Is Gastrinoma a Medical Disease?

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Zollinger-Ellison syndrome (ZES) is a rare disease. Its management concerns symptoms related to the gastric acid overproduction that characterizes the syndrome and to the gastrin-producing tumor(s) usually located in the duodenal wall and/or the endocrine pancreas. Acid hypersecretion is now controlled by the use of powerful antisecretory agents. Management of the malignant process(es) has become the primary goal of modern strategy: it aims first at curing the disease and second at prolonging patient survival by prevention of hepatic metastasis. In patients with the sporadic form of the disease and without liver metastases, it is currently possible to localize and to surgically remove the endocrine tumor(s). This progress has been made feasible by refinements in modern medical imaging. At present, however, disease cure, even in the most favorable conditions, is not be greater than 30 to 50 percent at five years. In patients with ZES integrated in the context of multiple endocrine neoplasia type I, disease cure rate is extremely low, although occasional patient survival can be as good or even better than in the sporadic group. Disseminated malignancy (liver and/or extra-abdominal lymph nodes or bone localization) remains the principal determinant of early death. Surgical treatment is usually precluded in such cases. Liver transplantation has not been successful in these patients.

INTRODUCTION

The use of powerful acid antisecretory agents, first H_2 receptor antagonists (H_2RAs)[e], then proton pump inhibitors (PPIs), in the last two decades has profoundly facilitated the management of the Zollinger-Ellison syndrome (ZES). Patients are no longer faced with the dreadful consequences of gastric acid overproduction, often treated by total gastrectomy, and care is now primarily focused on management of the malignant process [1, 2, 3].

Initially, however, management strategies were difficult to assess: patient series were small, as is the case for rare diseases. Patient follow-up was too short to provide a clear appreciation of the natural history of the disease, and medical technology (especially medical imaging) was still in its early stage of development. However, by the late 1980s the respective roles of medical and surgical management of the disease appeared increasingly clear [4, 5, 6]. Medical treatment aimed at controlling acid overproduction and related-symptoms, at slowing, even in some cases at reducing the patient's chances of a fatal outcome due to liver metastases (when non-resectable), and eventually at antagonizing the gastrin-induced overproliferation of gastric fundic enterochromaffin-like (ECL) cells [7, 8]. Surgery aimed at attempting to cure the disease in favorable conditions by tumor removal and to prevent metachronous liver metastases development [1, 9, 10, 11]. Surgery sometimes, also aimed at eradication of ECL-omas [10].

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[e]Abbreviations: GRESZE, Groupe de Recherche et d'Étude sur le syndrome de Zollinger-Ellison; ZES, Zollinger-Ellison syndrome; H_2RA, H_2 receptor antagonist; PPI, proton pump inhibitor; ECL, enterochromaffin-like; MEN-I, multiple endocrine neoplasia type I; PCNA, proliferating cell nuclear antigen; STZ, streptozotocin; 5FU, 5 fluoro-uracil.

It soon appeared, however, that gastrinoma management was more complex than initially anticipated. Understanding of the oncologic process remains incomplete. We are not able to explain why some patients, even with liver metastases, undergo a relatively indolent course, or why metastases to lymph nodes on the one hand and to liver on the other hand, although both indicate malignancy, behave differently, only the latter influencing patient survival.

Indications and contraindications of surgery remained, therefore, highly controversial with firm opponents to surgery arguing that, except in very rare and selected cases [12], there is a minute chance of a long-term satisfactory cure rate (15 percent according to Hirschowitz's experience and a review of 15 series by Ellison et al. [13]). On the contrary, many other groups, including the NIH group at Bethesda and our group in Paris, on the basis of the results of earlier experience, advocated explorative laparotomy in the sporadic form of the disease, except in patients with diffuse liver metastases. The NIH group extended this indication even to ZES patients with multiple endocrine neoplasia type I (MEN-1) [3], provided an imageable tumor was found. We did not adopt this recommendation, as it was not supported by the results of a long-term follow-up of 45 consecutive patients followed in our institution [14, 15].

