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Review

Gastric carcinoids: Review a propos of two cases

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SUMMARY

Gastric carcinoids are neoplasms originating from the endocrine cells of the gastric wall and represent less than 1% of all gastric tumours. Their frequency appears to be rising in parallel with the increasing use of upper gastrointestinal endoscopy and the development of techniques for specific immunohistochemical study of gastric biopsies. The pathophysiological classification of gastric carcinoids into three types is clinically useful. The majority (75-80%) belong to Type I, which is associated with chronic atrophic gastritis type A. They develop as a response to chronic hypergastrinaemia, causing sequentially hyperplasia, dysplasia and neoplasia of the ECL (enterochromaffin-like) cells. They follow a benign clinical course and only exceptionally metastasize. Type II carcinoids (5-13%) are also associated with hypergastrinaemia and develop in patients with the Zollinger-Ellison syndrome as part of multiple endocrine neoplasia type 1 (MEN1). They have a slightly higher malignant potential than type I carcinoids. Type III includes the sporadic gastric carcinoids (14-25%) which are invasive tumours with metastases often present at the time of diagnosis. They are not associated with hypergastrinaemia and require more aggressive surgical treatment than types I and II. We review the current management approaches and report two cases of gastric carcinoids, one demonstrating that classification of these tumours is not always straightforward and the other highlighting the importance of extensive endoscopic sampling in the setting of multiple gastric polypoid lesions.

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INTRODUCTION

Carcinoids are tumours originating from neuroendocrine cells of the gut, bronchial tree or thymus.[1,2] Lubarsch (1888)[3] is credited with the first detailed description of such tumours in the gastrointestinal tract (ileum) while Ranson (1890)[4] described a patient with a tumour of the terminal ileum, hepatic metastases, diarrhoea and postprandial exacerbation of dyspnoea. In 1907, Oberndorfer introduced the term "carcinoid" (Karzinoid) to contradistinguish the more benign course of these rare tumours from that of the much commoner adenocarcinomas.[5] Their incidence is estimated at 1-8.4 cases per 100.000 persons per year.[6-8] The majority (67.5-73.7 %) are located in the alimentary tract, followed by the lungs and bronchi.[8,9]

Gastric carcinoids can stem from any of the various neuroendocrine cells (Table 1), which constitute 1-2% of all epithelial cells of the stomach.[10-12] The majority (80%) originate from enterochromaffin-like (ECL) cells, the dominant gastric neuroendocrine cells, found mainly in the fundus and body of the organ.[13-16] The first two cases were described by Askanazy in 1923[17] and for a long time they were considered extremely rare tumours. In 1961, Christodoulopoulos and Klotz listed 79 cases published in the international literature,[18] while by 1979 the number had risen to about 100.[19] Their diagnosis was usually delayed and was often made at autopsy.[18] The advent of endoscopy, in association with the development of more sophisticated techniques for pathological evaluation of gastric biopsies was followed by a rise in the relative frequency of gastric carcinoids.[20] This varies significantly among published series, fluctuating between 3% and 41% of all gastrointestinal tract carcinoids.[6,8,9,16,21,22]

Table 1. Neuroendocrine cells in the human stomach[10-12].

Cell type	Main Location	Secretory product	Frequency (%)
ECL	Fundus-Corpus	Histamine	30-50
EC	Antrum	Serotonin	10
G	Antrum	Gastrin	30
D	Antrum	Somatostatin	20
A	Fundus-Corpus	Glucagon	
X (A-like)	Fundus-Corpus	?Endothelin	
?P/D1	Fundus-Corpus	?Ghrelin	

ECL: Enterochromaffin-like cell, EC: enterochromaffin cell

Nevertheless, they remain generally rare, representing less than 1 % of all gastric neoplasms.[6,8] In this article we review the literature with the emphasis on the management of patients with gastric carcinoids, and present two cases highlighting possible pitfalls in the diagnosis and classification of these rare tumours.

CLASSIFICATION AND PATHOGENESIS

The considerable confusion in the literature regarding the classification of gastric carcinoids[2,23] reflects the lack of an established classification system for carcinoids in general. So, the historic term "carcinoid" has been used loosely to describe a wide variety of tumours with neuroendocrine character, irrespective of anatomical site, histological grade of malignancy and clinical behaviour.[24,25] The division, according to embryological origin, into *foregut, midgut* and *hindgut* carcinoids[24] is of limited clinical use because it does not correlate well with the clinical behaviour and prognosis. In an effort to formulate a prognostically meaningful classification, Capella et al[1] proposed the division of neuroendocrine tumours (NET) into "well-differentiated NET" and "neuroendocrine carcinomas". According to this classification, which was subsequently endorsed by WHO,[26] the term "carcinoid" should be reserved only for well-differentiated neuroendocrine tumours of the stomach, bowel, bronchial tree and thymus, while the neoteric terms "malignant carcinoid" and "atypical carcinoid" were introduced for the description of well-differentiated neuroendocrine carcinomas at these anatomical sites.

Gastric carcinoids are divided into two broad categories: *gastrin-dependent*, associated with hypergastrinaemia, and *non-gastrin dependent* or *sporadic.* Gastrin-dependent carcinoids are further subdivided into two groups: those associated with chronic atrophic gastritis type A (CAG-A) and those associated with the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1 (MEN1).[16,27]

Carcinoids associated with CAG-A, also known as *Type I* gastric carcinoids, are the commonest (79.6%).[27] Hypergastrinaemia is thought to be the main pathogenetic factor in this type of tumour.[28-32] High gastrin levels lead to hyperplasia – dysplasia and finally neoplastic transformation of the histamine-secreting ECL cells of the gastric mucosa.[31,33,34] This hypothesis is based on the observation of gastric carcinoids developing in laboratory animals with omeprazole-induced hypergastrinaemia[35]. It should nevertheless be noted that no such lesions have been observed in man, despite prolonged use of proton-pump inhibitors.[36-38] It appears that some genetic factor, possibly related to mutations of gene *Regl-α* also plays a role. The assumed physiological function of this gene is the suppression of ECL cell proliferation in response to gastrin.[27]

Type I carcinoids:

