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Prospective Study of the Natural History of Gastrinoma in Patients with MEN1: Definition of an Aggressive and a Nonaggressive Form

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The natural history of pancreatic endocrine tumors (PETs) in patients with MEN1 is largely unknown. Recent studies in patients with sporadic PETs show that in a subset, tumor growth is aggressive. To determine whether PETs in patients with MEN1 show similar growth behavior, we report results from a long-term prospective study of 57 patients with MEN1 and Zollinger-Ellison syndrome. All patients had tumor imaging studies yearly, and the mean follow-up was 8 yr. Only patients with PETs 2.5 cm or larger underwent abdominal surgical exploration. Hepatic metastases occurred in 23%, and in 14% tumors demonstrated aggressive growth. Three tumor-related deaths occurred, each due to liver metastases, and in each, aggressive tumor growth was present. Overall, 4% of the study group, 23% with liver metastases and 38% with aggressive disease, died. Aggressive growth was associated with higher gastrins and larger tumors. Patients with liver metastases with aggressive growth differed from those with liver metastases without aggressive growth in age at MEN1 onset or diagnosis and primary tumor size. Survival was decreased ($P = 0.0012$) in patients with aggressive tumor growth compared with those with liver metastases without aggressive growth or with no liver metastases without aggressive growth. Based on these results a number of factors were identified that may be clinically useful in determining in which patients aggressive tumor growth may occur. These results demonstrate in a significant subset of patients with MEN1 and Zollinger-Ellison syndrome, aggressive tumor growth occurs and can lead to decreased survival. The identification of prognostic factors that identify this group will be important clinically in allowing more aggressive treatment options to be instituted earlier. (*J Clin Endocrinol Metab* 86: 5282–5293, 2001)

THE NATURAL HISTORY of pancreatic endocrine tumors (PETs) in patients with MEN1 is almost entirely unknown. This exists despite the fact 40- 90% of MEN1 patients develop a PET (1–4). In recent studies 15–33% of patients with MEN1 die of malignant PETs (5–8), and in at least two studies it was the leading cause of disease-related death (5, 8). In the future it is likely that the natural history of PET and other malignant neuroendocrine tumors that occur in MEN1 (thymic, bronchial, and gastric carcinoids) (3, 7, 9) will become even more important determinants of long-term survival. This is occurring because in the past a significant percentage of patients died of complications from the hormone excess states produced by various neuroendocrine tumors and PETs (2, 4, 5, 7, 10, 11). This included complications of peptic ulcer disease due to Zollinger-Ellison syndrome (ZES), renal failure secondary to hyperparathyroidism, complications of pituitary disease, or death due to some other functional PET (2, 5, 7, 11). All of these complications can now be dealt with medically or surgically (3, 8, 12), and with the recent development of long-acting depot somatostatin analogs, the ability to treat these disorders long term will be further improved. Therefore, patients with MEN1 are now living longer, and the natural history of the neuroendocrine tumors and PETs these patients develop will become an increasingly important determinant of long-term survival.

Recent studies with sporadic PETs demonstrate that the aggressiveness and rates of growth of both the primary tumor and hepatic metastases are not uniform and can be highly variable in different patients (13–20). In the best studied PET, patients with gastrinomas, long-term studies demonstrate that in approximately one fourth of patients the gastrinoma pursues an aggressive growth pattern, with a 10-yr survival of 30%, whereas in the remaining 75% of patients the gastrinoma pursues an indolent growth pattern with a 10-yr survival rate of 95% (14, 15, 18). Furthermore, in patients with sporadic metastatic PETs, liver metastases in a minority of the patients demonstrate aggressive growth, whereas in the majority they demonstrate indolent growth (13, 19). Tumor-related deaths occur almost entirely in the aggressive-growth group (13, 19). In studies in patients with sporadic PETs, various clinical, laboratory, and tumoral characteristics have been defined that help distinguish these two groups of patients and can be useful for clinical management (13, 15, 16, 19). Whether similar growth patterns exist for PETs in patients with MEN1 or whether similar prognostic variables can be identified is at present not established from any prospective study.

The present study was aimed at addressing this question

Abbreviations: CT, Computed tomography; MRI, magnetic resonance imaging; PET, pancreatic endocrine tumor; SRS, somatostatin receptor scintigraphy; ZES, Zollinger-Ellison syndrome.

by prospectively analyzing the PET's growth behavior in 57 consecutive patients with MEN1 with ZES. Because the gastric acid hypersecretion can be controlled in all of these patients (21), and the patients do not routinely undergo surgical exploration for cure (22–24), it was possible to systematically study the tumor growth characteristics and to attempt to define prognostic factors.

Subjects and Methods

Patients and general methods

Eighty consecutive patients with ZES associated with MEN1 evaluated between June 1972 and July 2000 were eligible for this prospective study. This study group represents all patients with ZES and MEN1 syndrome enrolled in the ongoing evaluation of ZES by the Digestive Diseases Branch approved by the Clinical Research Committee of NIDDK, NIH. Patients were eligible for the present study if they had yearly follow-up evaluations, including imaging studies. Twenty-three patients with ZES and MEN1 initially evaluated at the NIH were not included in this study because of a failure to follow the protocol or because they declined to enter the protocol.

