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Diagnosis and Treatment of ECL Cell Tumors

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The diagnosis of ECL-omas is easy to perform. In patients with Zollinger-Ellison syndrome (ZES), ECL-omas are almost always observed in the setting of multiple endocrine neoplasia type I. In patients without ZES, the first step is to discard non-gastrin-related sporadic ECL-omas whose prognosis is poor. By contrast, prognosis of ECL-omas in patients with ZES or chronic atrophic gastritis is good. Metastases are rare, and tumor-related deaths are exceptional. In both conditions, ECL-omas measuring less than 1 cm should be treated by endoscopic polypectomy and survey. Treatment modalities (surgery, endoscopic polypectomy) for larger tumors are still discussed. The impact of endoscopic ultrasonography on the therapeutic decision has not yet been evaluated. Considering the good prognosis of these tumors, aggressive surgery could be limited to selected patients. Multicentric studies should be undertaken to determine the best treatment modalities.

INTRODUCTION

In man, fundic, well-differentiated, carcinoid tumors mainly composed of ECL cells (ECL-omas) are observed in clinical conditions associated with sustained chronic hypergastrinemia, such as Zollinger-Ellison syndrome (ZES)[d] (type 1 ECL-omas) [1-4] and chronic atrophic gastritis type A (CAG-A) (type 2 ECL-omas) [4-18], and also independently from hypergastrinemia, where they are called sporadic ECL-omas (type 3 ECL-omas) [4, 11, 19]. By contrast to the gastrin-related carcinoids, sporadic ECL-omas are most often single, large and deeply invasive. Furthermore, patients with sporadic ECL-omas often die from liver metastases. The main clinicopathological differences between the three types of ECL-omas are summarized in Table 1 [4].

Owing to major differences in natural history and mortality between gastrin-related ECL-omas and sporadic ECL-omas, treatment modalities vary markedly. In patients with sporadic type 3 tumors, total gastrectomy with "en bloc" removal of regional lymph nodes is mandatory when unresectable liver metastases are not present and systemic therapy (chemotherapy or other antitumoral therapies) when they are present [4, 8, 9, 16, 19]. In patients with gastrin-related ECL-omas, the optimal management is not clearly established. Therefore, this review will only concern management (i.e., diagnosis and treatment) of ECL-omas encountered in patients with CAG-A and with ZES.

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[d]*Abbreviations:* ZES, Zollinger-Ellison syndrome; CAG-A, chronic atrophic gastritis type A; MEN 1, multiple endocrine neoplasia type 1.

DIAGNOSIS OF FUNDIC ECL-OMAS

The diagnosis of ECL-omas is easily performed by the histological analysis of endoscopic biopsies of the polyps, as it will be discussed below. In patients with ZES, ECL-omas mainly occur in patients with multiple endocrine neoplasia type 1 (MEN 1). Therefore, performing a diagnosis of ECL-oma in ZES patient must lead to an extensive search for MEN 1. In patients without ZES, the initial step is to formally discard sporadic ECL-omas (i.e., those occurring in non-atrophic fundic mucosa) and also the poorly-differentiated neuroendocrine carcinomas that are not considered as ECL-omas and adenocarcinomas. The first part of this section will focus on conditions favoring ECL-oma development for both types of tumors.

