring staging system according to tumor-node-metastasis[26]

T-primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	*In-situ* tumor/dysplasia (< 0.5 mm)
T1	Tumor invades lamina propria or submucosa and < 1 cm
T2	Tumor invades muscularis propria or subserosa or > 1 cm
T3	Tumor penetrates serosa
T4	Tumor penetrates serosa and/or invades adjacent structures
N-regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M-metastases	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastases
Stage	
0	Tis N0 M0
1	T1 N0 M0
2A	T2 N0 M0
2B	T3 N0 M0
3A	T4 N0 M0
3B	Any T N1 M0
4	Any T Any N M1

Type-I gastric carcinoids

GC1s are neuroendocrine tumors of the gastric mucosa originating from ECL cells in response to chronic hypergastrinemia associated with chronic atrophic gastritis (CAG), either autoimmune or due to *Helicobacter pylori* infection. GC1s are the most frequent GCs, accounting for 70%-80% of all gastric NENs.

Pathogenesis: The ECL cells constitute the largest endocrine cell population of the gastric body and fundus mucosa; they express CCK-2 (gastrin) receptors, mediating cell growth and histamine secretion, and stimulate acid secretion from the adjacent parietal cells[27-29].

Due to the progressive destruction of gastric parietal cells, achlorhydria causes chronic hypergastrinemia, which in turn is responsible for ECL cell hyperplasia and sometimes dysplasia, which over time may lead to ECL cell carcinoid development[30,31].

Among the factors influencing the trophic sensitivity of ECL cells to hypergastrinemia, the female gender is the most relevant one: the ECL cell hyperplasia is found more frequent in female than in male CAG patients. Furthermore, the decrease in ECL cells density with age increasing does not occur in women[32]. GCs associated with hypergastrinemia are more common in female subjects, whereas sporadic GCs, which develop through a gastrin-independent mechanism, occur mostly in males.

ECL cell hyperplasia may disappear when the hypergastrinemia is abolished. SSAs may be used to inhibit gastrin release and thus reduce the ECL cell hyperplasia[33]. Some morphometric studies have showed that antrectomy was responsible for a reduction of the ECL cell volume *vs* the total volume of endocrine cells, while octreotide reduced the volume of all endocrine cells[34].

In addition to chronic autoimmune atrophic gastritis, also the proton pump inhibitors, the use of which has been increasing worldwide, can induce gastric achlorhydria and consequent hypergastrinemia, even if the actual association with an increased risk of GCs has not been demonstrated yet[35]. Probably, hypergastrinemia does not represent the only risk factor predisposing to the development

of gastric NENs, as not all GCs are associated with hypergastrinemia (see gastric carcinoid type Ⅲ) and not all the conditions associated with hypergastrinemia lead to neoplastic proliferation. This may also be promoted by genetic background, intragastric environmental changes related to achlorhydria and/or intramucosal modifications occurring in CAG, which have been implicated in the pathogenesis of gastric adenocarcinoma. Finally, factors such as prostanglandins and lymphokines, locally released during chronic inflammation, as in the case of CAG, may play a role in the pathogenesis of GCs[36,37].

Clinical and endoscopic features: These lesions, typically multicentric/multiple, small, usually with polypoid appearance (up to 78% according to Merola[21]) and localized in the oxyntic atrophic mucosa, are characterized by slow growth (low proliferative index Ki-67, *i.e.,* G1 according to the World Health Organization classification) and a low tendency to local or distal invasion. Only larger lesions (> 1 cm) are associated with lymph node or other organ spreading (in 3%-8% and 2% of cases, respectively), with a 5-year survival > 95%. These neoplasms only seldom have a functional syndrome, as in almost all cases they do not secrete specific hormones. Their detection is usually incidental or achieved during CAG follow-up. It is estimated that about 2.4%-5% of CAG patients develop GC1s in their lifetime, with an annual incidence of approximately 0.4% to 2.4%[9,11].

Since CAG is associated with chronic hypergastrinemia, GC1s typically occur in the form of recurrent lesions. Moreover, even after endoscopic resection, up to 67% of GC1s recur after a mean time of 24 mo, with a reported trend to evolve in less differentiated lesions.