The diagnosis of ZES was established as described previously (25) by measuring basal acid output (26, 27) and serial fasting gastrins. The diagnosis required an elevated fasting serum gastrin concentration in the presence of gastric acid hypersecretion (basal acid output, >15 mEq/h in patients without previous gastric acid reducing surgery or >5 mEq/h in patients with previous gastric acid-reducing surgery) and a positive gastrin provocative test (an increase in serum gastrin ≥200 pg/ml after secretin stimulation or with calcium infusion ≥395 pg/ml) (28). Blood for serum gastrin levels measurements were obtained while the subject was fasting, and levels were determined by Bioscience Laboratories (New York, NY) and Mayo Clinical Laboratories (Rochester, MN). Diagnostic criteria for the presence of MEN1 in a patient with ZES included establishing the diagnosis of ZES as described above in combination with clinical and/or biochemical evidence of hyperparathyroidism, pituitary disease, or a family history compatible with MEN1 syndrome (21, 29). A secondary pancreatic endocrine syndrome was defined as described previously (14) and involved the development of a second symptomatic PET syndrome after initial presentation with ZES, which included insulinomas, the carcinoid syndrome, glucagonomas, VIPomas, GRFomas, ACTHomas, or somatostatinomas. During follow-up three patients developed insulinoma, one patient developed the carcinoid syndrome, and no patients any of the other functional syndromes.

Study protocol

During the initial evaluation at the NIH, all patients underwent a comprehensive interview and physical examination, with particular attention to the history and presence of symptoms compatible with gastric acid hypersecretion (14). Patients were also asked about personal or family history of nephrolithiasis or other symptoms compatible with the presence of the MEN1 (21, 29). The onset of ZES was determined as the time of onset of continuous symptoms compatible with gastric acid hypersecretion (14, 15). The time of diagnosis of ZES was determined as the point when the patient had laboratory values compatible with this diagnosis. The onset of MEN1 was determined as the time of onset of symptoms compatible with MEN1, including nephrolithiasis, pituitary disease, symptomatic PET, detection of a PET, abnormal plasma values of hormones, or serum calcium compatible with MEN1-associated endocrinopathies (9). The time of diagnosis of MEN1 was determined as the time at which the patient for the first time had laboratory values compatible with MEN1 as described above or was told by a physician they had MEN1. To determine the extent of gland involvement all patients initially and at each follow-up had a determination of PTH (midmolecule), 5-HIAA, total calcium, albumin, PRL, insulin, gastrin, and urinary cortisol or hydroxysteroid from 1974 on. Determinations of plasma glucagon, proinsulin, GH, and ionized calcium were added in 1985, and those of PTH (immunoradiometric assay), plasma serotonin, somatostatin, proinsulin, ACTH, and pancreatic polypeptide were added in 1995. Magnetic resonance imaging (MRI) or computed tomography (CT) of the pituitary and adrenal glands was also performed from 1975 on.

Investigations to define the extent and localization of the gastrinoma included esophagogastroduodenoscopy using a videoendoscopy system (Olympus Corp., Lake Success, NY). Tumor imaging studies were performed as described previously (22) and included bone scanning, abdominal ultrasonography (since 1972), CT with or without iv and oral contrast (since 1975), MRI (since 1988), and selective abdominal angiography (since 1972) with or without an intraarterial secretin provocative test (20, 22, 30, 31). Since June 1994 somatostatin receptor scintigraphy (SRS) was performed after iv injection of 6 mCi [^{111}In-diethylenetriamine pentaacetic acid-DPhe^{1}]octreotide and whole body views, spot views of the abdomen and SPECT imaging were obtained (31). Since November 1995 endoscopic ultrasound using a fiberoptic echoendoscope (UM 20, Olympus Corp., Lake Success, NY), chest CT scan, and MRI of the thoracic and lumbar spine were performed (20).

If patients were suspected of having metastases to the liver based on imaging studies, the diagnosis of metastatic gastrinoma to the liver was confirmed by either CT- or ultrasound-guided percutaneous liver biopsy or by laparotomy whenever possible (32, 33). If there was evidence of an extrahepatic lesion of 2.5 cm or larger and there was no evidence of diffuse metastatic liver disease, patients underwent exploratory laparotomy (n = 41) (22, 23, 32). Since 1987, at laparotomy patients underwent duodenal transillumination, and duodenotomy was performed routinely (22, 32, 34). PETs within the pancreas were enucleated if possible, and a distal pancreatectomy was not routinely performed (32). Postoperatively, patients were evaluated at 3–6 months and then yearly (22, 25).

Patients with liver metastases (n = 13) were evaluated every 3–6 months (19, 20). Evaluations included studies to assess growth of the primary tumor and/or metastatic disease (bone scanning, ultrasound, CT scan, MRI, and, if results were unclear, selective abdominal angiography), and since 1994 patients also underwent SRS. Since 1995, MRI of the spine was performed to assess the presence of bone metastases as described previously (20). Bone metastases were determined using bone scanning, MRI of the spine, SRS, and changes in follow-up examinations (20). If the diagnosis still remained unclear, bone biopsies were performed (20). Patients who did not have tumor resection due to negative imaging studies (n = 3), or the presence of only smaller lesions (<3 cm; n = 12), were reevaluated yearly and if surgery was not performed due to unresectability with diffuse hepatic metastases (n = 1) follow-up was every 3–6 months.

In patients with liver metastases, after histological confirmation no antitumor treatment was given initially, and the growth of liver metastases was evaluated by repeating imaging studies every 3–6 months as described above (19). If on repeat imaging no growth was seen, growth was reassessed at 3- to 6-month intervals (19). If growth was seen, patients were treated with either interferon (5×10^6 units/d) or chemotherapy (streptozotocin, fluorouracil, and doxorubicin). Patients who initially had metastases that were limited to one lobe of liver or that were considered potentially resectable were considered for exploratory laparotomy and partial hepatic resection (n = 2) (32).