- are usually diagnosed in older patients (mean age 63 years), mostly women (71%)[39,27,40] and are often discovered during endoscopy for investigation of anaemia or abdominal pain,[39,40]
- are usually multiple (in >50% of cases[27] and small (usually <1 cm), and appear as polypoid lesions, occasionally with central ulceration,[41]
- are located in the body and fundus of the stomach,[29] and do not extend beyond the submucosa,[27]
- are often asymptomatic and only rarely metastasize (2-14% of those larger than 2 cm, mainly to lymph nodes),[16,27,41,42]
- are usually associated with pentagastrin-fast achlorhydria and hypergastrinaemia,[30,43]
- are often associated with pernicious anaemia.[29,16,39,44] In view of the known association of pernicious anae-

mia with autoimmune disorders (e.g. thyroiditis, vitiligo, diabetes mellitus, adrenal insufficiency, rheumatoid arthritis) it is not surprising that these conditions have relatively higher prevalence in patients with Type I gastric carcinoids.[39] Borch noted the presence of gastric carcinoids in 2-9 % of patients with pernicious anaemia.[42] Although these patients are at risk of developing carcinoids, the latter are usually benign[45,46] and for this reason some authors do not recommend routine endoscopic follow-up of patients with pernicious anaemia.[45] This contrasts with the opinion of other workers, who suggest regular endoscopic monitoring, especially of young patients.[47]

Prognosis of Type I carcinoids is generally good[27,29,34,39,47-51] and deaths occurring during follow-up are unlikely to be related to the carcinoid. Endoscopic resection is easy and usually curative and an operation is seldom needed.[52] The latter may be necessary for relatively large or numerous (>5) tumours, or following the occasional relapse of an endoscopically removed carcinoid. In selected cases, antrectomy can lead to tumour regression[13,27,49,53] (Figure 1).

Type II gastric carcinoids are those associated with the Zollinger-Ellison syndrome in patients with MEN1.[27,28,31,34,50,54] This is the most uncommon type (5-1% of all gastric carcinoids[27,41,43,55]). In this setting, hypergastrinaemia plays the same pathogenetic role as in Type I carcinoids,[31] with the possible additional involvement of some genetic factor.[34,56] Loss of heterozygosity at locus 11q13 (where the *MEN1* gene has been mapped) is frequently found in gastric carcinoids of this type.[57,58] In general, Type II carcinoids have few differences from Type I tumours, the main ones being:

- size often >1 cm,[29]
- tendency to metastasize locally in up to 30% of cases,[16,27,29]
- same frequency in both sexes,[27] and
- younger mean age of patients (45 years).[27]

Their management and prognosis are similar to those of Type I tumours[30,43,52] (Figure 1).

Type III includes the sporadic cases of gastric carcinoids,[28,32,49,50] which are also relatively uncommon (14-25%).[27,41,43] They:

- are usually large (>1 cm) and solitary, with normal-appearing mucosa,[27]
- are invasive and show atypical histology associated with malignant clinical behaviour,[59]
- often metastasize[28,30] (>60% at time of diagnosis[16]),
- are not associated with hypergastrinaemia or specific clinical manifestations, apart from rare cases presenting with atypical carcinoid syndrome thought to result from histamine production.[16,43]
- are more common in men (75%),[16,27]
- develop in middle-aged persons (mean age 53),[27] and
- contain ECL cells and a variety of other endocrine cells[16,27] and often produce serotonin.[41]

It is thought that a complex genetic background is involved in their pathogenesis, which does not involve hypergastrinaemia. Abnormalities of p53 and other genes have been implicated.[34]

In view of its aggressive nature and significant mortality,[27,60] this type of carcinoid should be treated with partial or total gastrectomy[52,43] (Figure 1).

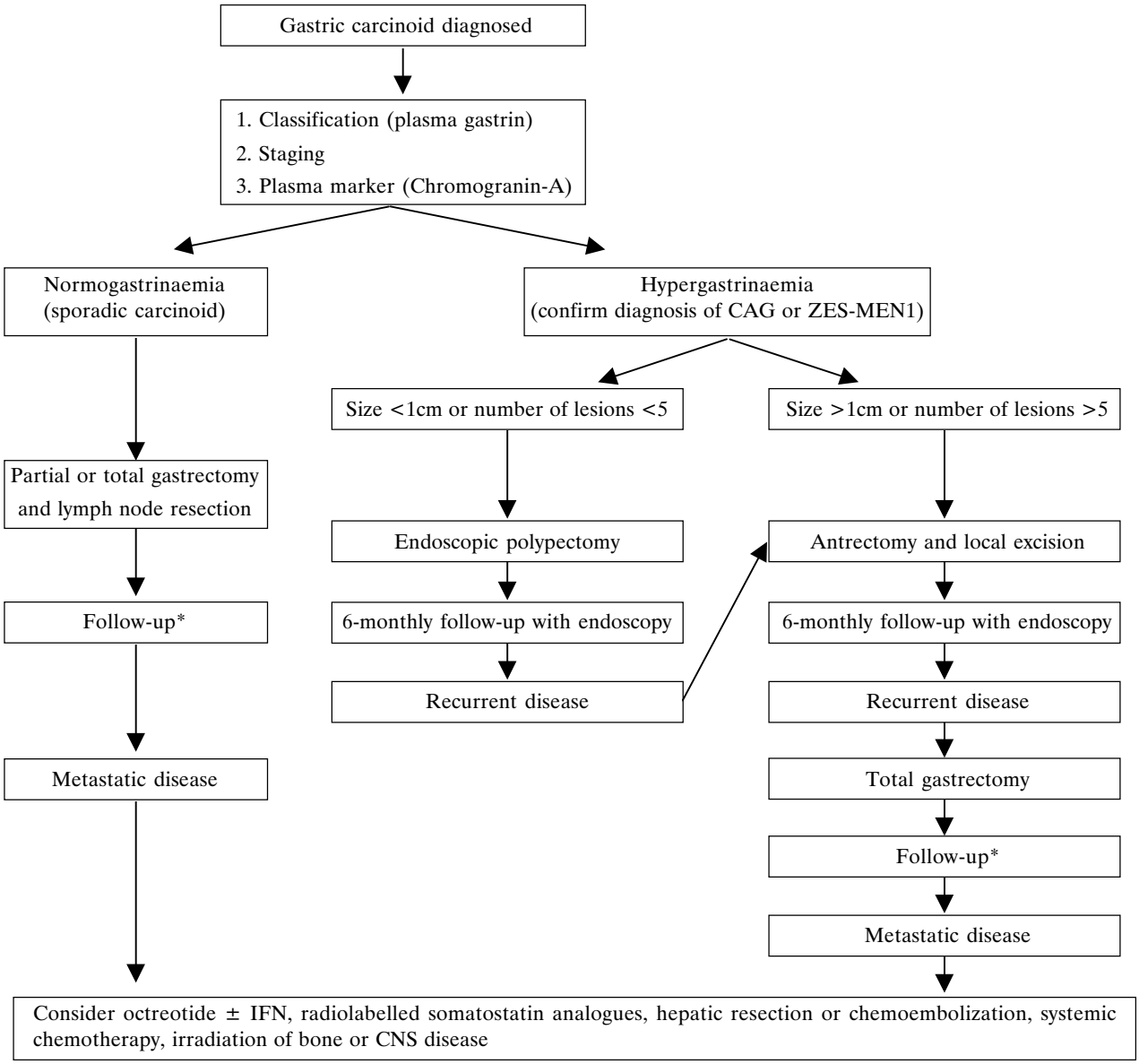
The main characteristics of the three types of gastric carcinoids are summarised in Table 2.