Patients with the ZES

Conditions favoring ECL-oma development in the ZES. In patients with ZES, ECL-omas are observed almost exclusively in the small subgroup of patients in whom ZES is part of MEN 1 [1, 2, 4, 20]. This subgroup represents about 20 percent of the patients with ZES. In our published series of 48 patients with ZES in whom a histological analysis of the fundic mucosa was performed, five had fundic argyrophil carcinoid tumors [1]. All these patients had MEN 1 and none had the sporadic type of the disease. In this group, the prevalence of such tumors was very high (29.5 percent). In the recent series from the NIH published as an abstract form, five (4 percent) among 116 consecutive patients with ZES who underwent fundic biopsies had carcinoids [20]. All these tumors were observed in patients with MEN 1, giving a prevalence of 24 percent in this group [20]. To our knowledge, fundic argyrophil carcinoid tumors have been observed in three patients with sporadic ZES [21-23]. In the two published cases, carcinoids were single and microscopic [21, 22]. Both patients had severe disease with multiple distant metastases not related to the fundic carcinoid tumors. Microcarcinoids were discovered incidentally on total gastrectomy specimen [22] and on random biopsies [21]. Follow-up of our published patient [21] confirmed that, two years later, MEN 1 was still absent. Another point demonstrating that in our series ECL-omas are very frequent in patients with ZES and MEN 1 is given by the very large incidence of new ECL-omas in a series of 21 patients with ZES (initially free of ECL-omas) who were endoscopically followed under omeprazole therapy [24]. ECL-omas developed in three (43 percent) among the seven patients with MEN 1 and in no patients with sporadic ZES (Table 2). Carcinoids appeared after 29, 48 and 69 months of follow-up. In the four other patients with MEN 1 but without carcinoids, the median follow-up was 34.5 months (range 19-56), and in the 14 patients with sporadic ZES, it was 34.5 months (range 4-79) [24].

In one patient with ZES and MEN 1, it was shown that the two copies of the MEN 1 gene were inactivated [25]. Because MEN 1 gene is a tumor suppressor gene, these genetic events probably explain the major impact of MEN 1 on ECL-oma development. This probably also explains why ECL-omas are often multiple. To our knowledge, fundic argyrophil cell dysplasia has not been observed in patients with sporadic ZES, except in our patient with carcinoids in whom dysplasia was noted before the diagnosis of carcinoid has been performed [1, 21, 26]. The level of ECL cell density can be as high in patients with sporadic ZES as in those with ZES and MEN 1 [1, 27]. Therefore, it is most likely that there is no direct histogenetic link between fundic ECL cell hyperplasia and dysplasia/carcinoid [25, 26].

Clinical and endoscopical diagnosis of ECL-omas: To our knowledge, fundic ECL-omas do not give specific symptoms in patients with ZES. These tumors are discovered incidentally during endoscopy showing polypoid formations or diagnosed on random biopsies of a non-polypoid mucosa (microcarcinoids) or at examination of total gastrectomy specimen [1-3, 22, 28].

Table 1. Clinicopathological characteristics of 191 patients with fundic ECLomas collected in four European pathology departments (from Ref. [4]).

Type (n)	Female (%)	Mean age (yr)	High gastrin levels (%)	ECL cell hyperplasia in fundic mucosa (%)	Multiple ECLomas (%)	Maximal size <1 cm/<2 cm (%)	Maximal invasion mucosa/ submucosa (%)	Lymph nodes (%)	Liver metastases (%)	Tumor related death (%)
CAG-A	71	63	92	100	57	77/99	27/91	2	2	0
(n=152)	*(n=152)*	*(n=152)*	*(n=39)*	*(n=55)*	*(n=152)*	*(n=150)*	*(n=67)*	*(n=41)*	*(n=41)*	*(n=144)*
ZES	50	45	100	100	92	36/82	18/91	30	8	9
(n=12)	*(n=12)*	*(n=12)*	*(n=12)*	*(n=12)*	*(n=12)*	*(n=11)*	*(n=11)*	*(n=10)*	*(n=12)*	*(n=11)*
Sporadic	26	55	11[a]	6[a]	7	30/77	0/24	71	69	27
(n=27)	*(n=27)*	*(n=27)*	*(n=9)*	*(n=17)*	*(n=27)*	*(n=27)*	*(n=17)*	*(n=14)*	*(n=13)*	*(n=26)*

The number of patients in whom information about the studied parameters were available is indicated in italics below.
[a] This patient had a tumoral subpopulation of gastrin cells.

Table 2. Development of fundic argyrophil dysplasia and carcinoids in 21 ZES patients treated with omeprazole during a median period of three years (from Ref. [24]).

Patients	Fundic argyrophil cell dysplasia[a]		Fundic argyrophil carcinoids[a]	
	At time of first biopsies (n)	At time of last biopsies (n)	At time of first biopsies (n)	At time of last biopsies (n)
Sporadic (n=14)	0	0	0	0
MEN 1 (n=7)	1[b]	+1	0	+3

[a] According to Solcia et al. [7].
[b] In a fundic polyp. The patient further developed carcinoids.