Several recent reports on large series of patients have provided very significant information on two relevant factors: 1) ZES patient survival depends essentially on the presence of distant metastases, which, in turn, seems to depend upon the size and the localization of the primary tumor(s), and 2) disease cure-rate by surgery seems to depend upon the clinical condition (with or without MEN-1) and the possibility of removal of the primary tumor as completely as possible [3]. Recent refinements in medical imaging, both pre- and intra-operatively, have been of great help to the surgeons. Further assessment of new technology is in progress, namely of intra-operative isotopic detection of the tumors using hand-held probes after ^{111}In-Pentetreotide administration. Additive information has been also sought for from the use of biological markers aiming at predicting the biological behavior of the tumor.

Tumor proliferation markers such as proliferating cell nuclear antigen (PCNA) or quantitative DNA analysis using flow cytometry have been performed by several groups on endocrine tumors of the pancreas [16, 17]. Results of PCNA studies indicated that the lower the frequency of cells expressing the antigen within the tumor, the better was the survival [16]. Similarly, a close statistical correlation has been found between the degree of quantitative abnormalities of primary tumor DNA content and tumor spread [17]. The prognostic significance of the CD44 expression in gastrinoma (i.e., restricted tumor spread, usually to lymph-nodes in CD44-positive tumors) in contrast to the CD44-negative tumors, which are more prone to be locally invasive and/or metastasize to the liver [18] has not been confirmed in a group of 10 gastrinoma patients studied by our group (unpublished observations).

DETERMINANTS OF SURVIVAL IN PATIENTS WITH ZOLLINGER-ELLISON SYNDROME.

Liver metastases are present in about 25 percent of ZES patients [1, 2, 3, 13]. Although individual patients with long-term survival have been observed in most centers caring for ZES patients, it is commonly observed that less than half of the ZES patients with liver metastases survive beyond five years [1, 2, 13, 19, 20] and less than 30 percent beyond 10 years [20]: the median survival at five years ranges from 17 to 53 percent. In contradistinction to liver metastases, the presence of lymph-node metastases, although as prevalent as liver metastases, does not seem to influence survival rate in ZES patients [1, 9, 20, 21].

It is not clearly established that chemotherapy or other medical therapies increase survival since no comparisons of randomized treatments against placebo have been performed.

In sporadic ZES cases, the determinants affecting the development of hepatic metastases clearly appear to be the size and the location of the primary tumor [13, 20]. Patients presenting with hepatic metastases have larger primary tumors than patients without metastases, while no such relationship exists between primary tumor size and development of lymph-nodes metastases [20]. In the NIH series, indeed, in patients harboring tumor(s) of more than 3 cm diameter, usually located in the pancreas, liver metastases were noted in 61 percent of the cases [20]. Pancreatic tumors, usually large, are associated with liver metastases in 52 percent of sporadic cases; seven percent of these patients have both lymph node and liver involvement [20]. In contrast, duodenal tumors, which usually are of small size, are associated with liver metastases in only five percent of the cases, while they are associated with regional lymph node involvement in the same proportion as in case of pancreatic primary(ies) [20].

These very important findings seem to be in keeping with the anatomical stratification proposed by Howard et al. [22], which sharply separates the patients having primary tumors located on the right of the superior mesenteric artery, within the so-called gastrinoma triangle, from those patients having pancreatic tumors to the left of the superior mesenteric artery; in the latter group, liver metastases were much more prevalent (56 percent of patients) and the actuarial survival was poor (less than 10 percent at 10 years).

EXPLORATIVE LAPAROTOMY IN PATIENTS WITHOUT DISTANT METASTASES

An oncological approach in the surgical management of tumors in patients with sporadic ZES has been vigorously suggested by several groups [1, 4, 23], and discussed by others [24].

Most encouraging results supporting such an approach have been suggested recently by the retrospective analysis of the clinical outcome of 98 ZES patients (including 15 MEN-1-ZES patients without liver metastases at first presentation) who submitted systematically to explorative laparotomy as compared to 26 patients, including 9 patients with MEN-1, who for diverse reasons did not undergo surgery [11]. Among the 98 patients with surgery, a tumor mass was found in 83 and removed without operative mortality. During follow-up (mean duration: 6.3 years ± 0.4; range: 0.7 to 16.8), liver metastases developed in only 3.1 percent of the patients who underwent surgery as compared to 23 percent of the patients who did not undergo surgery (p < .003). Disease-specific actuarial survival was 100 percent at 15 years in the group in whom surgery was performed. In contrast, two deaths related to progression of liver metastases, were noted in the non-operated group. Although the difference in survival between these two groups of patients did not reach statistical significance, these findings are of the utmost importance, suggesting a high benefit in terms of prevention of hepatic metastases. This approach clearly deserves further testing by prospective evaluation.