CLINICAL MANIFESTATIONS

Epigastric pain, vomiting, upper gastrointestinal haemorrhage and iron deficiency anaemia are common clinical manifestations of symptomatic gastric carcinoids,[39,40] although in the majority of cases these tumours represent incidental endoscopic findings. The clinical picture depends on the size and location of the tumour, its secretory products, the presence of hepatic metastases and the coexistence of associated conditions (e.g. pernicious anaemia and other autoimmune disorders in Type I carcinoids, ZES and MEN1 manifestations in Type II carcinoids). Large tumours (usually Type III carcinoids) can present with symptoms of gastric outlet obstruction.[61] In contrast to small bowel carcinoids, development of the typical carcinoid syndrome is unusual (5%).[18] Atypical carcinoid syndrome manifesting as episodic flushing due to histamine release can occur in Type III (sporadic) carcinoids.[16] Isolated cases of ectopic ACTH production by gastric carcinoids manifesting as Cushing's syndrome have also been described.[62-64]

DIAGNOSIS AND STAGING

The diagnosis is usually made by *endoscopic biopsy*. The tumours appear as submucosal masses or small, yellowish (a result of cholesterol and lipid accumulation



* There are no published data regarding optimal follow-up. The authors recommend 6-monthly measurements of plasma chromogranin-A if the preoperative levels were elevated. Somatostatin receptor scintigraphy (or alternative scintigraphic method), CT or MRI could be considered in selected cases.

IFN: interferon, CNS: central neural system.

Figure 1. Algorithm for the management of patients with gastric carcinoid. Modified from Gilligan et al.[52]

within the tumour) polypoid protuberances, occasionally with a central erosion or ulceration. Because of their submucosal location, a standard biopsy may be insufficient to obtain adequate diagnostic material, and a partial polypectomy with endoscopic snare excision or a ultrasonographically guided needle biopsy are preferable.[65] It is also rewarding to take biopsies from the surrounding gastric mucosa in order to confirm or exclude the presence of atrophic gastritis.

Microscopy reveals the typical appearances of foregut carcinoid consisting of monomorphic, small or medium sized, round or polygonal cells with variably eosinophilic cytoplasm and uniform, central, round nuclei with fine chromatin pattern, small nucleoli and absent or scanty mitoses. Features of cellular atypia are present in Type III carcinoids and include nuclear polymorphism,

Table 2. Main characteristics of gastric carcinoids. Modified from Modlin IM, Lye KD, Kidd M.[9]

	Type I	Type II	Type III
Frequency	68-83 %	5-13 %	14-25 %
Mean age	63 years	45-50 years	49-53 years
Sex	F:71 % F:M=2-3:1	F:M=1:1	F:M=1:3
Tumor site	Fundus or body	Fundus	Antrum or fundus
Tumor characteristics	Usually multicentric, polypoid	Usually multicentric	Single, solitary
Tumor size	Usually < 1	> 1 cm (usually 1-2 cm)	> 1 cm (usually 2-5 cm)
Histopathology	ECL cell lesion; progression: hyperplasia to dysplasia to neoplasia	ECL cell lesion; progression: hyperplasia to dysplasia to neoplasia	Any gastric endocrine cell without preneoplastic status, lesion normal adjacent mucosa
Biological behavior	Slow growth; rarely metastasizes (2-14%)	Slow growth; may metastasize (30% lymph nodes, 10% distal)	Relatively aggressive; frequent metastases to regional nodes (55%) and liver (24%)
Coexistent diseases	Autoimmune diseases (thyroiditis, Addison's disease, diabetes, pernicious anaemia, vitiligo, rheumatoid arthritis)	MEN-1 (Manifestations from pituitary, parathyroid glands, and endocrine pancreas)	–
Symptoms	Often asymptomatic	Possibly manifestations of MEN-1 syndrome	Non-specific clinical manifestations. Rarely atypical carcinoid syndrome
Plasma gastrin level	Elevated	Elevated	Normal
Gastric acid output	Low or absent	High	Normal or low
Secretin test	Negative	Positive	Negative

prominent nucleoli, slight increase in mitotic activity and small areas of necrosis. Occasionally entirely different cell types, e.g. plasmacytoid, spindle-shaped and poorly differentiated cells may be present, making difficult the differential diagnosis from other tumours, including lymphoma, leiomyoma, hamartoma or carcinoma.[40] The tumour shows various patterns of growth including trabecular or ribbon-like with anastomosing features, solid, nodular or insular cords, nest, rosette-like or pseudoglandular formations or any combination of the above. The majority are confined within the mucosa and submucosa but more aggressive tumours can infiltrate the muscularis propria and serosa, expanding to the mesentery. Local lymph node metastases as well as distant metastases, mainly to the liver can also be present at the time of diagnosis.