In our series, the diagnosis of ECL-omas was always established after that of ZES [1]. No precise data in the literature have specifically concerned the conditions of carcinoid diagnosis in ZES. Because carcinoids have been found at examination of surgically-resected stomach specimen before the availability of potent antisecretory drugs or shortly after the initiation of such therapy, it is probable that ECL-omas can develop early in the course of ZES [1, 2].

Except MEN 1, no clinical condition seems to be associated with an increased risk in ECL-omas (Table 3) [1]. Sex-ratio of patients with ECL-omas is about 1 [1, 4]. Age at diagnosis is variable, as is duration of ZES [1]. Gastrin levels are high (up to 140 times the upper limit of normal), but one patient had low serum gastrin levels (twice this limit) [1]. Type and duration of antisecretory treatments seem to have no influence [1]. The only condition in which microscopic ECL-omas could be suspected is the presence of fundic argyrophil cell dysplasia on random biopsies [21, 24].

When macroscopic, ECL-omas are usually small (< 1 or 2 cm) and multiple (Tables 1 and 3) [1, 4]. At time of initial diagnosis, we observed a predominant localization just above the antro-fundic transitional zone [1]. Typically, tumors are umbilicated.

To our knowledge, no seric marker that could suggest the presence of ECL-omas has been tested in ZES. ECL-omas secrete chromogranin A [29], histamine [30] and alpha HCG [31]. Syversen et al. have suggested that serum chromogranin A levels in ZES reflect the ECL cell mass [29]. However, this marker has not been tested as a diagnostic tool of ECL-omas in ZES patients. Increased levels of alpha HCG in ZES seem to be related to the gastrinoma mass [32]. Therefore, it is probable that this marker is not useful for suspecting ECL-omas.

Patients with CAG-A

In patients without ZES, the first step is to affirm that the patient has CAG-A, in order to discard sporadic ECL-oma. The minimal investigations to be performed are: a) multiple biopsies (at least four) in the non-tumoral fundic mucosa (mucosa must be atrophic, argyrophil cell hyperplasia is most often present) and biopsies of any mucosal abnormality in order to discard other associated lesions (early adenocarcinoma, etc.); b) pentagastrin-acid output determination (achlorhydria must be present); and c) serum gastrin level measurement (hypergastrinemia is almost always present) and antral biopsies (standard staining, G-cell staining). When CAG-A is diagnosed, a search for pernicious anemia should be undertaken.

Conditions favoring ECL-oma development: In patients with CAG-A, there are no predictive signs of ECL-oma development. Serum gastrin levels are very high in CAG-A patients with ECL-omas and often higher, but not always, than in CAG-A patients with

Table 3. Characteristics of six personal published cases of ZES patients with fundic argyrophil carcinoid tumors at time of their detection (modified from Refs. [1] and [21]).

Sex-age (yr)	Men 1 (+/-)	ZES duration (yr)	Antisecretory treatment (duration)	Serum gastrin (pg/ml)	Fundic lesions
F-55	+	12	Anti-H2 (5 yr)	14000	100 polyps[a]
M-36	+	15	Anti-H2 (5.5 yr), then Om (3.5 yr)	4193	Several polyps[b]
M-36	+	2	Anti-H2 (2 yr)	2390	Microcarcinoids[c]
F-49	+	28	Anti-H2 (7.5 yr), then Om + SMS (4 yr)	4718	12 polyps[d]
M-52	+	8	Anti-H2 + P (6.5 yr), then Om (7.5 yr)	229	1 polyp[e]
F-69[f]	-	12	Anti-H2 (3 mo), then Om (1 yr)	520	1 microcarcinoid (0.65 mm)

Normal serum gastrin level: 100 pg/ml.
Anti-H2: H2-receptor antagonists; Om: omeprazole; P: pirenzepine; SMS: octreotide.
[a] Total gastrectomy three months later; maximal carcinoid size: 1 cm; 1 lymph node: Grimelius-positive and gastrin-negative.
[b] Total gastrectomy four years later (serum gastrin: 13883 pg/ml), hundreds of ECLomas, maximal carcinoid size: 4 cm.
[c] Discovered fortuitously on gastrectomy specimen performed for non-compliance to treatment.
[d] One fundic polyp (corresponding to argyrophil cell dysplasia) was removed at the end of anti-H2 treatment (serum gastrin: 1063 pg/ml).
[e] One year later: 3-4 polyps (serum gastrin: 500 pg/ml).
[f] This patient has bone and liver metastases from gastrinoma.