DETERMINANTS OF DISEASE-CURE BY SURGERY

In contrast to sporadic ZES patients, in whom it appears reasonable to attempt tumor eradication in the absence of non-resectable liver involvement, in patients with MEN-1-ZES exploratory laparotomy is seldom indicated (other than for symptomatic associated-endocrine secretion), as the chance of a definite cure by surgery is very low. Parathyroid surgery is often indicated and should take place before any form of abdominal surgery.

Indeed, in this clinical setting, anatomical distribution and tumor morphology are different from sporadic cases, being usually multiple, disseminated throughout the

duodenopancreatic area, of small size, and perhaps associated with endocrine cell hyperplasia. Several types of pancreatic endocrine cell proliferation may coexist in MEN-1 patients. One of the most puzzling situations has been the association of gastrin and insulin overproduction within pancreatic tumors as noted in 13 percent of cases of ZES with MEN-1 in our experience. Figure 1 represents the basic flow chart adopted at the Bichat-Claude Bernard Hospital for the detection of MEN-1. The oral calcium tolerance test has been evaluated prospectively in our institution in 28 patients with normal fasting total plasma calcium to detect primary hyperparathyroidism [25].

Fasting total and ionized calcium and PTH 1-84 levels were measured, and nephrogenous cAMP was calculated during a two-hour baseline period and during a two-hour period after the oral administration of 1 g inorganic calcium. The diagnosis of normocalcemic primary hyperparathyroidism was established when, during the oral calcium tolerance test, plasma ionized calcium concentration increased to supranormal values and only a minimal reduction in plasma PTH concentration and nephrogenous cAMP excretion was observed. Among the patients with normal fasting total calcium levels, the test established the diagnosis of normocalcemic primary hyperparathyroidism in five (20 percent) and of hypercalcemic primary hyperparathyroidism in three patients. In nine percent of the patients with apparently sporadic type of the ZES (no other endocrinopathy and no familial disease), normocalcemic primary hyperparathyroidism was the sole manifestation of MEN-1. Thus, in this prospective study, a diagnosis of normocalcemic primary hyperparathyroidism was established in four out of 23 ZES patients with normal basal serum calcium levels [25].

The management strategy in patients with ZES-MEN-I that has been adopted at the Bichat Hospital derives from the experience gained with the aggressive surgical approach that was applied to these patients from 1959 to 1981 [14, 15]. As illustrated in Figure 2, 36 patients underwent some form of gastrinoma surgery. After surgery 22 patients were judged tumor-free and seven had residual tumor. On subsequent follow-up, only one remained, apparently cured after 96 months; in all other cases, persisting clinical or biologic abnormalities have been noted, and overt tumor(s) recurrence has been documented.

Clinical assessment :

- Neuroglycopenia symptoms | suggesting associated
                            | insulinoma or
- Diabetes and skin lesions | glucagonomas

- Nephrolithiasis, | suggesting primary
  polyuro-polydypsia | hyperparathyroidism

- Family history of peptic ulcer disease
  or endocrine diseases

- Genetic testing when appropriate

Laboratory and Imagery Screening :

- Parathyroid function
  . serum Ca and phosphorus level (3 days)
  . urinary Ca and phosphorus outputs (3 days)
  . urinary cyclic AMP output if necessary
  . serum PTH
  . oral calcium tolerance test if necessary
- Pituitary function
  . serum prolactin levels (3 days)
  . sella turcica CT scan or MNR
- Adrenals
  . serum K
  . serum free cortisol at 8 am and 6 pm
  . urinary free cortisol output
  . adrenal CT scan
- Fasting blood glucose
  . insulin
  . C-peptide
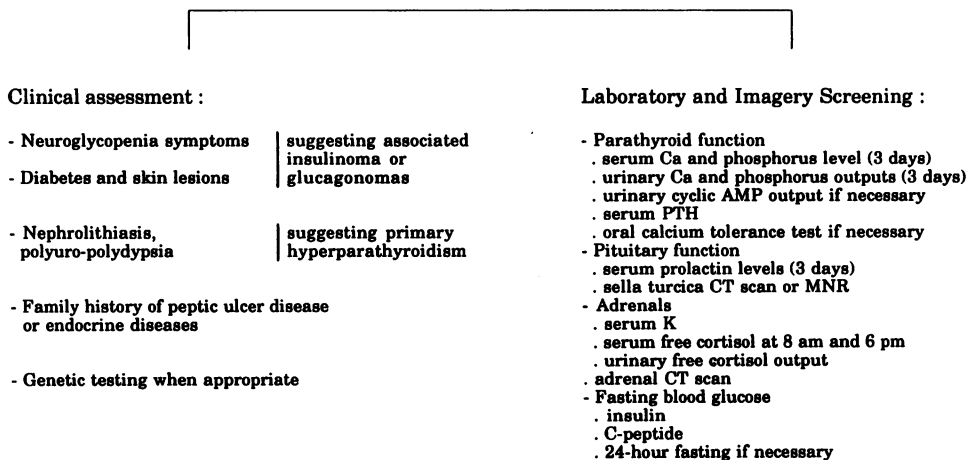 . 24-hour fasting if necessary