Histochemically gastric carcinoids are argyrophilic. Nowadays staining with silver salts is only of historical interest as it has been superceded by *immunostaining* with antibodies to a variety of molecules contained in the neuroendocrine granules of carcinoid tumours.[16,40,60] Among them, staining for Chromogranin-A is the most useful, being positive in practically all cases, followed by synaptophysin and neuron-specific enolase.

Measurement of *plasma gastrin* levels allows the differentiation of gastrin-dependent (Types I and II) from sporadic (Type III) gastric carcinoids. Hypergastrinaemia in the absence of evidence of CAG-A requires further investigation in the direction of ZES-MEN1, including a secretin-provocation test.

Staging begins with the assessment of the depth of gastric wall infiltration. This can be achieved in 90% of cases with endoscopic ultrasound (EUS), while the same technique allows detection of infiltrated perigastric lymph nodes in 75% of cases.[66,67] Information about both gastric wall infiltration and extragastric extent of disease can also be obtained by CT, which has a reported sensitivity of 87% in hepatic metastases detection,[68,69] and MRI. Modern CT-based imaging techniques like dedicated multi-detector CT of the stomach allow high-quality multiplanar reformation and three-dimensional reconstruction of gastric images and are promising, high sensitivity tools to be used as an adjunct to endoscopy for preoperative staging.[70] Positron emission tomography (PET-scanning) can be helpful and has been used for diagnosis and follow-up of carcinoid tumors but experience with this method remains limited.

Carcinoids are usually rich in somatostatin receptors,

mainly of subtype 2 (SSTR2), for which octreotide, a synthetic somatostatin analogue, has high affinity. Scintigraphy with radioactively labeled (indium-111 diethylenetriamine pentaacetic acid) octreotide (In-111 DTPA Octr), or OctreoScan, is a sensitive and specific tool enabling not only the mapping of regional and distant metastases but also the intraoperative detection of neuroendocrine tumours using hand-held gamma cameras.[71-73] OctreoScan has now displaced the previously popular but of low specificity iodine-131 metaiodobenzylguanidine (MIBG) scanning. An other alternative to somatostatin receptor scintigraphy (SRS) is immunoscintigraphy, which employs monoclonal antibodies to chromogranin-A and can be used for diagnostic and staging purposes, especially in cases of tumours poor in somatostatin receptors.[76]

Plasma Chromogranin-A is the most useful peptide marker in the diagnostic work-up and the follow-up after treatment of gastric carcinoids,[77,78] while urinary 5-HIAA measurement is not helpful in view of the low serotonin content of foregut carcinoids.

TREATMENT

Due to the rarity of these tumours, evidence from large, randomized studies is lacking and the recommendations are based on small, uncontrolled series. As mentioned above (see discussion of individual carcinoid types in the classification section), endoscopic or surgical resection is the initial approach in all types of gastric carcinoid. Surgery is the only potentially curative treatment for patients with carcinoid tumors in general, and this applies even in the presence of metastases.[79] In the case of metastatic gastric carcinoid, gastric surgery has the additional theoretical advantage of ameliorating hypergastrinaemia, which represents the main trophic stimulus for many of these tumours.[80] An algorithmic description of the recommended management of patients with a newly diagnosed gastric carcinoid is presented in Figure 1.

All patients with gastric carcinoids will need regular, life-long follow-up, the kind of which may vary depending on the initial treatment. It may include endoscopy, measurements of plasma levels of markers of disease activity and a range of imaging methods, most notably the highly sensitive SRS. It is important to avoid depending on one modality alone to assess disease status. For example, falsely negative SRS can occasionally be a result of either down-regulation of SSTR on carcinoid cells following administration of steroids, chemotherapy or prolonged courses of somatostatin analogues or the emergence of clones of tumour cells lacking somatostatin receptors.[81,82] It should also be noted that, beside monitoring the original tumour, follow-up should include thorough screening for common cancers (colon, breast, lung, prostate), as it is known that synchronous or metachronous second malignancies occur commonly in patients with gastrointestinal carcinoids.[83,84]

The detection of metastatic carcinoid should not be seen as a catastrophic event, in view of the fact that many of these tumours are slow-growing and patients can remain asymptomatic for years. A period of observation may therefore allow for a decision to be made concerning optimal supportive care or more specific antitumour treatments. On the other hand, it is becoming increasingly apparent that an appreciable percentage of the tumours are more aggressive, necessitating the development of effective treatment protocols. The approach to the treatment of metastatic gastric carcinoid is generally similar to that of the much commoner metastatic intestinal carcinoid.

The advent of somatostatin and its analogues has generated new prospects for medical treatment of SRS-positive metastatic carcinoid. Somatostatin is a 14-aminoacid peptide that inhibits the secretion of growth hormone and most gastrointestinal hormones by binding to G-protein-coupled transmembrane receptors (of which there are 5 subtypes, SSTR1-5). Octreotide, a 8-aminoacid long-acting somatostatin analogue has a plasma half-life of 1,5-2 hr and acts by binding mainly to SSTR2. Other long-acting analogues are lanreotide and the more recently introduced octreotide acetate. Octreotide at low doses was used in the 1980s for symptomatic control of carcinoid syndrome[85] and it was later realized that these analogues given at higher doses might also retard carcinoid tumour growth.[86] Ferraro et al[87] showed that administration of octreotide controlled the growth of ECL cells in the setting of atrophic gastritis-related hypergastrinaemia. Other investigators have shown that somatostatin analogues could induce regression of both hypergastrinaemia-related[88,80] and sporadic[89] gastric carcinoid tumours. It therefore appears that somatostatin analogues are well suited for the management of metastatic gastric carcinoid, as they exert inhibitory action on both the trophic stimulus (gastrin) and the tumour itself. These agents have an excellent safety profile but cannot be used in children for fear of stunt linear growth, which is a major adverse effect. Other adverse effects include steatorrhoea, which may require pancreatic enzyme replacement, and development of

gallstones. Local irritation at the site of injection is a common complaint. Some therapeutic regimens have successfully combined somatostatin analogues with interferon,[90] an immunomodulating agent shown to benefit some patients with advanced carcinoid tumours even when used as monotherapy.[91]