For each patient the number and size of each measurable tumor were determined in transverse sections of an imaging modality. The measurements were performed with a caliper on a hard copy image using an accompanying scale. The volume of the tumor was calculated using $V = 4/3\ \pi r^3$, where the r was the radius of the tumor. The growth rate was calculated as the percent volume increase per month over the time of the study (19). The rate of change in the most rapidly growing hepatic or extrahepatic tumor was used to determine the growth category. Patients were stratified into three groups based on tumor growth rate. Patients were classified as having a nonaggressive form of ZES if there was no growth or less than a 25% increase in volume per month (n = 49) either with (n = 5; group 1) or without (n = 44; group 2) liver metastases at all yearly evaluations. Patients were classified as having an aggressive form of ZES if there was an increase in tumor growth of 25% or more in volume per month or the appearance of a new lesion(s) at any follow-up evaluation (n = 8).

No patients were lost to follow-up. Death due to ZES was defined

TABLE 1. Laboratory and clinical characteristics of patients with aggressive or nonaggressive pancreatic endocrine tumors with ZES with MEN1

Characteristics	No. (%)		
	Aggressive tumor (n = 8)[a]	Nonaggressive tumor (n = 49)[a]	*P* value
Age at study end (yr)[b]			
Mean ± SEM	42 ± 4	49 ± 2	NS
Range	24–58	27–76	
Gender (female)	5 (63)	23 (47)	NS
Age of onset of MEN1 (yr)			
Mean ± SEM	26 ± 4	30 ± 1	NS
Range	13–49	12–51	
Age of diagnosis of MEN1 (yr)			
Mean ± SEM	31 ± 3	37 ± 2	NS
Range	23–50	12–61	
Age of onset of ZES (yr)			
Mean ± SEM	30 ± 3	33 ± 1	NS
Range	21–49	12–55	
Age of diagnosis of ZES (yr)			
Mean ± SEM	31 ± 3	38 ± 2	NS
Range	23–49	17–61	($P = 0.057$)
Duration from ZES onset to ZES diagnosis (yr)			
Mean ± SEM	1.7 ± 0.5	4.9 ± 0.7	NS
Range	0.5–4.8	0–19.6	($P = 0.057$)
Duration from ZES onset to liver metastases (yr)[c]			
Mean ± SEM	6.8 ± 1.5	16.1 ± 4.9	
Range	1.6–13.5	3.0–32.5	
Duration from ZES diagnosis to liver metastases (yr)[c]			
Mean ± SEM	5.0 ± 1.1	11.1 ± 3.6	
Range	0–8.8	0.6–22.5	
Duration from MEN1 onset to liver metastases (yr)[c]			
Mean ± SEM	8.5 ± 2.2	18.5 ± 6.3	
Range	1.6–18.2	3.1–35.5	
Follow-up duration at NIH (yr)			
Mean ± SEM	8.1 ± 2.5	8.1 ± 1	NS
Range	1.0–18.7	0.3–26.8	
Family history of MEN1	7 (88)	37 (76)	NS
Fasting gastrin (pg/ml)[d]			
Mean ± SEM	40,000 ± 13,000	4000 ± 1400	0.0001
Range	600–110,000	93–50,000	
Median	37,500	650	
Basal acid output (mEq/h)[d]			
Mean ± SEM	53 ± 10	32 ± 4	NS
Range	31–74	3–100	($P = 0.060$)
Maximal acid output (mEq/h)[d]			
Mean ± SEM	67 ± 14	52 ± 5	NS
Range	47–93	10–99	
Gastric-acid reducing surgery[e]	2 (25)	12 (24)	NS
MEN1-associated tumors			
Parathyroid	7 (88)	49 (100)	NS
Pituitary	2 (25)	23 (47)	NS
Adrenal	3 (38)	11 (22)	NS
Gastric carcinoid	5 (63)	10 (20)	0.024
Bronchial carcinoid	1 (12)	4 (8)	NS
Thymic carcinoid	0 (0)	3 (6)	NS
Other tumors[f]	2 (25)	13 (27)	NS
Secondary pancreatic endocrine syndromes[g]	1 (12)	3 (6)	NS
Underwent exploratory laparotomy	7 (88)	34 (69)	NS
Liver metastases present	8 (100)	5 (10)	<0.00001
Bone metastases present	3 (38)	0 (0)	0.0019

[a] Aggressive or nonaggressive PET behavior is as described in *Materials and Methods*. Aggressive was defined as tumor growth of 25% volume increase or more/month or the appearance of any new lesion. Nonaggressive was defined as either no growth or less than 25% volume increase in tumor size/month.

[b] Age at time of study analysis or time of death.

[c] Eight patients with aggressive disease and 5 of 49 patients with nonaggressive disease had liver metastases.

[d] Normal values: fasting gastrin, <200 pg/ml; basal acid output, <10.5 mEq/h (males), <5.6 mEq/h (females) (27); maximal acid output, <48 mEq/h (males), <30 mEq/h (females) (27).

[e] Four patients had total gastrectomy, four patients had Billroth I or II gastrectomy, and six patients had a vagotomy.

