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EDITORIAL

Gastric carcinoids: Between underestimation and overtreatment

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Abstract

Gastric carcinoids (GCs), which originate from gastric enterochromaffin-like (ECL) mucosal cells and account for 2.4% of all carcinoids, are found increasingly in the course of upper gastrointestinal tract endoscopy. Current nosography includes those occurring in chronic conditions with hypergastrinemia, as the type 1 associated with chronic atrophic gastritis, and the type 2 associated with Zollinger-Ellison syndrome in multiple endocrine neoplasia type 1, and type 3, which is unrelated to hypergastrinemia and is frequently malignant, with distant metastases. The optimal clinical approach to GCs remains to be elucidated, depending upon type, size and number of carcinoids. While there is agreement concerning the treatment of type 3 carcinoids, for types 1 and 2, current possibilities include simple surveillance, endoscopic polypectomy, surgical excision, associated or not with surgical antrectomy, or total gastrectomy. Moreover, the recent introduction of somatostatin analogues represents a therapeutic option of possibly outstanding relevance.

Key words: Gastric carcinoids; Endocrine tumors; Well-differentiated tumors; Hypergastrinemia; Chronic atrophic gastritis; Zollinger-Ellison syndrome; Multiple endocrine neoplasia tupe 1; Enterochromaffin-like cells

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INTRODUCTION

The term gastric carcinoid (GC) describes inadequately the pathological continuum of a wide spectrum of distinct neoplasms that arise from gastric enterochromaffin-like (ECL) cells. Carcinoid tumors represent a variety of significantly diverse lesions, which are distinct from adenocarcinomas in their etiology, biological behavior and prognosis. Over the past 5 years, a marked increase in reports addressing GCs has been evident[1]. These tumors are also known by their modern term of gastric neuroendocrine tumors, although the term carcinoid is still commonly used. This review focuses on the biology, diagnosis and treatment of GCs.

EPIDEMIOLOGY

GC tumors that arise from ECL cells have long been considered as rare lesions, and account for less than 2% of all carcinoids tumors and less than 1% of all stomach neoplasms[1-3]. However, recent reviews have indicated that the incidence of GCs may be on the rise[4-6]. In fact, a recent analysis[4] of the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) database by Modlin *et al* found that, from 1992 to 1999, GCs comprised 8.7% of all gastrointestinal carcinoid tumors. Also, during the period 1950-1999, a total of 562 GCs were recorded in the NCI databases, but from 2000 to 2004, in the SEER database, 1043 new GCs have been reported, which comprises 11.7% of all gastrointestinal carcinoid tumors[7]. On the other hand, a major decline in incidence and mortality of gastric adenocarcinomas has been described over several decades[8]. The male:female ratio for GCs is about 1:2, with 64% of carcinoids found in women, whereas males are almost twice as likely to develop non-carcinoid

Table 1 Characteristics of GC types

	Type 1	Type 2	Type 3
Percentage (%)	70-85	5-10	15-25
Tumor characteristics	Often small, multiple, polypoid, multicentric	Often small, multiple, polypoid, multicentric	Single, > 1-2 cm, polypoid and often ulcerated
Mean age at diagnosis (yr)	63	50	55
Gender	Females > males	Females = males	Males > females
Associated conditions	Chronic atrophic gastritis type A	ZES/MEN1	Sporadic
Serum gastrin levels	Increased	Increased	Normal
pH of gastric juice	Increased	Low	Normal
Ki-67 (%)	Usually < 2	Usually < 2	Usually > 2
Metastases (%)	2-5	< 10	> 50

gastric-cancer (ratio male:female 1.71)[3].

The reasons for the recent marked increase in GCs are unknown, although the wide use of screening upper endoscopy, the routine habit to obtain biopsies in the course of upper gastrointestinal endoscopy, the application of specific immunohistological identification techniques, and a greater clinical focus on the subject may contribute to increased detection of GCs[9]. On the other hand, our knowledge on the biological basis of these tumors, as well as on the complex interplay between genetic and environmental factors that ultimately results in GC development, are still partial. Hypergastrinemia represents a necessary condition for the development of type 1 and type 2 GCs, even if not sufficient[5,10]. The widespread use of proton pump inhibitors can also induce gastric achlorhydria, thus contributing to hypergastrinemia[11,12], even if it is not clear that it has a real association with an increased risk of GCs. On the other hand, the importance of genetic and molecular background remains to be elucidated. Loss of heterozygosity at the multiple endocrine neoplasia type 1 (MEN-1) gene locus 11q13 has been found in all type 2 tumors that are associated with Zollinger-Ellison syndrome/MEN-1, but also in 17%-73% of type 1, and in 25%-50% of type 3 GCs, although these tumors do no develop in MEN-1 patients[13]. A role for the apoptosis-inhibiting protein BCL-2 has also been proposed, with the hypothesis that the anti-apoptotic activity of BCL-2 may contribute to the development of carcinoid tumors by extending the exposure of hyperplastic ECL cells to other so-far-unknown oncogenic factors[14]. Mcl-1 protein expression also increased specifically in human hypergastrinemia-associated type 1 GC tumors. Gastrin-induced mcl-1 expression may therefore be an important mechanism that contributes toward type 1 GC development[15].