Receptor-targeted therapy with a radioactive isotope attached to a somatostatin analogue or MIBG, is currently being used on an experimental basis in patients with unresectable tumours. Encouraging preliminary results have been reported with ^{111}In-labelled octreotide,[92] ^{123}I-labelled MIBG[93] and ^{90}Yttrium-labelled octreotide.[94]

Various chemotherapeutic agents alone or in combination have been employed for treating metastatic carcinoids. Most protocols have included classical cytotoxic drugs like 5-fluorouracil (5-FU), streptozotocin, anthracyclines, alkylating agents, cisplatin and etoposide, but the results in general have been poor, as is the case with slow-growing, well-differentiated tumours.[21,95] Selecting the most effective chemotherapy for the individual patient by means of drug resistance testing on cells cultured from tumour biopsies, is a promising technique currently under investigation.[96]

Many aggressive approaches have been applied to the treatment of hepatic metastases, ranging from simple resection of isolated lesions to liver transplantation.[97,98] Successes have also been reported with radiofrequency ablation[99] and hepatic artery chemoembolization,[100] while multimodality treatment protocols are becoming increasingly popular.[96,101] Finally, irradiation should be considered in cases with metastatic bone or CNS disease.[102]

CASE REPORTS

Case 1

A 66-year-old man with recurrent upper GI bleeding underwent oesophago-gastro-duodenoscopy, which revealed the presence of a small (<1 cm) polypoid lesion in the body of the stomach near the antrum, without signs of bleeding. Histology of the endoscopically excised polyp was compatible with a carcinoid, showing mucosa and submucosa infiltration by tumour consisting of small, uniform cells with regular, normochromatic nuclei and scanty mitoses, forming microglandular, trabecular and insular patterns. Tumour cells were immunoreactive for chromogranin-A, synaptophysin, neuron-specific enolase and gastrin. Because of continuing melaenas, the patient underwent surgery leading to the discovery and resection of an ulcerated leiomyoma of the jejunum, to which the GI bleeding was eventually ascribed. Laboratory investigations including biochemical profile, 24-hour urinary 5-HIAA estimation and computerized tomograms of the abdomen were within normal limits. Seven years later the patient was remaining in excellent health, although endoscopic ultrasonographic examination of the stomach was showing a 6.9 x 5.3 mm hypoechogenic submucosal lesion at the site of the originally excised carcinoid, with no perigastric lymphadenopathy. There was associated hypergastrinaemia at 557 pg/ml (normal range 0-110 pg/ml) with no evidence of either atrophic gastritis (normal histology and serum B12 levels, absent autoantibodies to parietal cells and intrinsic factor) or MEN1 syndrome (normal hormonal profile and CT imaging) and therefore a tentative diagnosis of sporadic, gastrin- producing NET of the stomach was made. In view of the small tumour size and absence of invasiveness, no further action was undertaken beyond close endoscopic monitoring.

Comment: Classification of gastric carcinoids based on the presence (Types I and II) or absence (Type III) of hypergastrinaemia can be difficult in the exceptional case of a sporadic, gastrin-producing, gastric NET. It should be noted that, although sporadic gastric carcinoids are usually comprised of ECL cells, they often exhibit a mixed cell population including gastrin-positive cells, the significance of which is unclear.[9] The finding of high levels of expression of precursor and mature gastrin peptides in gastric carcinoids, together with the gastrin receptor, suggests that these tumours express the gastrin autocrine-paracrine pathway and could explain why some carcinoids do not regress after surgical procedures that lower serum gastrin.[103]

Case 2

A 41-year-old female was referred for upper GI endoscopy during the course of investigations for incidentally discovered iron deficiency anaemia. She had a history of a radiologically diagnosed duodenal ulcer, for which she was taking omeprazole and was asymptomatic at the time of the examination. Endoscopy revealed the presence of multiple friable polyps, sized 0.2-1.5 cm, in the fundus and body of the stomach, while the surrounding mucosa appeared normal. Histological examination of the biggest (maximal diametre 1.5 cm) of four endoscopically removed polyps was compatible with a hyperplastic/regenerative gastric polyp with no evidence of neoplasia. Examination of the other three polyps (maximal diametre 0.4 cm) showed infiltration of the mucosa and submucosa by tumour consisting of small,

uniform cells with a trabecular or glandular pattern of growth and mild cellular atypia. Mitoses were less than 2 per 10 high-power optical fields and Ki-67 positivity was present in less than 2% of neoplastic cells. Immunocytochemical staining was positive for chromogranin-A and synaptophysin. A diagnosis of well-differentiated NET of the stomach was made and on further investigation the patient was also found to have low levels of serum vitamin B12 (129 μg/L, normal range 270-900 μg/L) combined with high titres of anti-parietal cell autoantibodies. Extensive endocrinological investigation excluded the presence of multiple endocrine neoplasia type 1 (MEN1). 24-hour urinary 5-HIAA excretion was within normal levels and CT-scanning of abdomen and thorax was negative for metastases. The tumour was classified as Type 1 gastric carcinoid and the patient was advised to have regular endoscopic follow-up and further polypectomies as necessary.