[f] Other tumors include uterine leiomyosarcoma (n = 2), esophageal leiomyoma (n = 2), melanoma (n = 3), rhabdosarcoma (n = 1), uterine adenocarcinoma (n = 1), colon adenocarcinoma (n = 1), breast adenocarcinoma (n = 1), bladder carcinoma (n = 1), basal cell carcinoma (n = 1), thyroid papillary carcinoma (n = 1), thyroid follicular adenoma (n = 1), renal papillary carcinoma (n = 1), and renal angiomyolipoma (n = 1).

[g] A secondary pancreatic endocrine syndrome was defined as the development during follow-up of an additional functional tumor syndrome besides ZES, including carcinoid syndrome (n = 1) and insulinoma (n = 3).

as death due to metastatic spread of the tumor (n = 3) or failure to control gastric acid hypersecretion leading to death (n = 0) (14).

Statistics

Estimated probabilities of survival were calculated and plotted according to the method of Kaplan and Meier. Differences with a significance level less than 0.05 are reported. In each table, $P < 0.0025$ is significant after correction for multiple comparisons; other values with $P < 0.05$ are noteworthy, but require confirmation in independent data. Values are expressed as the mean ± 1 SEM. Fisher's exact test, Mann-Whitney test, and log-rank test were used.

Results

Because the aim of this study was to prospectively assess tumor growth in patients with MEN1 with ZES, serial imaging studies were essential for patients to be included in this protocol. Fifty-seven patients fulfilled the study requirement of regular yearly evaluation and were included in this prospective study. Of the 57 patients, 100% had serial ultrasound studies and CT scans, 90% had serial MRIs, 82% had serial SRS studies, 80% had at least 1 abdominal angiography, and 69% had serial bone scans. Eleven (19%) patients died during the study, with 3 deaths due to ZES, whereas 8 patients died of causes unrelated to ZES.

In 8 patients (14%) the PETs demonstrated an aggressive growth pattern, and in 49 patients (86%) they demonstrated a nonaggressive growth pattern (Table 1). There was no difference between the patients with aggressive or nonaggressive disease in age at study end, gender, age at MEN1 onset or diagnosis, age at ZES onset or diagnosis, duration from ZES onset to ZES diagnosis, duration of follow-up at the NIH, the percentage of patients with a family history of MEN1, the percentage having prior gastric acid-reducing surgery, the magnitude of maximal acid output, the rate of occurrence of many of the other MEN1-associated tumors (*i.e.* parathyroid, pituitary, adrenal, carcinoids of bronchus or thymus), development of a secondary PET syndrome, or the percentage of patients undergoing abdominal exploration (Table 1). Patients with aggressive disease had significantly higher serum gastrin levels ($P = 0.0001$), a short disease duration from ZES onset to diagnosis or liver metastases and from diagnosis to liver metastases ($P < 0.00002$), possibly a higher rate of developing gastric carcinoid tumors ($P = 0.024$ without correction for multiple comparisons), and more frequent liver ($P < 0.00001$) or bone ($P = 0.0019$) metastases. All 8 patients (100%) with aggressive disease had liver metastases, with 6 patients (75%) developing the metastases during study follow-up. In contrast, only 5 of the 49 patients (10%) with nonaggressive disease had liver metastases, of whom 4 patients (8%) developed the metastases during the study follow-up (Table 1). These latter 4 pa-

TABLE 2. Tumor location and extent in 41 patients who underwent surgery with an aggressive or nonaggressive form of ZES with MEN1

Tumor extent	No. (%)		
	Aggressive tumor (n = 7)	Nonaggressive tumor (n = 34)	Total (n = 41)
Gastrinoma			
Primary without metastases	0	8 (24)	8 (20)
Lymph node metastases without primary	0	6 (18)	6 (15)
Metastases with primary	7 (100)	20 (59)	27 (66)
Lymph node	6 (86)	18 (53)	24 (59)
Liver metastases[a]	7 (100)[b]	4 (12)	11 (27)
Bone metastases[c]	2 (29)[d]	0 (0)	2 (5)
Primary tumor location[e]			
Duodenum only	2 (29)	16 (47)	18 (44)
Pancreas only	2 (29)	9 (26)	11 (27)
Duodenum and pancreas	3 (43)	3 (9)	6 (15)
Unknown[f]	0	6 (18)	6 (15)
Gastrinoma resected before liver metastases[g]	5 (71)[h]	3 (9)	8 (20)
Time from gastrinoma resection to liver metastases (yr)			
Mean ± SEM	4.6 ± 0.6[i]	14.2 ± 4.6	8.2 ± 2.3
Range	3.7–6.8	6.6–22.5	3.7–22.5
Nonfunctional pancreatic endocrine tumors removed[b]	2 (29)	16 (47)	18 (44)
Size			
Mean ± SEM	2.2 ± 0.8	2.2 ± 0.4	2.2 ± 0.3
Lymph node metastases present	1 (14)	3 (9)	4 (10)

P values are compared to patients with nonaggressive disease.

[a] Liver metastasis was confirmed by histology in eight patients and was identified by a change in SRS and other imaging studies in three patients.

[b] At surgery, pancreatic tumors were enucleated whenever possible, and a routine distal pancreatectomy was not performed (32).

[c] Bone metastases were determined as described previously (20).

[d] $P < 0.0001$.

[e] Twenty patients had multiple primary tumors, including all 7 patients with aggressive disease and 13 patients with nonaggressive disease.

[f] Metastatic gastrinoma to lymph nodes without a primary tumor located at surgery.

[g] Of the 10 patients with liver metastases, 2 patients underwent cytoreductive surgery without previous gastrinoma resection, and 1 other patient had an unresectable primary with liver metastases.

[h] $P < 0.026$.