CLASSIFICATION

GCs are endocrine tumors of the gastric mucosa that originate from ECL cells[12,13,16-20]. These tumors are classified into three distinct types (Table 1).

Type 1 (GC-1) includes the vast majority (70%-85%) of GCs and is closely linked to chronic atrophic gastritis type A, characterized by decrease acidity, resultant hypergastrinemia and subsequent ECL cell hyperplasia. The spectrum of ECL cell lesions includes hyperplasia (simple, linear and micronodular), dysplasia, and eventually, carcinoids[21]. The lesions are located in the gastric fundus and body and are multicentric, polypoid, small, limited to the mucosa or submucosa, without angioinvasion, well-differentiated, and tend to display benign behavior. It is more frequent in females.

Type 2 (GC-2) accounts for 5%-10% of GCs, is associated with ZES and occurs almost exclusively in the context of MEN-1. MEN-1/ZES patients usually have small duodenal or pancreatic gastrinomas causing hypergastrinemia and subsequent ECL proliferation. The increased incidence of GC-2 in patients with MEN-1 (13%-37%), who display loss of heterozygosity at the MEN-1 gene locus, versus patients with sporadic ZES (0%-2%), supports the genetic role in the pathogenesis of GCs. Type 2 GCs are usually multiple and small, and have low-grade malignancy, although up to 35% of cases are metastatic at presentation. Unlike GC-1, GC-2 is equally frequent in male and female patients[22,23].

Type 1 and type 2 GCs are both associated with hypergastrinemia. In the first case, hypergastrinemia is secondary to hypo/achlorhydria caused by the destruction of gastric parietal cells. In the second case, it is caused by the presence of a primary gastrinoma that, on the contrary, causes hyperchlorhydria. Therefore pH of gastric juice and blood test are useful to discriminate the presence of pernicious anemia by ZES/MEN1. Pernicious anemia is characterized by increased gastric juice pH, low vitamin B12 and presence anti-parietal cells and/or anti intrinsic factor antibodies. The presence of ZES/MEN1 is characterized by low gastric juice pH or better by a basal acid output $\geqslant$ 15 mEq/h. This condition can be investigated by testing a full evaluation of pituitary and parathyroid function, in addition to genetic analysis.

Type 3 (GC-3) represents 15%-25% of GCs, is not related to hypergastrinemia, is characterized by a far more aggressive course, and presents with lymph node and distant metastases in more than 50% of cases. Lesions are typically solitary, larger than 1-2 cm, ulcerated and deeply invasive. They are usually located in the gastric fundus and body, but may occur also in the antrum. This type of GC is more frequent in males[1,3,12,17,18]. Unlike GC-1 and GC-2, GC-3 may be associated with an atypical carcinoid syndrome that

Table 2 Clinicopathological characteristics of endocrine tumors of the stomach according to WHO classification[23]

Well-differentiated tumor-carcinoid
Benign behavior: confined to mucosa-submucosa, non-angioinvasive, ≤ 1 cm in size, non-functioning
ECL cell tumor of corpus-fundus associated with hypergastrinemia and chronic atrophic gastritits (CAG) or MEN1 syndrome
Serotonin-producing tumor
Gastrin-producing tumor
Uncertain behavior: confined to mucosa-submucosa, > 1 cm in size, or angioinvasive
ECL cell tumor with CAG or MEN1 syndrome or sporadic
Serotonin-producing tumor
Gastrin-producing tumor
Well-differentiated endocrine carcinoma-malignant carcinoid
Low-grade malignant, deeply invasive (muscularis propria or beyond), or with metastasis
Nonfunctioning
ECL cell carcinoid, usually sporadic, rarely in CAG or MEN1 syndrome
Serotonin-producing tumor
Gastrin-producing tumor
Functioning
ECL cell carcinoid with atypical carcinoid syndrome
Serotonin-producing carcinoid with syndrome
Gastrin-producing carcinoma-malignant gastrinoma
ACTH-producing carcinoma with Cushing syndrome
Poorly differentiate endocrine carcinoma-small cell carcinoma, high grade malignant, usually non-functioning, occasionally with Cushing syndrome