Comment: This case of gastric carcinoids coexisting with hyperplastic/regenerative polyps highlights the need for thorough endoscopic sampling in the setting of multiple polypoid lesions of the stomach. Even in endoscopically unremarkable mucosae, extensive sampling of both the lesser and greater curvatures is recommended in hypergastrinaemic patients, as it has been shown that the rate of diagnosis of dysplastic and carcinoid lesions correlates with the number of specimens examined.[104]

REFERENCES

1. Capella C, Heitz Ph U, Hofler H, et al. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. Virchows Arch A (Pathol Anat), 1995; 425:547-560.
2. Arnold R. Das Carcinoid - Eine in Frage gestellte Entität? Chirurg 1997; 68:132-135.
3. Lubarsch O. Über der primären Krebs des ileum, nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberkulose. Virchows Arch, 1888; 111:281-317.
4. Ranson WB. A case of primary carcinoma of the ileum. Lancet, 1890; 2:1020-1023.
5. Oberndorfer S. Karzinoide Tumoren des Dünndarms. Frankfurt Zellforsch Pathologie, 1907; 1:426-429.
6. Godwin J. Carcinoid tumors: an analysis of 2837 cases. Cancer, 1975; 36:560-569.
7. Berge T, Linell E. Carcinoid tumours: frequency in a defined population during a 12-year period. Acta Pathol Microbiol Scand [A], 1976; 84:322-330.
8. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. Cancer, 1997; 79:813-829.
9. Modlin IM, Lye KD, Kidd M. Carcinoid tumors of the stomach. Surg Oncol 2003; 12:153-172.
10. D'Adda T, Bertele A, Pilato FP, Bordi C. Quantitative electron microscopy of endocrine cells in oxyntic mucosa of normal human stomach. Cell Tissue Res 1989; 255:41-48.
11. Bordi C, D'Adda T, Azzoni C, Ferraro G. Classification of gastric endocrine cells at the light and electron microscopical levels. Microsc Res Tech 2000; 48:258-271.
12. Rindi G, Necchi V, Savio A, et al. Characterisation of gastric ghrelin cells in man and other mammals: studies in adult and fetal tissues. Histochem Cell Biol 2002; 117:511-519.
13. Eckhauser FE, Lloyd RV, Thompson NW, et al. Antrectomy for multicentric, argyrophil gastric carcinoids: a preliminary report. Surgery 1988; 104:1046-1053.
14. Solcia E, Bordi C, Creutsfeldt W, et al. Histopathological classification of nonantral gastric endocrine growths in man. Digestion 1988; 41:185-200.
15. Bordi C, Yu JY, Baggi MT, et al. Gastric carcinoids and their precursor lesions. Cancer 1991; 67:663-672.
16. Rindi G, Luinetti O, Cornaggia M, et al. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology 1993; 104:994-1006.
17. Askanazy M. Zur Pathogenese der Magenkrebse und über ihren gelegenlialen Keimen in der Magenwand. Dtsch Med Wochenschr 1923; 49:49-51.
18. Christodoulopoulos J, Klotz AP. Carcinoid syndrome with primary carcinoid tumor of the stomach. Gastroenterology 1961; 40:429-435.
19. Rogers LW, Murphy RC. Gastric carcinoid and gastric carcinoma. Morphologic correlates of survival. Am J Surg Pathol 1979; 3:195-202.
20. Modlin IM, Kevin DL, Kidd M. A 50-year analysis of 562 gastric carcinoids: Small tumor or larger problem? Am J Gastroenterol 2004; 99:23-32.
21. Arnold R. Medical treatment of metastasizing carcinoid tumors. World J Surg 1996; 20:203-207.
22. Solcia E, Fiocca R, Sessa F, et al. Morphology and natural history of gastric endocrine tumours. In: Hakanson R, Sundrler F, eds. The stomach as an endocrine organ. Elsevier, Amsterdam 1991, p 473-498.
23. Klöppel G, Perren A, Heitz PU. From carcinoids to a biologically and prognostically relevant classification of the neuroendocrine tumours of the gastrointestinal tract and the pancreas. Acta clin Croat 2002; 41:285-294.
24. Williams ED, Sandler M. The classification of carcinoid tumours. Lancet 1963; 1:238-239.
25. Williams ED, Siebenmann RE, Sobin LH. Histological typing of endocrine tumours. International histological typing of tumours, No 23, World Health Organization, Geneva 1980.
26. Solcia E, Klöppel G, Sobin LH, (In collaboration with 9 pathologists from 4 countries). Histological typing of endocrine tumours. Second Edition. WHO international histological classification of tumours. Springer, Berlin, 2000.
27. Rindi G, Bordi C, Rappel S, et al. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and