Management of type-I gastric carcinoid - a clinical challenge

GC1s are usually treated conservatively. The European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines have suggested that annual surveillance is sufficient in case of GC1s with a diameter < 10 mm ø[8]. This approach is supported by some reports[24,38-40] which suggest that careful endoscopic follow-up might represent a reasonable safe option in selected patients. However, further studies evaluating larger cohorts during a longer follow-up period are necessary in order to support this clinical behavior, as some cases of progressive malignant GC1s have already been reported[17-19,41].

Accordingly, the ENETS guidelines recommend endoscopic resection whenever possible, even in the presence of small carcinoids (diameter < 1 cm ø) and for up to 6 polyps not involving the muscularis propria[8]. Endoscopic mucosal resection (EMR) and submucosal dissection (ESD), characterized by a high rate of efficacy and a low risk of complications, have been suggested for treating GCs[42-46] but the complete endoscopic eradication is not always feasible because carcinoids may be multifocal or submucosal. Many small studies have shown that the combination of endoscopic resection and surveillance of GC1s was a good treatment for lesions without local or distant spreading. Merola *et al*[21] reported a 100% survival rate and no metastases in endoscopically treated patients; however, the recurrence rate was up to 68% after endoscopic resection. A lower recurrence rate (18% and 0.4%) is reported in recent Turkish[46] and Japanese studies[20] in which patients with GC1s were treated with EMR or ESD and followed up over a median of five years. Possible differences of the recurrence rates among these studies can depend on the difficulty to determine whether the lesions detected during follow-up endoscopies are true recurrences or simply small lesions missed at the initial endoscopy. Furthermore, more advanced endoscopic techniques, such as ESD and the routine use of chromoendoscopy, have been undertaken in Eastern countries, probably contributing to lower recurrence rates.

Currently, when dealing with the deep invasion of the gastric wall and detection of positive resection margins after endoscopic mucosal resection, local surgical tumor resection is generally performed. On the other hand, as this type of tumors are often multiple and recurrent, antral resection is recommended as it aims to avoid chronic gastrin stimulation of ECL cells and even if the long-term benefits of antrectomy remain uncertain[47,48]. Indeed, a further recurrence has been described in up to 20% of all cases and the surgical approach is more invasive and at higher risk of complications. However, in the case of disease progression or recurrence after local surgical resection, partial or total gastrectomy along with lymph node dissection should be carried out as suggested in the current guidelines[8].

Overall, the optimal treatment for GC1s remains controversial in view of their usually benign course, but also of their tendency to recur: a controlled study comparing the outcomes of endoscopic surveillance, endoscopic resection, surgical approach and SSAs treatment of GC1s is yet to be carried out.

SSAs

Historical perspectives: The history of SSAs begins in 1973 when Brazeau and Guillemin discovered a GHRH antagonist, which they called somatostatin and which appeared to be widely distributed in the organs and nervous system[49] of animals and humans.

Noteworthy, native somatostatin plays an important regulatory role in neurotransmission and secretion, by preventing the release of the growth hormone, thyroid-stimulating hormone, gastrointestinal hormones, pancreatic enzymes and neuropeptides It is not suitable though for long-term clinical application due to its short half-life (< 3 min) and the impact of rebound hypersecretion. Therefore, synthetic drugs

were developed with improved pharmacokinetic characteristics. SSAs have been used since 1980 to control the symptoms related to gastroenteropancreatic NENs, especially carcinoids and VIPomas, due to their characteristic of expressing somatostatin receptors (SSTR).

Long-acting SSAs have been used as a medical treatment of both functioning and non-functioning neuroendocrine tumors, due to the SSAs capability to inhibit hormone release and neoplastic growth by binding to specific high-affinity SSTR. Two different SSAs, octreotide and lanreotide, which principally bind to receptor subtypes 2 and 5, are clinically used with comparable effectiveness. Recently, pasireotide, a SSA with high affinity to all types of somatostatin receptors, has been introduced, even if its use is still restricted to those patients with partial/nil response to octreotide and lanreotide[50].