Table 3 Proposed TNM staging system for GC tumors[7]

	Primary tumor		
	Depth of invasion		Size
T1	Up to and including muscularis propria		≤ 3 cm
T2	Beyond muscularis propria		≤ 3 cm
T3	Up to and including muscularis propria		> 3 cm
	Beyond muscularis propria		> 3 cm
	Lymph node		
N0	No lymph node metastasis		
N1	Regional lymph node metastasis		
	Distant metastasis		
M0	No distant metastasis		
M1	Distant metastasis		
Disease stage	T	N	M
Ⅰ	T1	Any N	M0
Ⅱ	T2	N0	M0
	T3	N0	M0
Ⅲ	T2	N1	M0
Ⅳ	T3	N1	M0
	Any T	Any N	M1

presents with itching, bronchospasm and cutaneous flushing, thought to be mediated by histamine released from ECL cells[1].

Also, type 4 GCs (GC-4) have been described[17]. This type of tumor is not derived from ECL cells, but from other endocrine cells of the stomach, such as those producing serotonin or gastrin. These tumors may have a very aggressive course and may be located in the gastric fundus, body or antrum.

According to the WHO classification[24], type 1 GCs are well-differentiated endocrine tumors with a benign or, more rarely, an uncertain behavior. Type 2 GCs are usually well-differentiated endocrine tumors, but may also be well-differentiated endocrine carcinomas with angioinvasion, invasion of muscularis propria, and metastases at regional lymph nodes, or less frequently at distant sites. Also, occasionally poorly differentiated endocrine carcinomas have been found in patients with ZES/MEN-1. Type 3 CGs may be well-differentiated endocrine tumors or carcinomas, but usually are poorly differentiated endocrine carcinomas with high mitosis rates and Ki-67 values, and regional and distant metastases (Table 2). Moreover, recently, a tumor-node-metastasis (TNM) staging, and a grading system, based on the proliferative status (mitotic count and Ki-67 index) have been suggested for GCs[7] (Table 3), but remain to be validated in clinical practice.

DIAGNOSIS

Diagnosis is currently made during upper gastrointestinal endoscopy performed for a variety of clinical reasons, such as abdominal pain, gastrointestinal bleeding, anemia and dyspepsia. The diagnostic accuracy and the correct characterization of GCs necessitate extensive sampling from both the antrum (two samples) and body-fundus (four samples), in addition to biopsies/removal of the largest polyps. Proliferation rate and degree of dysplasia of gastric endocrine cells may often be difficult to identify with standard histopathological procedures. Histochemistry with chromogranin A (CgA) and synaptophysin assessment is of relevance in identifying hyperplasia, dysplasia and malignant transformation of ECL cells[20,25,26]. Also, immunohistochemical determination of the proliferative index Ki-67 and evaluation of the mitotic index, by counting number of mitosis per 10 high-power fields, are mandatory[27], with a negative prognostic meaning when Ki-67 is > 2% and mitotic index is > 2.

Endoscopy and sampling for histology are currently

considered sufficient when faced with small type 1 and type 2 GCs, reserving endoscopic ultrasound (EUS) for tumors > 1 cm in size[27]. EUS can give information about the location and depth of lesions and local spread, or even highlight the primary gastrinoma in GC-2. EUS can also allow fine-needle aspiration of submucosal lesions.

Computed tomography, magnetic resonance imaging and somatostatin receptor scintigraphy are required for larger tumors, those shown to be invasive by EUS, and type 3 GC, in order to detect distant metastases[27]. The minimal biochemical tests in GC patients include serum gastrin and CgA levels, the most important generic marker for neuroendocrine tumors, with evaluation of gastric juice pH. These tests should be performed at diagnosis. Moreover, determination of CgA could be of relevance in the course of follow-up[5,21,27].

PROGNOSIS

GCs are usually considered as largely benign in prognosis, even if it depends on the type of GC tumor and the extent of the disease. Prognosis ranges from an indolent course for type 1 GCs to the worst one for type 3 GCs.