behavior. World J Surg 1996; 20:168-172.
28. Akerstrom G. Management of carcinoid tumors of the stomach, duodenum, and pancreas. World J Surg 1996; 20:173-182.
29. Kloppel G, Clemens A. The biological relevance of gastric neuroendocrine tumors. Yale J Biol Med 1996; 69:69-74.
30. Cattan D. Tumeurs carcinoides gastriques. Rev Prat 1997; 47:863-867.
31. Bordi C. Gastric carcinoids. Ital J Gastroenterol Hepatol 1999; 31(Suppl 2):S94-7.
32. Brundler R, Gebbers JO, Criblez D. Das Magenkarzinoid. Pathogenese und Therapie. Schweiz Med Wochenschr 1999; 129:945-950.
33. Solcia E, Fiocca R, Villani L, Luinetti O, Capella C. Hyperplastic, dysplastic, and neoplastic enterochromaffin-like-cell proliferations of the gastric mucosa. Classification and histogenesis. Am J Surg Pathol. 1995; 19(Suppl 1):S1-7.
34. Solcia E, Rindi G, Larosa S, Capella C. Morphological, molecular, and prognostic aspects of gastric endocrine tumors. Microsc Res Tech 2000; 48:339-48.
35. Havu N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. Digestion 1986; 35:42-55.
36. Arnold R, Koop H. Omeprazole: long term safety. Digestion 1989; 44 (suppl 1):77-86.
37. Lamberts R, Creutzfeldt W, Struber HG, et al. Long-term omeprazole therapy in peptic ulcer disease: Gastrin, endocrine cell growth, and gastritis. Gastroenterology 1993; 104:1356-1370.
38. Klinkenberg-Knoll EC, Festen HP, Jensen JB, et al. Long-term treatment with omeprazole for refractory reflux esophagitis: Efficacy and safety. Ann Intern Med 1994; 121:161-167.
39. Gough DB, Thompson GR, Crotty TB, et al. Diverse clinical and pathologic features of gastric carcinoid and the relevance of hypergastrinemia. World J Surg 1994; 18:473-479.
40. Thomas RM, Baybick JH, Elsayed AM, Sobin LH. Gastric carcinoids: an immunohistochemical and clinicopathologic study of 104 patients. Cancer 1994; 73:2053-8.
41. Sitaraman SV, Goldfinger SE. Diagnosis of the carcinoid syndrome. UpToDate, 9.1, 1999.
42. Borch K. Atrophic gastritis and gastric carcinoid tumours. Ann Med 1989; 21:291-297.
43. Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med 1999; 340:858-368.
44. Moses RE, Frank BB, Leavitt M, Miller R. The syndrome of type A chronic atrophic gastritis, pernicious anemia, and multiple gastric carcinoids. J Clin Gastroenterol 1986; 8:61-65.
45. Kokkola A, Sjoblom SM, Haapiainen R, et al. The risk of gastric carcinoma and carcinoid tumours in patients with pernicious anaemia. A prospective follow-up study. Scand J Gastroenterol 1998; 33:88-92.
46. Hsing AW, Hansson LE, McLaughlin JK, et al. Pernicious anemia and subsequent cancer. A population-based cohort study. Cancer 1993; 71:745-750.
47. Sjoblom SM, Sipponen P, Jarvinen H. Gastroscopic follow-up of pernicious anemia patients. Gut 1993; 34:28-32.
48. Borch K, Renvall H, Kullman E, Wilander E. Gastric carcinoid associated with the syndrome of hypergastrinemic atrophic gastritis. Am J Surg Pathol 1987; 11:435-444.
49. Ahlman H, Kolby L, Lundell L, et al. Clinical management of gastric carcinoid tumors. Digestion 1994; 55(Suppl 3):77-85.
50. Bordi C, Azzoni C, D'Adda T, et al. Neuroendokrine Tumoren des Magens. Pathogenese, Klassifikation und Klinik. Pathologe 1997; 18:313-321.
51. Cadiot G, Cattan D, Mignon M. Diagnosis and treatment of ECL cell tumors. Yale J Biol Med 1998; 71:311-323.
52. 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; 90:338-352.
53. Hirschowitz BI, Griffith J, Pellegrin C, et al. Rapid regression of enterochromaffin cell gastric carcinoids in pernicious anemia after antrectomy. Gastroenterology 1992; 102:1409-1418.
54. Cadiot G, Laurent-Puig P, Thuille B, et al. Is the multiple endocrine neoplasia type 1 gene a suppressor for fundic argyrophil tumors in the Zollinger-Ellison syndrome ? Gastroenterology 1993; 105:579-582.
55. Lehy T, Mignon M, Cadiot G, et al. Gastric endocrine cell behaviour in Zollinger-Ellison patients on long term anti-secretory treatment. Gastroenterology 1989; 96:1029-1040.
56. Calender A, Giraud S, Porchet N, et al. Etude clinicogenetique de la NEM1: donnees physiopathologiques recentes et applications cliniques. Dans le cadre du GENEM. Groupe d'Etude des Neoplasies Endocriniennes Multiples. Ann Endocrinol (Paris) 1998; 59:444-451.
57. Debelenko LV, Emmert-Buck MR, Zhuang Z, et al. The multiple endocrine neoplasia type I gene locus is involved in the pathogenesis of type II gastric carcinoids. Gastroenterology 1997; 113:773-781.
58. D'Adda T, Keller G, Bordi C, Hofler H. Loss of heterozygosity in 11q13-14 regions in gastric neuroendocrine tumors not associated with multiple endocrine neoplasia type 1 syndrome. Lab Invest 1999; 79:671-677.
59. Granberg D, Wilander E, Stridsberg M, et al. Clinical symptoms, hormone profiles, treatment, and prognosis in patients with gastric carcinoids. Gut 1998; 43:223-228.
60. Yu JY, Wang LP, Meng YH, Hu M, Wang JL, Bordi C. Classification of gastric neuroendocrine tumors and its clinicopathologic significance. World J Gastroenterol 1998; 4:158-161.
61. Green ST, Drury JK, Mc Callion J, Erwin L. Carcinoid tumour presenting as recurrent gastric outlet obstruction. A case of long-term survival. Scott Med J 1987; 31:54-55.
62. Hirata Y, Sakamoto N, Yamamoto H, Matsukura S, Imura H, Okada S. Gastric carcinoid with ectopic production of ACTH and beta-MSH. Cancer 1976; 37:377-385.
63. Marcus FS, Friedman MA, Callen PW, Churg A, Har-