[i] $P = 0.0014$.

tients were classified as nonaggressive because during the follow-up at the NIH there has been no change in the size or number of liver metastases. The difference between patients with or without aggressive disease was suggestive, but not significant, for the age at ZES diagnosis (31 *vs.* 38 yr; $P = 0.057$) and basal acid output (52 *vs.* 32 mEq/h; $P = 0.060$; Table 1).

Forty-one patients underwent exploratory laparotomy, so that exact information on tumor extent and location (Table 2) as well as tumor size was available (Table 3). Gastrinomas were found in all patients at surgery, and PETs were enucleated in 44% of patients. Twenty percent had primary gastrinoma without metastases, 66% had primary tumor with metastases, and 15% had gastrinoma in the lymph node with no primary tumor found (Table 2). In the 66% of patients with primary tumor and metastases, metastases were found in lymph nodes (59%), liver (27%), or bone (5%; Tables 2 and 4). With respect to primary gastrinoma location, 59% of patients had duodenal gastrinoma, 41% had pancreatic gastrinoma, and 15% had unknown primary gastrinoma location (Table 2).

There was no significant difference between patients with aggressive disease and nonaggressive disease in the percentage of patients having primary gastrinoma without metastases, the percentage of patients having metastatic gastrinoma found in lymph nodes only, the rate of lymph node metastases, the distribution of primary tumor location, the percentage of patients also having nonfunctional PETs found at surgery, and its size or association with lymph node metastases (Table 2). Patients with tumors demonstrating aggressive growth had a higher rate of developing liver ($P < 0.0001$) or bone metastases ($P < 0.026$), were more likely to have undergone gastrinoma resection before developing liver metastases ($P = 0.0014$), and had a shorter time from gastrinoma resection to the detection of liver metastases ($P < 0.0001$; Table 2).

Previous studies have demonstrated in patients with MEN1 and ZES that gastrinoma location and size are important predictors of aggressive growth (14, 15, 18, 35, 36). For the 41 patients undergoing exploratory laparotomy pancreatic gastrinomas were significantly larger than duodenal gastrinomas (*i.e.* 2.8 ± 0.5 *vs.* 1.1 ± 0.1 cm; $P < 0.0006$; Table 3). There was no significant difference between patients with aggressive and nonaggressive disease in the percentage of patients with duodenal gastrinoma larger than 1 cm or in the mean size of a duodenal gastrinoma (Table 3). However, patients with aggressive disease more frequently had pancreatic gastrinoma larger than 3 cm ($P < 0.0001$) as well as a larger mean size of pancreatic gastrinoma, if present ($P = 0.0003$; 5.3 *vs.* 1.8 cm′ Table 3).

There was no significant difference in the rate of lymph node, liver, or bone metastases between patients with aggressive and nonaggressive disease and with only a primary pancreatic gastrinoma or only a primary duodenal gastrinoma found at surgery (Table 4). Bone metastases were exclusively seen in patients with aggressive disease, and there was no difference in the rate of occurrence with respect to primary gastrinoma location (Tables 1 and 4). No patients with unknown primary gastrinoma location developed liver or bone metastases (Table 4).

Over the 28 yr of the study liver metastases were identified in 13 patients (Tables 1 and 4). In 8 of the 13 patients (62%) the metastases demonstrated aggressive growth (Table 5). Figures 1 and 2 show the imaging studies in two patients with aggressive disease and Fig. 3 is an example of a patient with nonaggressive disease. There was no significant difference between patients with liver metastases with or without aggressive tumor growth in the percentage with a positive family history of MEN1, the fasting serum gastrin level, the basal acid output, the percentage of patients having MEN1-associated tumors in different locations or the primary gastrinoma location (Table 5). However, patients with aggressively growing liver metastases were younger at the age of onset or diagnosis of MEN1 and more frequently had a gastrinoma 3 cm in diameter or larger (Table 5). Furthermore, there was no significant difference in the duration of ZES onset to liver metastases or in the mean duration of follow-up at the NIH (8.9 ± 2.3 *vs.* 10 ± 4.1 yr) with the 5 patients with nonaggressive disease having follow-ups of 2.4, 3.9, 4.5, 15, and 23 yr, respectively.

An analysis of survival of patients with aggressive disease and nonaggressive disease with or without liver metastases demonstrated a significant difference ($P = 0.0012$; Fig. 4). The 5-yr survival of patients with aggressive disease in which disease-related deaths were assessed was 88% (95% confidence interval, 53–98%), whereas it was

TABLE 3. Comparison of gastrinoma size with its location in patients with an aggressive or nonaggressive form of ZES with MEN1

Gastrinoma size and location[a]	No. (%)		
	Aggressive tumor (n = 7)[b]	Nonaggressive tumor (n = 34)[b]	Total (n = 41)
Pancreatic tumor size (cm)[c]			
0.5–2	0	9 (26)	9 (22)
2.1–3.0	0	3 (11)	3 (7)
>3	5 (71)[d]	0 (0)	5 (12)
Mean ± SEM	5.3 ± 0.9[e]	1.8 ± 0.2	2.8 ± 0.5
Range	3.5–8	0.5–3	0.5–8
Duodenal tumor size (cm)[c]			
0.2–1.0	0	11 (32)	11 (27)
1.1–2	2 (29)	5 (14)	7 (17)
Mean ± SEM	1.4 ± 0.2	1.0 ± 0.1	1.1 ± 0.1
Range	1.2–1.5	0.2–2	0.2–2
Unknown primary tumor[f]	0	6 (18)	6 (15)

Results are from 41 patients who underwent surgical exploration. *P* values are compared to patients with nonaggressive disease.