Figure 1. Work-up schedule of patients with Zollinger-Ellison syndrome (ZES for the detection of multiple endocrine neoplasia type I (MEN I) (Bichat-Claude Bernard Hospital).

Table 1. Main demographic, clinical and evolutive features of 45 cases of ZES-MEN I compared to 127 sporadic ZES followed at Hospital Bichat-Claude Bernard (1959-1989).[a]

	ZES-MEN I (n = 45)	Sporadic ZES (n = 127)
Percent patients	26	74
Sex ratio male/female	1.8	2.3
Malignancy percent	47	55
• Liver metastasis	31	30
• Other metastasis[b]	16	25
Death toll[a,c]		
• Total (%)	38	44
• Related to LM (%)	12	36

[a]Median follow-up 95 months (17-278); [b]predominantly lymph nodes; [c]death toll related to liver metastases progression tended to be less in ZES-MEN I (p = 0.11).

Furthermore, in seven patients, metachronous liver metastases developed after a median delay of 88.5 months (range six to 108 months). Only two patients in this group had a gastrinoma with a diameter larger than 3 cm at surgery. It is worth noting that all but one of these operated patients were apparently free of tumor after surgical exploration. The latter findings, rather than the relatively high death rate during the first half of our experience (1959-1974, i.e., before the advent of H_2RA), reassures us in the interventionist strategy that we adopted.
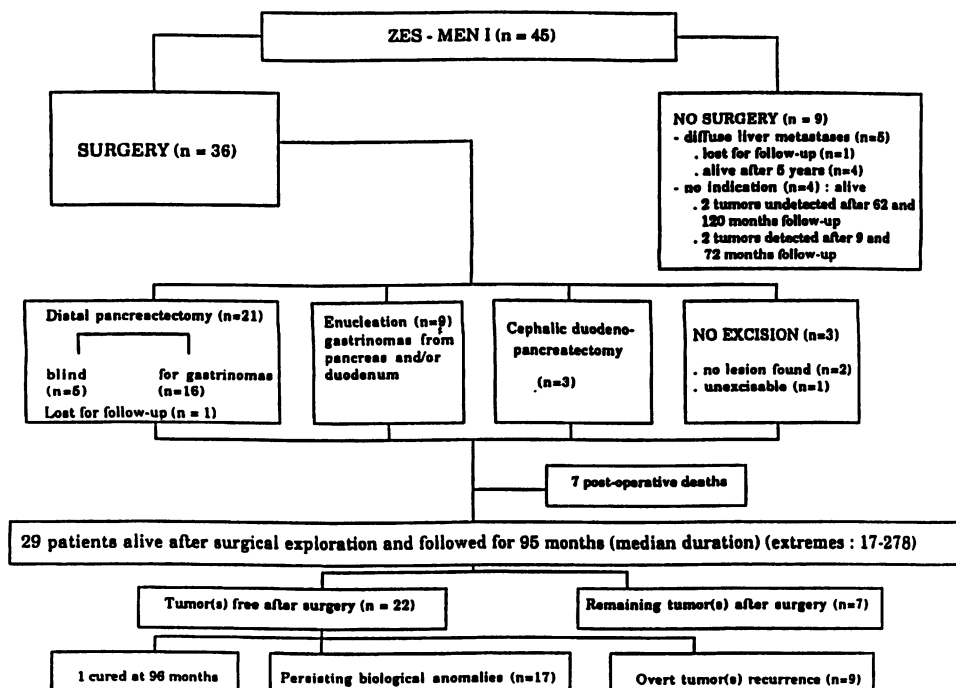

Figure 2. Experience gained with the surgical management and follow-up of 45 patients with Zollinger-Ellison syndrome (ZES) associated with multiple endocrine neoplasia type I (ZES-MEN I) at Hospital Bichat. Bichat ZES series 1959-1989: 172 patients.