Rappel and colleagues[28] reported an overall survival rate of 78% in 110 patients with GCs, with the highest rate (100%), when aged-corrected, in the 88 patients with GC-1. Therefore, the authors concluded that patients with GC-1 tumors have a life expectancy comparable to that of the general population. Type 2 GCs have a similar outcome to type 1 GCs, although their overall survival is closely related to the course of the associated gastrinoma, with a 5-year survival of 62%-75%[29]. Type 3 GCs have the worst prognosis and are typically associated with an overall 5-year survival of < 50%[2]. On the other hand, in an update of the SEER database study by Modlin *et al*[4], the 5-year survival rate was 63% for all GCs, 21.2% for metastatic disease, and only 69.1% in the subset of patients with localized lesions. Moreover, a cumulative analysis of GCs in the SEER database from 1992 to 1999 has indicated that distant metastases or regional spread were evident in 10%-30% of cases at the time of diagnosis, thus suggesting that the widespread opinion regarding the benign behavior of GC tumors should be revised.

A further frustrating finding is represented by the lack in the last 30 years of changes in mean overall survival for patients with GCs, as well as for those with other gastroenteropancreatic neuroendocrine tumors[9,30], despite the increased proportion of patients diagnosed at an earlier stage of the disease. However, it should be noted that many variables, other than types of GC, can affect the overall prognosis, such as age, gender, ethnicity, tumor size, depth of invasion, lymph node involvement, distant metastasis, degree of differentiation, and histological subtype.

MANAGEMENT

The clinical approach to GCs is largely dependent upon the type and size of lesions (Figure 1). Management of type 3 GC is fairly clear and comparable to that used for gastric adenocarcinomas, which includes partial or total gastrectomy with extended lymph node resection[1,3,12,16] in the absence of visceral metastases, or systemic chemotherapy if surgery is not feasible, even if, so far, the results are not very encouraging. The questionable efficacy of conventional cytotoxic chemotherapy has prompted investigation of novel therapeutic approaches for patients with advanced carcinoid. These include the use of targeted radiotherapy, as well as regimens incorporating inhibitors of angiogenesis (e.g. bevacizumab) and small molecule tyrosine kinase inhibitors (e.g. sunitinib). The treatment of metastatic liver disease includes hepatic resection, embolization of the hepatic artery, radiofrequency ablation and cryoablation[31].

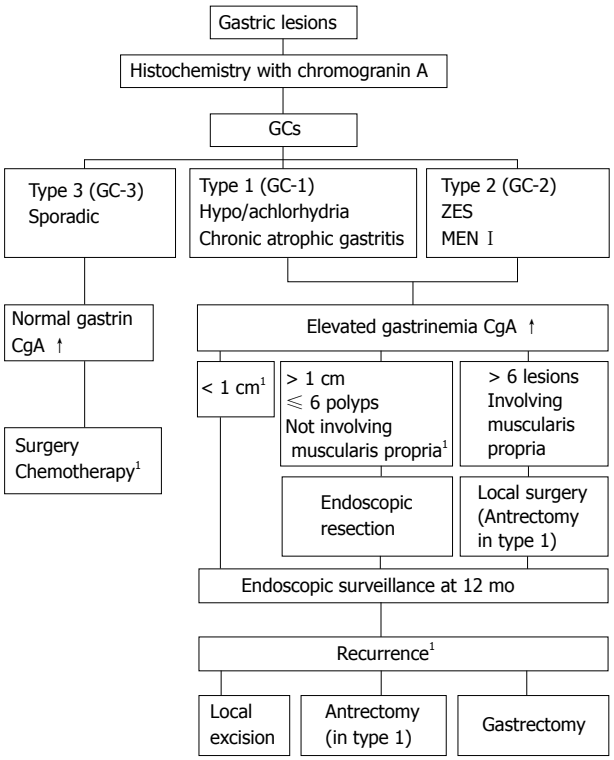

Figure 1 Management flow chart of GCs according to ENETS guidelines[26]. [1]Consider SSAs.

We consider the more controversial management of types 1 and 2 GCs, which are characterized by more benign biological behavior. In GC-1, a conservative approach based on endoscopic resection seems to be the treatment of choice when the size (< 1 cm) and the number (< 3-5) of the tumors render it feasible[1]. However, recently the European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines[27] have suggested that annual surveillance is appropriate when dealing with patients with type 1 GC of less than 10 mm in size. This practical approach is supported by some reports[28,32,33] that suggest that the above careful endoscopic follow-up represents a reasonable and safe option in selected patients. However, further studies including a more consistent number of patients and

with an adequately long follow-up are necessary to support this statement. In fact, despite their usually benign biological and clinical course, type 1 GCs can sometimes exhibit a not entirely negligible mortality rate, as deducible from series with long follow-up[4]. In case of tumors > 10 mm and with up to six polyps not involving the muscularis propria at EUS examination, endoscopic resection remains the reference approach[27]. In the presence of deep gastric parietal wall invasion and positive margins following endoscopic mucosal resection, surgical resection of the tumor should be carried out[27]. Once again, it should be noted that, with these tumors often being multiple and recurrent, antral resection, aimed at avoiding chronic ECL cell stimulation by ongoing hypergastrinemia, is recommended, which is effective in 80% of type 1 tumors[27,34-36]. Moreover, in the case of malignant transformation or recurrence despite local surgical resection, partial or total gastrectomy with lymph node dissection should be performed, as suggested by current guidelines[27].