[a] Gastrinoma size refers to the diameter of the largest gastrinoma reported by the pathologist. Ten patients had multiple duodenal, four patients had multiple pancreatic, and six patients had pancreatic and duodenal gastrinomas.

[b] One patient with aggressive disease and 15 patients with nonaggressive disease did not undergo abdominal surgical exploration.

[c] Four patients and two patients in the aggressive and nonaggressive categories, respectively, had pancreatic and duodenal tumor, and two patients and eight patients had multiple duodenal tumors, respectively.

[d] $P < 0.0001$.

[e] $P = 0.0003$.

[f] Gastrinoma was found in lymph nodes only.

TABLE 4. Comparison of the extent of gastrinoma in patients with and without an aggressive form of ZES with MEN1 with primary gastrinoma in different locations

Site of primary gastrinomas	No. (%)		
	Aggressive tumor (n = 7)	Nonaggressive tumor (n = 34)	Total (n = 41)
Pancreatic primary only	2 (29)	9 (26)	11 (27)
With lymph node metastases	1 (14)	5 (15)	6 (15)
With liver metastases	2 (29)	3 (9)	5 (12)
With bone metastases	0	0	0
Duodenal primary	2 (29)	16 (47)	18 (44)
With lymph node metastases	2 (29)	12 (35)	14 (34)
With liver metastases	2 (29)	1 (3)	3 (7)
With bone metastases	1 (14)	0	1 (2)
Pancreatic and duodenal primaries	3 (43)	3 (9)	6 (15)
With lymph node metastases	3 (43)	1 (3)	4 (10)
With liver metastases	3 (43)	0	3 (7)
With bone metastases	1 (14)	0	1 (2)
Unknown primary[a]	0	6 (18)	6 (15)
With liver metastases	0	0	0
With bone metastases	0	0	0

Data are from 41 patients who underwent surgical exploration. None of the differences between patients with aggressive or nonaggressive tumors was statistically significant.

[a] Patients in whom only metastatic disease was found.

TABLE 5. Comparison of characteristics of patients with liver metastases with ZES and MEN1 with or without aggressive pancreatic endocrine tumors

Characteristics	No. (%)		*P* value
	Aggressive disease (n = 8)	Nonaggressive disease (n = 5)	
Age (yr; mean ± SEM)			
Onset of MEN1	25.6 ± 3.9	35.7 ± 3.8	0.030
Onset of ZES	29.7 ± 3.2	38.1 ± 1.8	NS
Diagnosis of MEN1	30.9 ± 3.0	44.6 ± 3.3	0.019
Diagnosis of ZES	31.4 ± 3.2	43.1 ± 2.7	NS
Disease duration (yr; mean ± SEM)			
ZES onset to diagnosis	1.7 ± 0.5	5.0 ± 1.7	NS
ZES onset to liver metastases	6.8 ± 1.5	16.1 ± 4.9	NS
Family history of MEN1	7 (88)	4 (80)	NS
Fasting gastrin (pg/ml)			
Mean ± SEM	40,000 ± 12,000	13,700 ± 9,000	NS
Median	37,500	5,000	
Basal acid output (mEq/h; mean ± SEM)	52.5 ± 9.5	34.2 ± 10.9	NS
MEN1-associated tumors			
Nonfunctional pancreatic endocrine tumor	2 (25)	2 (40)	NS
Parathyroid	7 (88)	5 (100)	NS
Pituitary	2 (25)	4 (80)	NS
Adrenal	3 (38)	2 (40)	NS
Gastric carcinoid	5 (63)	2 (40)	NS
Primary gastrinoma location[a]			
Duodenum	5 (62)	1 (20)	NS
Pancreas	6 (75)	4 (80)	NS
Gastrinoma size			
≥3 cm	8 (100)	2 (40)	0.035

[a] Data are from 11 patients who underwent surgical exploration, 7 patients with aggressive and 4 patients with nonaggressive disease, and 2 patients who had tumor localization by imaging studies.

100% (95% confidence interval, 92–100%) for patients with nonaggressive disease with or without liver metastases (Fig. 4).

Discussion

The long-term natural history of PETs in patients with MEN1 is almost completely unknown. This lack of information has occurred for a number of reasons. First, there are no large prospective studies that have systematically addressed the natural history of PETs in patients with MEN1, and thus most data are from retrospective studies (2, 5, 7, 8, 10, 24, 37–39). Second, in older studies 10–91% of the patients died from complications of the hormone excess states, including refractory acid-peptic disease, renal failure secondary to nephrolithiasis, pituitary disease, or another functional PET syndrome (*i.e.* insulinoma, *etc.*) (2, 4, 7, 10). As a result of early death from the hormone excess state, in early studies few patients lived beyond 50 yr of age (2). Therefore, although PETs can be the first manifestation of MEN1 (29, 40), PETs characteristically are diagnosed 5–15 yr after the onset of hyperparathyroidism