Table 2. Comparative clinical characteristics of 185 ZES patients according to their benign or malignant course.

	Clinical course	
Characteristics	Benign Percent patients: 76	Malignant Percent patients: 24
Present with liver metastases (%)	0	19
Develop liver metastases (%)	0	5
MEN I (initial evaluation) (%)	21	6 (uncommon)
Time from onset to diagnosis (years)	Long (mean 5.9)	Shorter 2.7 (mean)
Size of primary tumor (%)	small ≤ 1	Large > 3
Location of primary tumor (%)	66, primarily duodenum	92, primarily pancreatic
Survival at ten years	96, excellent	30, poor

*i.e., no liver metastasis development. N.B. All patients without MEN I and liver metastases underwent surgery. From Weber et al. [20] with the permission of the Editor.

Actuarial survival, at 15 years, in the ZES-MEN-1 patients followed in our institution was 63 percent, thus slightly better than in sporadic cases (45 percent) [26]. In addition, when the mortalities for both categories of ZES were compared (Table 1), a trend in favor of the ZES-MEN I group was noticeable in terms of death related to liver metastatic progression. When deaths unrelated to liver metastases were excluded from our evaluation, survival rate after a median follow-up of 95 months (range: 17 to 278) for the whole population was 78 percent, a figure close to the one reported by Weber et al. [20]. It is possible, as suggested by the prospective long-term study of the large group of patients studied at the NIH by Weber et al. [20], that there are two forms of ZES with strikingly different clinical outcomes. A comparison of the main clinical characteristics of these two groups of patients is illustrated in Table 2.

Will such *a posteriori* stratification and its consequent ZES management-guidelines benefit the patients not only with regard to survival but also for disease cure? According to results reviewed by Fraker and Norton [23], and our own experience up to 1985 [1], the chance of a definite cure by tumor removal in those patients without distant metastases and without MEN-1 approximated 18 to 20 percent in patients with pancreatic gastrinomas, and up to 40 to 65 percent in those patients with extra-pancreatic gastrinomas (i.e., tumors located in the duodenal or the gastric wall, isolated lymph node metastasis) [1]. Altogether in the NIH experience, however, the cure rate at five years appears to be about 30 percent, although this rate amounted to 58 percent at three months [27]. In the group

Table 3. Requirements for efficacious surgical tumor eradication in ZES patients: Present Hospital Bichat-Claude Bernard strategy.

- MEN I exclusion:
    - Thorough iterative endocrinological assessment
    - Oral calcium tolerance test (I^{ary} HPT early diagnosis)
- Liver, bone and other site metastases exclusion (surgery contraindications)
- Precise tumor(s) localization
    - Conventional imagery (MNR and CTS)
    - Upper digestive endoscopy
    - EUS (for pancreas, duodenum and peripancreatic lymph nodes)
    - SRS: preoperative (interest for patient management)

MNR, magnetic nuclear resonance; CTS, computerized tomography scan;
EUS, endoscopic ultrasonography; SRS, somatostatin-receptors scintigraphy.

Table 4. Results of endoscopic ultrasonography (EUS), upper gastrointestinal endoscopy (UGI), computerized tomography (CTscan), for diagnosis of duodenal, pancreatic and lymph node gastrinomas in 22 ZES patients followed at Hospitals Beaujon (Clichy), Bichat-Claude Bernard (Paris) and Reims.