Overall, despite a generally benign prognosis, the recommended approach in selected subgroups of GC-1 patients appears disproportionately aggressive, and the long-term benefits of antrectomy are still uncertain[34]. Indeed, in some cases, the tumors may become autonomous and no longer gastrin-dependent, and therefore, continue to grow after antrectomy. An octreotide suppression test has been proposed[37] to predict the beneficial outcome from antrectomy, by measuring histidine decarboxylase (HDC) mRNA in the pre- and post-treatment biopsy specimens. In fact, HDC is the enzyme that catalyzes the synthesis of histamine from histidine in ECL cells, a process that is gastrin dependent. A marked decrease in HDC mRNA after octreotide administration indicates that the tumor is still likely to be gastrin dependent.

In extreme situations, i.e., when the biological behavior of the tumor is well defined and definitely benign or malignant, the current guidelines are clear and unambiguous. Conversely, they are less clear for GCs with uncertain behavior, which show atypical characteristics, such as elevated Ki-67, or submucosal invasion, even if they are smaller than 1 cm. Moreover in this situation, according to current guidelines, only endoscopic follow-up is indicated, therefore, information about deep invasion and margin infiltration is not available. At present, relevant controversies and doubts remain in these particular subgroups of patients. It should be stressed that the overall approach is based mainly on the tumor size, but this parameter may not represent the only prognostic factor. Recent studies[38,39] have suggested that proliferation indexes such as Ki-67 are of relevance, but the current best aggregate indicators of prognosis and malignancy seem to be the evidence of invasive growth and the presence of regional or distant metastases (TNM staging system)[38]. At present, however, the criteria to delineate the degree of malignancy remain unclear, and the histological analysis often fails to define precisely the likelihood of aggressive or metastatic potential.

Over the last few years, somatostatin analogues (SSAs) have been used in the treatment of patients with either GC-1 or GC-2[40-45], based on their capability to inhibit gastrin release from the antral G cells, thus reducing ECL cell hyperplasia. However, biotherapy is not currently recommended in patients with type 1 and 2 tumors, except in the rare patients with functioning tumors, and in type 2 patients if indicated for an underlying disease (i.e., other endocrine tumors). Preliminary reports[41] have shown that SSAs have some beneficial effects, for example, by reducing the size and number of carcinoids tumors after 6 mo of treatment. Moreover, the treatment with long-acting SSAs given at monthly intervals for a period of at least 6 mo produces significant suppression in gastrin and CgA levels[40]. Overall, however, the best schedule of treatment remains to be defined.

The management of type 2 GC has to be approached in the context of the MEN-1 syndrome that is present in these patients. As for type 1 GC, endoscopic treatment can be an option, whereas gastric surgery should be performed only in highly selected patients, particularly if the histological examination shows the features of poorly differentiated endocrine tumors. The treatment of type 2 GCs is further complicated by the controversies regarding the treatment of gastrinoma in MEN-1. Currently, no definitive evidence exists that surgery decreases the mortality in MEN-1 or the likelihood that clinically important metastases will develop. Then, the question of whether or not to recommend duodenal-pancreatic surgery in patients with MEN-1 who have pharmacologically controllable ZES and no other clinically evident hormonal excess syndrome is a difficult one. In these cases, the SSA octreotide has been demonstrated to be effective at reducing tumor growth[43].

CONCLUSION

A lot of controversies still exist about the optimal treatment of GC tumors. In fact, endoscopic follow-up could have some risk and is expensive, which leads to further examinations. On the other hand, a more aggressive approach, based on endoscopic or surgical resection may represent over-treatment, with possible unnecessary side effects and high costs. Treatment with long-acting SSAs may therefore represent an alternative option that, even if expensive, seems to be both efficient and safe. Based on the current lack of validated recommendations[40,41,44,45], SSAs should probably be reserved for tumors with atypical characteristics or for multiple small tumors, when surgery is not feasible or judged excessive, and when iterative endoscopic removal is too fastidious or impractical.

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