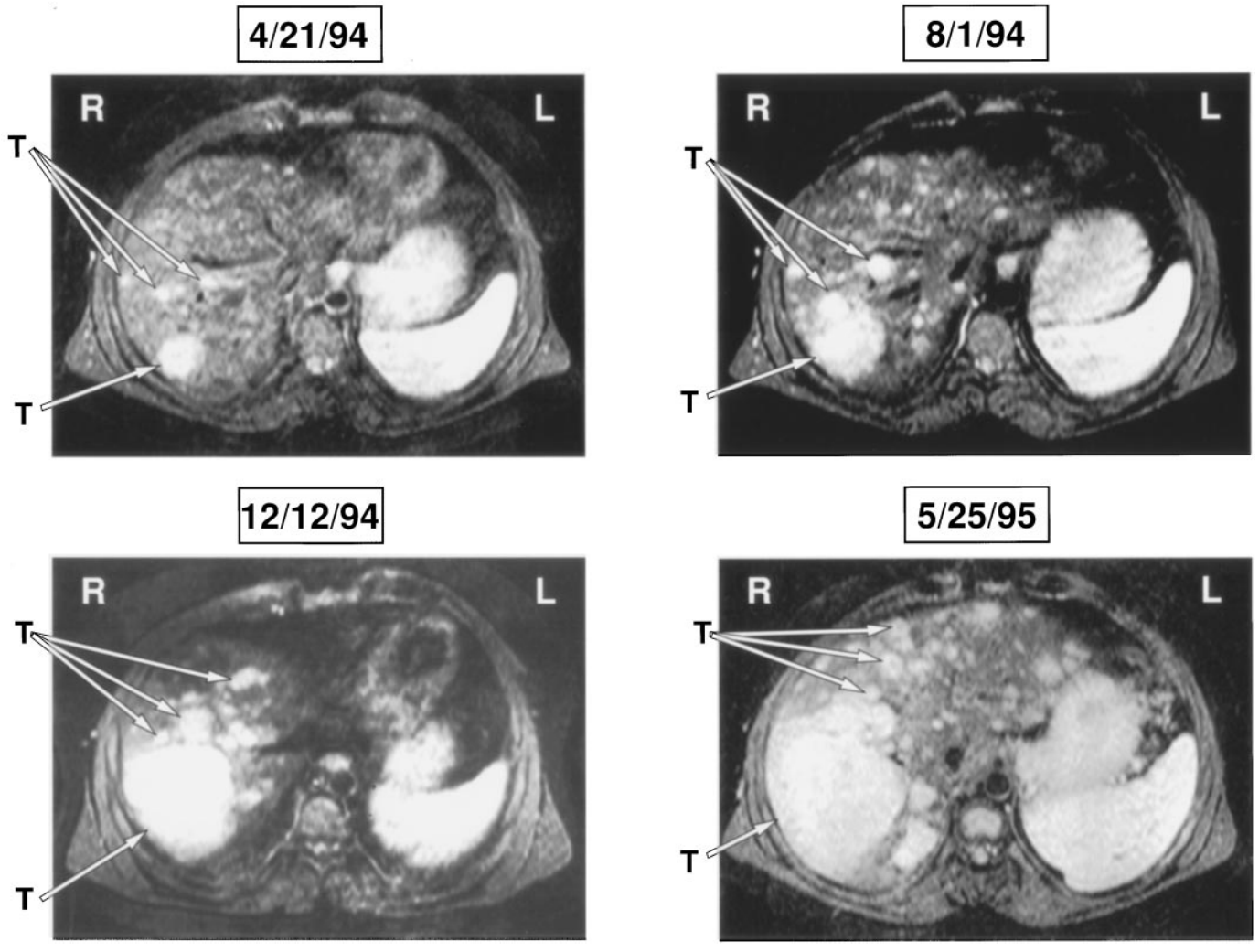

FIG. 1. A patient with ZES and MEN1 with aggressive disease with rapidly growing hepatic metastases. Four consecutive short inversion-time inversion-recovery MRI show progressively enlarging right hepatic lobe metastases. This patient (NIH 181149) developed liver metastases shortly after presenting with a pancreatic tail tumor precluding surgical exploration. Metastatic gastrinoma was confirmed by percutaneous CT-guided liver biopsy. He failed treatment with various chemotherapy regimens as well as interferon-α. The patient died shortly after developing metastases in the bone. He also had pituitary and parathyroid disease.

in patients with MEN1 (12, 41) and are frequently diagnosed in the 35–50 yr age range (12, 21, 40, 41). The follow-up on many patients with PETs with MEN1 before death was short. Third, detailed imaging studies were rarely used in these studies, and until recently, sufficiently sensitive imaging modalities did not exist. In many studies only ultrasound was used, or occasionally CT scanning without contrast was used; therefore, tumor progression or growth could be easily missed. Recent studies demonstrate ultrasound and CT scanning will detect 30–50% of PETs, and their ability to detect these tumors is size dependent, detecting 0–20% for PETs less than 1 cm and 70–100% 3 cm or more (30). Lastly, many patients with MEN1 with PETs were often diagnosed late in their course, and therefore the full natural history and growth of the PET could not be established.