bour J. Successful therapy of an ACTH-producing gastric carcinoid APUD tumor: report of a case and review of the literature. Cancer 1980; 46:1263-1269.
64. Heitz PU, Kloppel G, Polak JM, Staub JJ. Ectopic hormone production by endocrine tumors: localization of hormones at the cellular level by immunocytochemistry. Cancer 1981; 48:2029-2037
65. Case records of the Massachusetts General Hospital. Case 9-1997. N Engl J Med 1997; 336:861-867.
66. Yoshikane H, Tsukamoto Y, Niwa Y, et al. Carcinoid tumors of the gastrointestinal tract: evaluation with endoscopic ultrasonography. Gastrointest Endosc 1993; 39:375-383.
67. Zimmer T, Ziegler K, Bader M, et al. Localisation of neuroendocrine tumours of the upper gastrointestinal tract. Gut 1994; 35:471-475.
68. Metz SA, McRae JR, Robertson PR. Prostaglandins as mediators of paraneoplastic syndromes: Review and update. Metabolism 1981; 30:299-316.
69. Oates JA. The carcinoid syndrome. N Engl J Med 1986; 315:702-704.
70. Ba-Ssalamah A, Prokop M, Uffmann M, Pokieser P, Teleky B, Lechner G. Dedicated Multidetector CT of the Stomach: Spectrum of Diseases. RadioGraphics 2003; 23:625-644.
71. Lamberts SWJ, Bakker WH, Reubi JC, Krenning EP. Somatostatin-receptor imaging in the localization of endocrine tumors. N Engl J Med 1990; 323:1246-1249.
72. Krenning EP, Kwekkebom DJ, Oei HY, et al. Somatostatin receptor scintigraphy in carcinoids, gastrinomas and Cushing's syndrome. Digestion 1994; 55(suppl. 3):53-9.
73. Wängberg B, Forssell-Aronsson E, Tisell LE, et al. Intraoperative detection of somatostatin receptor-positive neuroendocrine tumours using indium-labelled DTPA-D-Phe-octreotide. Br J Cancer 1996; 73: 770-5.
74. Krenning EP, Kooij PPM, Pauwels S, Breeman WAP, Postema PTE. Somatostatin receptor: Scintigraphy and radionuclide therapy. Digestion 1996; 57(suppl. 1):57-61.
75. Meko JB, Doherty GM, Siegel BA, Norton JA. Evaluation of somatostatin-receptor scintigraphy for detecting neuroendocrine tumors. Surgery 1996; 120:975-983.
76. Carretta A, Chiesa G, Magnani P, et al. Imaging of bronchial carcinoid tumors associated to Cushing syndrome with 111In-Octreoscan scintigraphy and immunoscintigraphy with anti- chromogranin monoclonal antibodies. Report of two cases. J Cardiovasc Surg (Torino) 1997; 38:191-194.
77. Janson ET, Holmberg L, Stridsberg M, et al. Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center. Ann Oncol 1997; 8:685-690.
78. Granberg D, Wilander E, Stridsberg M, Granerus G, Skogseid B, Oberg K. Clinical symptoms, hormone profiles, treatment, and prognosis in patients with gastric carcinoids. Gut 1998; 43:223-228.
79. Norton JA. Surgical management of carcinoid tumours: role of debulking and surgery for patients with advanced disease. Digestion 1994; 55:98-103.
80. Kouraklis G, Misiakos E, Glinavou A, Raftopoulos J, Karatzas G. Management of enterochromaffin-like gastric carcinoid tumour metastasized to the liver. Scand J Gastroenterol 2002; 37:246-248.
81. Lamberts SWJ, van der Lely A-J, de Herder WW, Hofland LJ. Drug therapy. Octreotide. N Engl J Med 1996; 334:246-254.
82. Jenkins SA, Kynaston HG, Davies ND, Baxter JN, Nott DM. Somatostatin analogs in oncology: a look to the future. Chemotherapy 2001; 47(Suppl. 2):162-196.
83. Gerstle JT, Kauffman GL, Koltun WA. The incidence, management, and outcome of patients with gastrointestinal carcinoids and second primary malignancies. Journal of the American College of Surgeons 1995; 180:427-432.
84. Habal N, Sims C, Bilchik AJ. Gastrointestinal carcinoid tumors and second primary malignancies. J Surg Oncol 2000; 75:310-316.
85. Kvols LK, Martin JK, Marsh HM, Moertel CG. Rapid reversal of carcinoid crisis with a somatostatin analogue. N Engl J Med 1985; 313:1229-1230.
86. Ruszniewski P, Ducreux M, Chayvialle JA, et al. Treatment of the carcinoid syndrome with the long acting somatostatin analogue lanreotide: a prospective study in 39 patients. Gut 1996; 39:279-283.
87. Ferraro G, Annibale B, Marignanti M, et al. Effectiveness of octreotide in controlling fasting hypergastrinemia and related enterochromaffin-like cell growth. J Clin Endocrinol Metab 1996; 81:677-683.
88. 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; 343:551-554.
89. Caplin ME, Hodgson HJ, Dhillon AP, et al. Multimodality treatment for gastric carcinoid tumor with liver metastases. Am J Gastroenterol 1998; 93:1945-1948.
90. Janson ET, Oberg K. Long-term management of the carcinoid syndrome: treatment with octreotide alone and in combination with alpha interferon. Acta Oncol 1993; 32:225-229.
91. Oberg K, Eriksson B. The role of interferons in the management of carcinoid tumors. Acta Oncol 1991; 30:519-522.
92. Krenning EP, Valkema P, Kooil PPM, et al. Peptide receptor radionuclide therapy with (Indium-111-DTPA-Phe)-Octreotide. J Nucl Med 1997; 38:47P.
93. Taal BG, Hoefnagel CA, Olmos RA, Boot H, Beijnen JH. Palliative effect of metaiodobenzylguanidine in metastatic carcinoid tumours. J Clin Oncol 1996; 14:1829-1838.
94. Otte A, Mueller-Brand J, Dellas S, et al. Yttrium-90-labelled somatostatin analogue for cancer treatment. Lancet 1998; 351:417-418.
95. Bukowski RM, Johnson KG, Peterson RF, et al. A phase II trial of combination chemotherapy in patients with metastatic carcinoid tumors: a Southwest Oncology Group study. Cancer 1987; 60:2891-2895.
96. Warner RR. Carcinoid case presentation and discussion:

the American perspective. Endocr Relat Cancer 2003; 10:489-496.
97. Que FG, Nagorney DM, Batts KP, Linz LJ, Kvols LK. Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 1995; 169:36-43.
98. Dousset B, Saint-Marc O, Pitre J, Soubrane O, Houssin D, Chapuis Y. Metastatic neuroendocrine tumors: medical treatment, surgical resection or liver transplantation. World J Surg 1996; 20:908-915.
99. Wessels FJ, Schell SR. Radiofrequency ablation treatment of refractory carcinoid hepatic metastases. J Surg Res 2001; 95:8-12.
100. Ruszniewski P, Rougier P, Roche A, et al. Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors: a prospective phase II study in 24 patients. Cancer 1993; 71:2624-2630.
101. Diaco DS, Hajarizadeh H, Mueller CR, et al. Treatment of metastatic carcinoid tumors using multimodality therapy of octreotide acetate, intra-arterial chemotherapy, and hepatic arterial chemoembolization. Am J Surg 1995; 169:523-528.
102. Shupak KD, Wallner KE. The role of radiation therapy in the treatment of locally unresectable or metastatic carcinoid tumors. Int J Radiat Oncol Biol Phys 1991; 20:489-495.
103. Smith AM, Watson SA, Caplin M, et al. Gastric carcinoid expresses the gastrin autocrine pathway. Br J Surg. 1998; 85:1285-1289.
104. Bordi C, Azzoni C, Ferraro G, et al. Sampling strategies for analysis of enterochromaffin-like cell changes in Zollinger-Ellison syndrome. Am J Clin Pathol 2000; 114:419-425.