In a multicenter study comparing the treatment with lanreotide (30 mg i.m. every 10 d) *vs* octreotide (200 μg s.c. twice or thrice daily) in 33 patients with carcinoid syndrome, O'Toole *et al*[51] did not evidence any significant differences with regard to symptom control. Again, both these analogs have been reported to have an antiproliferative effect *in vitro*[52,53]. Data from uncontrolled prospective and retrospective clinical series[54-56] showed tumor shrinkage and disappearance in response to either short-acting SSAs alone or when combined with interferon-α. Further trials have reported tumor stabilization in up to 50% of patients, but without complete regression. More recently, two randomized double-blind placebo-controlled prospective studies[57,58] have clearly supported the antiproliferative effects of SSAs with a prolonged progression-free-survival in patients affected by enteropancreatic neuroendocrine tumors and treated with octreotide LAR (long-acting release) and lanreotide. However, there is need for additional studies, including patients with a primary tumor outside the midgut, in order to demonstrate the antiproliferative effects of octreotide. Again, further controlled trials in larger cohorts of patients are strongly required in order to identify the predictive factors of response and to confirm whether such a response may positively influence the patients' survival rate.

Benefits of SSAs therapy: The antineoplastic effects of somatostatin and SSAs are both direct and indirect, the former depending on the direct binding to tumor cells, the latter ones mediated through the inhibition of growth factors, angiogenesis and the immune system. The anti-tumour effect of SSAs may include both cytostatic (growth arrest) and cytotoxic (pro-apoptotic) mechanisms[59-62]. SSAs may also inhibit the insulin-like growth factor-Ⅰ secretion, thought to be involved in recurrence, growth and aggressiveness of some endocrine and non-endocrine tumors[63]. In a systematic analysis of data from 62 published studies about antiproliferative effects of SSAs[64], tumor growth stabilization was observed for a period of 8-16 mo in about 50% of the patients, and tumor regression in about 10%-20% of patients.

Unfortunately, tachyphylaxis can develop after months or years on treatment, probably due to the development of resistant cell clones within the tumor, whereas it does not seem related to any down-regulation of the number of somatostatin receptors on the cell surface.

Another relevant antiproliferative effect of SSAs is based on their capability to inhibit the production and secretion of many angiogenic factors, thereby reducing the tumor growth rate[65]. Therefore, SSAs may suppress tumor growth either directly, through their effect on SSTR expressing cells, or indirectly, *via* the inhibition of angiogenic factors, such as VEGF[66].

Finally, SSAs have an antisecretive role, as supported by a study by Fykse *et al*[67] in which five patients with hypergastrinemia and GCs were every month treated with octreotide LAR over one year with the consequent significant reduction in tumor burden, ECL cell grade of hyperplasia and the normalization of circulating chromogranin A levels. A further study[23] reported a significant reduction in gastrin levels and tumor regression in three patients suffering from Zollinger-Ellison syndrome and treated with lanreotide or octreotide for one year. Despite the small number of patients included in these studies, the results suggest that SSAs both inhibit gastrin secretion and growth of these tumors.

Side effects of SSAs therapy: Generally, SSAs are safe, easy to use and well tolerated with infrequent mild side effects, the most common being abdominal discomfort, bloating, diarrhea (related to the inhibition of pancreatic enzymes) usually self-limiting after the first few months of therapy. The development of cholestasis is reported in up to 60% of patients and can be partially prevented by orally administered ursodeoxycholic acid. Impaired glucose tolerance and bradycardia have also been occasionally reported[68].

Somatostatin analogs ... for many gastric carcinoids

Endoscopic resection has proved to represent a safe effective treatment for GC1s as it is associated with a 100% survival rate, even if recurrences have been described with a frequency of up to 67% of all patients endoscopically treated[21]. Indeed, GC1s are frequently multiple and can present submucosal invasion; in addition, they are sometimes undetectable at UGE, as they present as microcarcinoids. Therefore, the endoscopic approach is not always effective or adequate and other treatment options are needed for some subgroups of "high risk" patients, *i.e.,* those with a multifocal or recurrent disease. Moreover GC1s can be considered a complication of another disorder

that involves the entire gastric mucosa, so that a locoregional treatment may not be appropriate and a systemic therapy is thus a more pertinent approach.