focal nodular hyperplasia without ECL-omas, with overlapping values between patients with and without carcinoids [5, 33, 34]. In a literature review, Cattan noted that, among 68 cases, 10 had gastrin levels between 4000 and 11000 pg/ml, 13 between 2000 and 4000 pg/ml, 18 between 1000 and 2000 pg/ml and 27 below 1000 pg/ml [35]. There were at least eight cases with gastrin levels below 500 pg/ml (i.e., 2.5-4 times the upper limit of normality that varies from 120 to 200 pg/ml in the different series [35]).

Age of patients presenting with ECL-omas is variable (from 15 to 88 years), but mean age is elevated (63 years) (Table 1) [4]. Sjöblom et al. have suggested that duration of pernicious anemia is longer in patients with ECL-omas than in patients without these tumors, all tumors being found in patients with more than five years disease duration [33]. However, evaluating the duration of pernicious anemia is difficult.

ECL-omas are more often observed in females than in males (Table 1) [4]. This might reflect the predominance of females among patients with pernicious anemia [6] or the influence of female sex on ECL cell proliferation. In patients with CAG-A, the influence of pernicious anemia on the degree of argyrophil cell hyperplasia is debated [6, 36]. In a literature review, 47 percent of ECL-omas (81 among 174 cases of CAG-A) occurred in patients with pernicious anemia [19]; therefore, it is not known whether pernicious anemia increases the risk of ECL-oma development in patients with CAG-A.

ECL-omas are often associated with an important linear or nodular ECL cell hyperplasia in the non-tumoral mucosa; however, the density of argyrophil cells was not significantly higher in patients with ECL-omas than in patients with nodular hyperplasia but without ECL-omas [12, 34]. In a patient without macroscopic ECL-oma and with argyrophil cell dysplasia, multiple fundic biopsies should be repeated to recognize microcarcinoids.

Diagnosis of ECL-omas in patients with CAG-A: These tumors are generally discovered incidentally because of non-specific symptoms (dyspepsia, nausea, pain, etc.) or on screening endoscopy [5, 6, 8, 10, 13, 14, 16, 18]. They never give rise to carcinoid syndrome nor to atypical carcinoid syndrome. Anemia due to iron deficiency or hemorrhage has been described [5, 14]. An old series showed that carcinoids can be detected before, at time, or after diagnosis of CAG-A [10]. However, recent series with systematic endoscopy showed that the rate of detection of carcinoids is higher at the first endoscopy (1.25 percent to 7.8 percent) and lower (0 percent to 3.6 percent) during the follow-up of those patients without carcinoids at the first endoscopy [6, 13, 37-40]. Roucayrol and Cattan also showed that no carcinoid developed in 19 patients followed for a mean time of 69 months (11-170 months) [41]. This suggests, as for other preneoplastic conditions, such as Barret's esophagus or liver cirrhosis, that the first screening examination is the most important in terms of detection rate.

Endoscopical aspects of ECL-omas in patients with CAG-A are similar to those of ECL-omas noted in patients with ZES, although they are less often multiple and more often of small size (Table 1). Most often, polypoid lesions in the stomach of patients with pernicious anemia do not correspond to carcinoids. In a series of 80 patients, 18 had antral and/or fundic polyps [13]. Among the 16 patients with available histological analysis of the polyps, eight (50 percent) had hyperplastic polyps, and one patient only had multiple carcinoids [13]. The polyps in the other patients corresponded to hyperplasia and severe dysplasia (n = 1), granulation tissue (n = 1), mucosa with atrophy (n = 3), mild dysplasia (n = 1) and inflammation (n = 1) [13]. In another series, 60 among 123 patients (49 percent) had one or several polypoid lesions [37]. They corresponded to benign hyperplastic and/or inflammatory gastric polyps (mostly in the body/corpus) in 52 patients (87 percent), to carcinoids in five, to adenoma (n = 1) and to early adenocarcinoma (n = 2) [37]. Therefore, all polyps, or the highest possible number, should be resected for full histological analysis, mainly in order to diagnose adenocarcinoma.