	True +	True -	False +	False -	Sensitivity (%)	Specificity (%)
Duodenal wall tumors						
EUS	5[a]	12	0	5	50	100
UGI endoscopy	4[b]	12[c]	0	6	40	100
CT scan	0	12	0	10	0	—
Pancreatic tumors						
EUS	3	18	0	1	75	100
CT scan	1	18	0	3	25	100
Lymph node tumors						
EUS	5	12	2	3	62.5	86
CT scan	0	14	0	8	0	100

[a]Two were not seen by upper gastrointestinal endoscopy; [b]one was not seen by EUS; [c]includes biopsy-negative nodules of duodenal mucosa, 2 to 4 mm in diameter in two patients. From Ruszniewski et al. [30].

of 42 patients, however, who were found to be disease-free after surgery as defined by no evidence of tumor on imaging studies, normal fasting gastrin level, and negative provocative test, the proportion of disease-free patients amounted to 62 percent at five years and a little less than 50 percent at nine years [27].

It is essential to emphasize that comparison of the survival curves in patients who underwent surgical exploration for possible complete tumor resection at the NIH [10, 20] showed no significant difference whether the patients were rendered disease-free or not.

PRESENT STRATEGY FOR ZES MANAGEMENT AT THE BICHAT-CLAUDE BERNARD INSTITUTION

The policy that has been presently adopted at the Bichat-Claude Bernard Hospital has been outlined in Table 3. It emphasizes the necessity before considering surgery in ZES patients: 1) to exclude the presence of MEN-1; 2) to eliminate the presence of distant metastatic spread; and 3) to make the strongest efforts at precise localization of the primary tumor(s). Modern medical imaging (i.e., endoscopic ultrasonography and somatostatin-receptor scintigraphy using ^{111}In-Pentetreotide) are of the greatest help as illustrated in Tables 4 and 5 [29, 30, 31]. As shown in Tables 5 and 6, somatostatin-recep-

Table 5. Interest of somatostatin scintigraphy in ZES patients. Results of prospective studies by NIH [31] and Hospital Bichat-Claude Bernard (1993 to 1995) [32, 33].

	NIH 1995* (n = 46)	Bichat 1995 (n = 21**, n = 68***)
In-tumor localization SE (percent)		
- Duodeno-pancreatic tumors*	54[†]	58
- Hepatic tumors	100	100
Patient management (percent)**	47	41

From: *Gibril et al. [31]: [†]calculation from available data in the abstract; **Cadiot et al. [32]; ***Bonnaud et al. [33].

Table 6. French experience with liver transplantation for metastases for neuroendocrine tumors (1989-1994) [43].

Actuarial survival[a]	One year	Two years	Five years
Carcinoids (n = 14)	78%	78%	78%
Other NET (n = 14)	28%	9%	—

tor scintigraphy is slightly less sensitive than ultrasonography in detection of primaries in the duodeno-pancreatic area. However both techniques are, in our experience, complementary since each one can reveal tumor masses undetected by the other [29, 32]. Concerning the detection of extrapancreatic gastrinoma, for instance, the combination of ultrasonography and somatostatin-receptor scintigraphy yielded positive results in 90 percent of our patients [32]. In addition to tumor localization, somatostatin-receptor scintigraphy has been evaluated at both the NIH and our institution in terms of patient management guidance, as shown in Table 5. More than 40 percent of the patients benefited from this major technological addition. From our experience, now including 78 patients with proven gastrinomas, somatostatin-receptor scintigraphy should be included in primary investigation of patients with biological diagnosis of gastrinoma and in selecting patients eligible for a curative surgery.

ROLE OF MEDICAL MANAGEMENT IN PATIENTS
WITH SECONDARY MALIGNANCY

Various therapeutic tools for liver metastases have been proposed, since surgery is rarely curative, except in some selected cases and in very specialized surgical centers [3, 34]. The experience of two surgical groups indicates that extensive resection including major hepatic resection is feasible, safe and can be repeated. Clinical outcome after hepatic resection, compared to the natural history of these tumors, demonstrates that this procedure is valuable in terms of symptoms palliation and prolongation of survival, provided a thorough selection of candidates for surgery and a significant resection of tumor deposits can be performed [34]. Partial hepatic resection can be combined with tumor debulking to facilitate the synergistic effect of various other forms of treatment such as chemotherapy, serial arterial embolization or repeated transient hepatic ischemia.

Vascular occlusive therapy of pancreatic endocrine tumors metastatic to the liver has been updated and discussed recently by Arcenas et al. [35]. Although it is beneficial in patients with liver metastasis originating from gut carcinoid tumors, efficacy in gastrinoma patients has not yet been sufficiently evaluated [35, 36].