SSAs have been proposed as a potential treatment in view of their antiproliferative, antisecretive and antiangiogenic effects, although they are not currently recommended according to both the ENETS[8] and NANETS guidelines[69] for type-1 GCs.

Of interest, Ferraro *et al*[70] observed that octreotide, given daily over six months, decreased fasting gastrin levels and ECL proliferation in patients with CAG and hypergastrinemia. Bakke *et al*[71] have reported a direct antiproliferative effect of octreotide on rat ECL cells.

SSAs have also been occasionally used in tertiary referral centres to treat single or multiple GC1s with diameter < 1 cm ø and low proliferative index[72]. When administered in a continuous way, SSAs have contributed to the reduction in number and size of GC1s and the suppression of circulating gastrin levels, by inhibiting gastrin release from antral G cells. However, a series by Jianu *et al*[73] has reported GC1 size increase and early recurrence after the SSA withdrawal in patients followed up over a median of 5 years from therapy discontinuation. One should consider though that such findings have not been confirmed by other studies.

Reasonably, after the development of a neuroendocrine neoplasm, other ECL cells can develop neoplastic proliferation in similar conditions (*e.g.*, chronic hypergastrinemia). Therefore, patients with recurrent GC1s should be considered at higher risk of developing other recurrences.

Somatostatin analogs ... not for all

Not all GC1 patients are to be treated with SSAs on the consideration that such a therapy comes with high costs attached and the 5-year survival rate of GC1 patients when regularly followed up with endoscopy remains good[74]. Accordingly, SSAs are better reserved to specific subsets of patients, such as those with recurrent or multifocal GC1s. Actually, no clear guidelines are currently available for patients presenting GC1 recurrence after repeated endoscopic resection. For these patients antrectomy has been proposed in spite of its invasiveness and possibly related complications[75]. Furthermore, some morphometric studies have demonstrated that octreotide reduced the overall endocrine cell volume[76], while antrectomy decreased only the volume of ECL cells.

A further treatment option can be that of multiple endoscopic resections; however, in the context of CAG, gastric mucosa is chronically and diffusely altered and GC1s are often multifocal, extended to submucosa and sometimes macroscopically undetectable, making endoscopic resection not always feasible and radical. In those countries where advanced endoscopic techniques are in place, management by endoscopy can also apply to multifocal GCs and GCs involving the submucosal layer and hence endoscopic resection is preferred as the first-line therapy. The far larger use of standard polipectomies instead of the more effective "*en bloc*" resection and ESD might account for the still high recurrence rates observed in some series[21].

Given the above considerations, we have recently reported on a series of CAG patients with recurrent GC1s, treated with SSAs until carcinoid disappearance and suppression of circulating gastrin values. For such patients SSAs have represented an efficient therapeutic option (Massironi *et al* submitted). As already reported, SSAs can exert an antiproliferative effect on neoplastic ECL-cells as well as other hyperplastic or dysplastic ECL-cells, which frequently accompanied GC1s, thus reducing the risk of further development[77]. Moreover, several studies[19] have reported that SSAs might significantly suppress intestinal metaplasia, which may be present in patients with chronic atrophic gastritis and may represent a risk factor for gastric adenocarcinoma[78,79].

Another pharmacological therapeutic option is represented in the near future by netazepide, an orally administered highly selective active gastrin/CCK-2 receptor antagonist, recently described as an effective treatment in animal models of ECL-cell tumours induced by hypergastrinemia[80]. Its use over a 12-wk period in a recent non-randomized trial was associated with a significant reduction in both the number of GC1s and the size of the largest tumour, of about 30%, and with the normalization of CgA levels, but not of gastrin values[81]. Nevertheless, randomized controlled trials involving longer-term treatment and larger cohorts of patients, are required to confirm these results.

CONCLUSION

Approval is still to come for specific indications, schedule and duration of therapy to avoid the undertreatment or overtreatment of recurrent GC1s. The duration of a SSA-based therapy may be guided by both the regression of GC and the suppression of gastrin levels. Finally, the comparison between new therapies, such as gastrin receptor antagonists and antibodies against progastrin-releasing peptides, and the traditional ones, such as the endoscopic or surgical approaches, can be useful in order to identify the most effective management approach.

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