The serum or plasma levels of the following peptides were not increased in patients with ECL-omas: calcitonin, parathyroid hormone, glucagon, motilin and somatostatin [6]. To our knowledge, serum chromogranin A has not been measured in these patients.

HISTOLOGICAL DIAGNOSIS OF ECL-OMAS IN PATIENTS WITH ZES OR CAG-A

ECL-omas observed in patients with ZES or with CAG-A have similar morphological aspects that have been well described by several authors [1, 2, 6, 7, 11, 19]. Tumors are well-differentiated, argyrophil, and immunoreactive for chromogranin A, synaptophysin and neuron specific enolase. Immunoreactivity for peptides is generally negative or only scattered cells are positive. No other fundic carcinoid tumors than ECL-omas have these morphological characteristics. If possible, and if it is necessary, the conclusive diagnosis of ECL cell tumor is done by the ultrastructural examination of the polyps that shows that most tumoral cells correspond to ECL cells. Tumoral ECL cells are well recognized by their granules, either typical, containing vesicular electron dense granules, or atypical, with non-vesicular granules displaying a coarsely granular structure. Other tumoral cell types can be present (EC, X, P/D1, A like). Routine detection of histamine in the tumors is difficult.

TREATMENT OF ECL-OMAS

Treatment of ECL-omas depends on their natural history and on the morbidity and mortality directly related to the tumors themselves and the applied therapies. Treatment modalities are largely debated in both conditions, except for tumors measuring less than 1 cm.

Patients with ZES

Although very few ECL-omas have been published in patients with ZES, the benign evolution of these tumors seems to be the rule [4, 19]. Metastases to local lymph nodes have been noted in three of 10 cases in the largest series and distant metastases in one of these three patients [4]. In a compilation of cases from literature review by the same authors, only three among 27 cases had lymph node metastases [19]. One patient with ECL-omas and liver metastases died from its metastases (Table 1) [4]. To our knowledge, this is the only case with ECL-oma-related mortality. It must be emphasized that the origin of metastases is very difficult to ascertain in these patients. Endocrine lymph node metastases are very frequent in patients with ZES and MEN 1, and liver metastases develop in about 10 percent of them [42, 43]. The only way to discriminate metastases of ECL-omas from metastases of gastrinomas or of other types of endocrine tumors is to perform ultrastructural analysis or *in situ* hybridization of the resected lymph nodes or liver metastases when immunohistochemistry using peptide antibodies is negative [44]. For example, negative immunohistochemistry using gastrin antibodies does not rule out the diagnosis of metastases from gastrinoma. To our knowledge, this has not been performed in the above-mentioned cases. Therefore, all cases with metastases must be cautiously discussed. Two of our patients with ZES-MEN 1 and ECL-omas further developed distant metastases (unpublished data), but there is no formal argument to attribute metastases to ECL-omas. One developed gastrin-immunoreactive liver metastases five years after total gastrectomy for multiple ECL-omas, and the other developed liver metastases not immunoreactive to gastrin antibodies and also multiple pulmonary nodules (not biopsied) two years after the diagnosis of one small ECL-oma. Another patient already had multiple pulmonary nodules several years before the diagnosis of ECL-omas was done.

Data concerning the evolution of size and number of ECL-omas during follow-up are sparse. In our experience, carcinoids slowly increased in number in the three patients not treated initially by total gastrectomy. Especially, one patient developed hundreds of tumors, which size reached 3-4 cm (Table 3) [1]. It must be also noted that the evolution in number and size is extremely difficult to assess endoscopically in those patients with enlarged gastric folds.

Because the number of published patients is very small, metastases are very rare and there are no clear data on tumor evolution, it is currently not possible to evaluate the relationship between any morphological characteristic, especially the depth of gastric involvement, and prognosis that would help therapeutic decisions. Therefore, it is not known whether endoscopic ultrasonography, which is accurate for demonstrating submucosal or deeper gastric wall involvement or lymph node involvement [45], has any interest for deciding treatment modality.