Considerable hope had been placed on systemic chemotherapy. Early experience with regimens using a combination of streptozotocin (STZ) and 5 fluoro-uracil (5FU) yielded the best response rates [37]. The median remission duration in the whole group of patients was only 17 months, but there was a trend toward longer survival (26 months) in the STZ-5FU group versus those receiving STZ alone (16.5 months). Valid interpretation of these results, however, remained uncertain in ZES because of the small number of ZES patients concerned (eight out of 84 endocrine pancreatic tumors) and because judgement criteria were essentially biological. Recent prospective studies [19, 38] included 21 and 25 ZES patients, respectively, and measured the response to therapy using both tumor-size regression and survival times. In our trial, STZ-5FU gave disappointing results including 1) only one case in which there was a major and long-lasting tumor size regression (greater than 50 percent with 55 months duration); 2), only three cases in which a minor, transient response was observed (25 to 50 percent tumor-size regression on CT scans); 3) stabi-

lization of tumor masses in 28 percent of cases; and 4) progression of liver masses in 68 percent of the patients [19]. Actuarial analysis revealed a median survival time of 28 months, 34 percent of patients were alive at five years [19].

Moertel and colleagues [38] compared STZ-5FU to chlorozotocin and to doxorubicin with STZ in various types of metastasized endocrine tumors. Although the combination of STZ and doxorubicin was the most effective, it still provided a relatively small chance of complete tumor-size regression (18 percent) and of long-term survival (around 30 percent of patients were alive at five years).

Treatment with the long-acting somatostatin analog, octreotide acetate, offers the theoretical advantage because it acts by inhibiting gastrin release together with gastric acid secretion and by antagonizing tumor growth. However, clinical use of octreotide is hampered by the easier use of potent antisecretory drugs while its effects on tumor size appears to depend upon the developmental stage of the tumor [39] and to be modest and inconstant [39, 40].

The advent of liver transplantation raises a challenging therapeutic option for liver metastases from endocrine gut tumors that are recognized as having a slow evolution [41]. Makowka et al. from Starzl's group [42] reported results from five such patients (one with gastrinoma). Their results appeared encouraging for two glucagonoma patients who remained disease-free 23 and 41 months later. The only gastrinoma patient, who was initially free of extrahepatic metastases, died eight months later from multiple lung and bone metastases.

A large French experience with liver transplantation for neuro-endocrine liver metastasis extending from 1989 to 1994 has been recently analyzed and published in an abstract form [43]: the main results are shown in Table 6. As can be noted, with the exception of gut carcinoids, results of liver transplantation are not encouraging for the pancreatic endocrine tumors inclusive of gastrinomas. In addition, a real problem for such a tremendous decision is when to perform liver transplantation? In a study of 35 patients with endocrine-type liver metastases including 20 cases of ZES, we looked for factors specific to endocrine-type liver metastases that could be used as major prognostic indicators of death and, thus, could be of help in selecting the appropriate time for liver transplantation [44]. Among the various elements assessed over a patient's observation period of 35 months (median duration; range: five to 136 months), only rapid expansion of metastatic volume of the liver (more than 25 percent within six months) seemed to be a major prognostic factor leading to consideration of liver transplantation in patients below 55 to 60 years without bone and lung metastases and non-responding to other forms of therapy.

There is insufficient experience with interferon in gastrinoma patients with liver metastases; interesting results obtained in carcinoid tumors suggest interferon could be worth testing in ZES patients, possibly in association with octreotide [45].

CONCLUSIONS

The role of medical treatment is essential in gastrinoma management for a large group of patients since :

1.   Unresectable hepatic metastases are present in about 25 percent of patients with ZES.

2. Surgery is usually unable to achieve disease-cure in MEN-1-ZES cases (25 percent of patients with ZES).

3. Recurrence rate is 50 percent at nine years without affecting survival, even in benign forms of sporadic ZES, according to the NIH stratification.

Results of the long-term study at the NIH suggest, however, that in sporadic forms of the disease, surgery could play a major role to prevent liver metastasis development; this

suggestion, however, requires further testing. Surgery, in any case, must be safe, performed by experienced surgical-medical teams. and restricted to simple procedures.

The time has probably come to initiate multicenter, multinational studies to test:

1. The NIH-proposed stratification between benign and malignant forms of ZES through retrospective and prospective, randomized clinical experiences.

2. The role of surgery in MEN-1-ZES patients.

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