Treatment indications for ECL-omas developing in patients with ZES are largely unknown. Treatment modalities include total gastrectomy, surgical resection of the tumors, endoscopic polypectomy, somatostatin analogues and survey. Most patients with ZES and MEN 1 have multiple endocrine tumors (gastrinomas and other endocrine types) in the duodenal wall and pancreas. Therefore, patients with ZES and MEN 1 are almost never cured by surgery [46, 47], if performed, and the fundic mucosa of these patients will be submitted to gastrin stimulation for life. Furthermore, ECL-omas are generally multicentric, and some have tendency to increase in number. Therefore, total

gastrectomy might be the best theoretical way to eliminate the tumors. The prognosis of ZES and MEN 1 essentially depends on the presence of liver metastases [42, 46]. The prognosis of patients without liver metastases at time of ZES diagnosis is excellent [42], 92 percent at 10 years in our recent experience [43]. Total gastrectomy could induce a higher morbidity and mortality than ECL-omas themselves and, furthermore, would limit the possibility of further duodenal or pancreatic resection, which might be necessary, for example, if insulinoma or a large tumor develops. Especially, duodenopancreatectomy is contraindicated in patients with previous gastrectomy. In several patients, including two of our series, total gastrectomy was performed because of hundreds of ECL-omas [1, 28]. In the first case, the decision to perform total gastrectomy was taken because no specific guidelines were available for accurate treatment at that time [28]. In the second case, the decision to perform total gastrectomy was taken because carcinoids were continuously increasing in number and size, and there was no remaining normal fundic mucosa. However, it is not known whether this attitude improved survival. Especially, as already mentioned in the latter patient in whom a non-curative left pancreatectomy had been performed earlier, liver metastases of gastrinomas developed five years later. The decision to perform total gastrectomy must take into account the other prognostic factors related to ZES and MEN 1. When total gastrectomy is decided, the surgeon should also resect duodenal gastrinomas and enucleate pancreatic tumors, if this does not significantly increase morbidity and mortality.

With the exception of the very rare patients with very large tumors (up to 10 cm), as described by Rindi et al. [4], or perhaps with tumors that extend beneath submucosa at endoscopic ultrasonography examination, single or small multiple ECL-omas are probably at best treated by endoscopic polypectomy followed by regular endoscopic survey.

Recent data in animals and in patients with ZES or CAG-A suggest that somatostatin analogues may have antiproliferative properties on fundic endocrine cells and ECL cells [48-54]. ECL cells and ECL-omas bear somatostatin receptors [55, 56]. ECL-omas can be visualized using Octreoscan scintigraphy [57]. In our unpublished experience, the fundic carcinoid uptake is often diffuse and not as high as for other endocrine tumors. The antitumoral properties of somatostatin analogues on ECL-omas in ZES has not been established [57]. In one patient, ECL-omas occurred and developed despite octreotide therapy [1]. Therefore, at the moment, it cannot be recommended to use somatostatin analogues with the only aim to treat ECL-omas. Similarly, somatostatin analogues have not been tested in the intention to reduce recurrence after endoscopic or surgical resection of ECL-omas.

Finally, there are no definite modalities for surveying the fundic mucosa of patients with ZES. In our department, endoscopy is performed yearly in all patients with the ZES (sporadic and MEN 1) in particular for ECL-omas detection. At each endoscopy, four to five fundic biopsies are done systematically. Grimelius staining is used to visualize argyrophil cells. In patients with ECL-omas, the survey is similar.

Treatment of ECL-omas in patients with CAG-A

More data exist about ECL-omas treatment in patients with CAG-A. Local lymph node involvement should be screened by endoscopic ultrasonography and distant metastases by CT scan or magnetic resonance imaging. Octreoscan scintigraphy has not yet been evaluated in this peculiar situation. Lymph node involvement and liver metastases are very rare, 2 percent in the largest series, without any ECL-oma-related death (Table 1) [4]. From a literature review, it has been shown that lymph node metastases were present in 17 (7.6 percent) among 224 patients and distant metastases in four (1.8 percent) patients [19]. In another literature review, lymph nodes were present in 3.2 percent of 156 patients and distant metastases in 1.3 percent [15]. Metastatic rates were higher in the previous series published by Carney et al.: eight (13 percent) patients had lymph node metastases

and three (5 percent) had liver metastases, with one (1.6 percent) related-death [10], but ulterior series showed that the related death was nil [4, 11, 15, 16, 37-40]. Life expectancy in patients with ECL-omas has been shown to be similar to that of an age-corrected control population [14, 15]. It must be emphasized that due to the relatively old age of these patients, mortality due to other causes than ECL-omas is very high during follow-up, 14 percent to 27 percent [4, 10, 14, 15, 37].

Although precise data are lacking, it is generally accepted that tumors measuring less than 1 cm do not metastasize, and tumors measuring more than 1 cm are at risk to give metastases [8, 27, 35, 58-60]. The major therapeutic problem is to define, among patients with tumors measuring more than 1 cm, the rare patients who are at risk for development of lymph node or liver metastases (i.e., to define the patients in whom the surgical resection of the tumors is mandatory and those who can be treated endoscopically). Data concerning the relationship between gastric wall depth involvement and metastases are sparse. In two series containing four patients with tumors measuring 1.0, 1.0, 1.2 and 1.5 cm, respectively, and metastases, no data concerning wall infiltration were given [4, 8]. Infiltration of the muscularis mucosa was noted in two patients with 2 cm- and 3 cm-carcinoids and metastases [59]. Among five cases with carcinoids measuring more than 1 cm (up to 1.7 cm), three patients had tumors that infiltrated into the muscularis mucosa, with invasion of the lymph vessels in two, but none had metastases [15]. By contrast, in this series, the maximal infiltration depth of 83 tumors measuring less than 1 cm was limited to the submucosa [15]. In a series of 14 patients, the only patient with lymph node metastases had serosal involvement and multiple carcinoids (one reaching 2 cm), none of the other 13 patients had carcinoids measuring more than 1 cm [5, 61]. The maximal depth involvement was limited to the submucosa in five studied patients [5, 61].

Spontaneous regression of ECL-omas measuring more than 1 cm (up to 1.5 cm) has been observed [62]. Antrectomy, leading to normalization of serum gastrin levels, also induced total or partial regression of ECL-omas [8, 59, 60]. Four studied patients had carcinoids measuring 1.2 cm or more (up to 3 cm) [8, 59, 60], and three of them had lymph node or liver metastases that were also resected [8, 59]. Finally, after surgical resection without antrectomy or after endoscopic polypectomy, the recurrence rate seems to be low [8, 10, 35, 37, 39, 58].

Treatment protocols vary [4, 8, 15, 35, 58, 63]. The clinical condition of the patients must be considered, because many are old and will die for other reasons. All authors agree to treat endoscopically tumors measuring less than 1 cm. Owing to the general benign evolution, surgery could be limited to patients with tumors larger than 1 cm in whom endoscopic ultrasonography shows infiltration of the muscularis mucosa or lymph node involvement. To our knowledge, only a few patients with fundic carcinoids have been studied by endoscopic ultrasonography [45]. Its accuracy for determining gastric wall depth involvement and local lymph node involvement is good [45]. Whether local surgical excision or antrectomy with surgical excision of the tumors are the best surgical treatments is not clearly established. The choice between these two modalities should rely on the number and size of the tumors. Indication for total gastrectomy is probably very rare.

Concerning survey, we propose: a) to always perform a first endoscopy with biopsies in all patients with CAG-A whatever the age; b) to stop survey in patients older than 70 years of age, unless adenoma, adenocarcinoma or severe dysplasia are present; c) in patients under 70 years, to survey (endoscopy with multiple biopsies) every three years those without ECL-omas and yearly those with ECL-omas.

CONCLUSIONS

After sporadic ECL-omas or other types of malignant tumors have been formally discarded, tumors less than 1 cm should be treated endoscopically, in both patients with ZES or CAG-A. For bigger tumors, therapeutic decisions should at best be discussed patient by patient. The various parameters that should be taken into account are: the clinical condition of the patient, the number and size of the tumors, the results of endoscopic ultrasonography, especially gastric wall depth and lymph node involvement, and also the results of the previous treatments. Treatment-related morbidity and mortality should be less than that of the ECL-omas themselves. Multicentric studies, including endoscopic ultrasonography, aiming to evaluate the different therapeutic modalities should be undertaken.

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