There are none of the limitations listed above in the present study, which was designed to determine prospectively the growth patterns of PETs in patients with MEN1 with ZES, which is the most common symptomatic malignant PET in these patients (1, 3, 8, 39, 42). The present study was prospective in design, with patients systematically followed at regular intervals. Second, none of the patients died from complications of the hormone excess state; therefore, the long-term natural history of the PETs could be determined. In contrast to older studies and similar to other recent reports (14), gastric acid hypersecretion was controlled medically in all patients. Furthermore, no patient developed renal failure because the hyperparathyroidism was appropriately treated surgically (3). Third, detailed tumor localization studies using multiple modalities allowed a prospective assessment of growth and progression of PETs. Fourth, because patients with MEN1 and ZES do not routinely undergo surgical exploration in our protocol unless a lesion 2.5 cm or larger is imaged (21–24, 32), the progression of smaller lesions could be assessed prospectively. Fifth, in contrast to most older studies, the present study included a large number

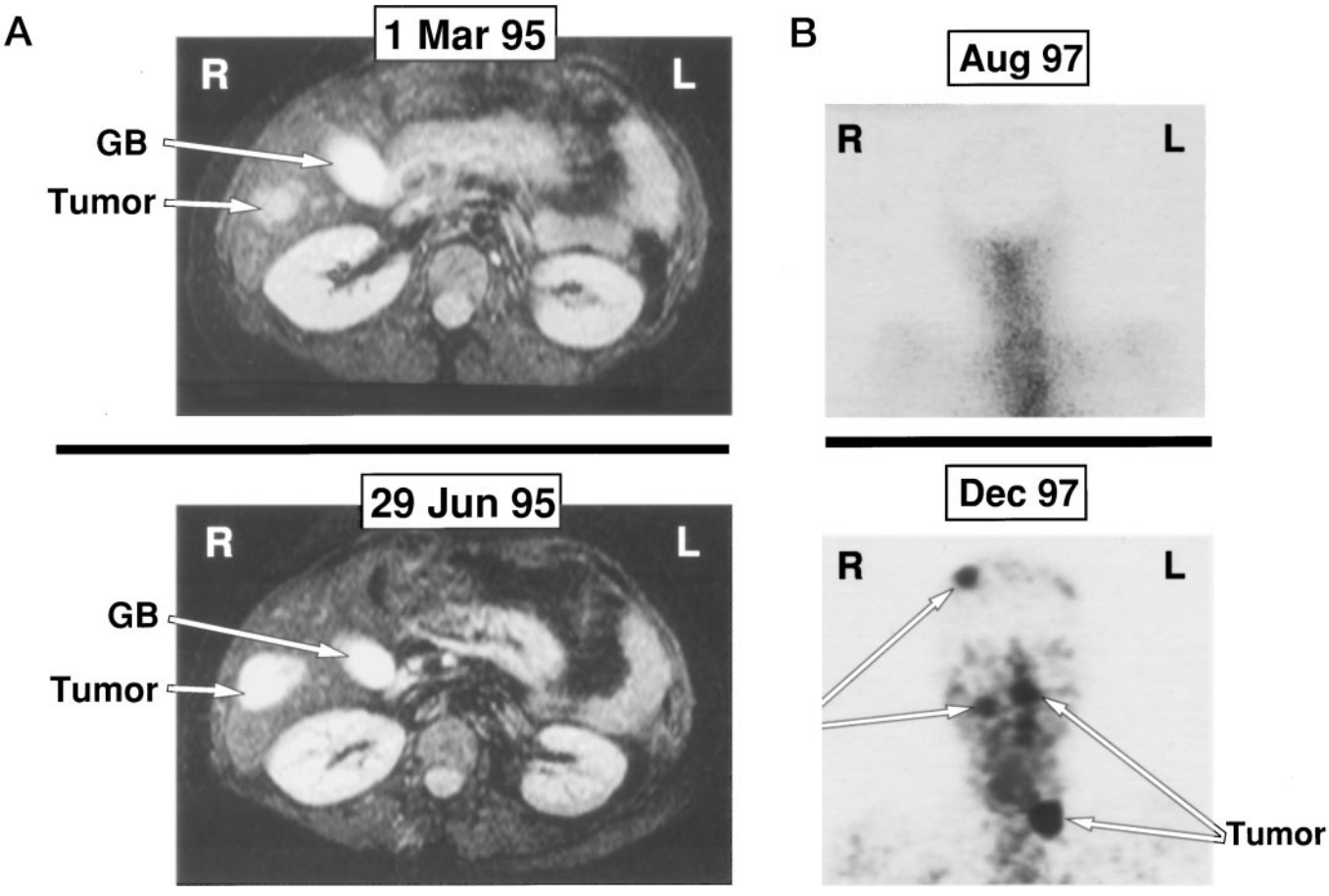

FIG. 2. A patient with ZES and MEN1 with aggressive disease, with development of bone metastases and increasing liver metastases. The MRI short inversion-time inversion-recovery images (*left panels*) show a right hepatic lobe metastasis increasing in size over 4 months, and the SRS (*right panels*) show the development of bone metastases over a 5-month period. This patient (NIH 168978) had a prior history of duodenal gastrinoma resection with a subtotal pancreatectomy for a 3-cm pancreatic endocrine tumor and developed liver metastases 3.5 yr later. Metastatic gastrinoma was confirmed by percutaneous CT-guided liver biopsy. Tumor growth continued despite treatment with chemotherapy (streptozotocin-5-fluorouracil-adriamycin), interferon-α, and octreotide as described in *Subjects and Methods*. She died shortly after developing bone metastases. She also had hyperparathyroidism and a gastric carcinoid tumor.

of patients with a PET (*i.e.* 57 patients) who underwent follow-up evaluations over an extended period (mean follow-up, 8 yr; range, 4.4 months to 27 yr). Because the growth patterns can be relatively slow in PETs compared with nonendocrine malignancies (16, 42), this extended evaluation period is essential to determine the PET's growth patterns.

Previous studies of patients with MEN1 show the PETs to characteristically have a low growth rate with excellent long-term survival (6, 15, 42–44). In a number of studies (15, 43–45), but not others (18, 39, 42, 46), patients with MEN1 and PETs are reported to have significantly better survival than patients with sporadic PETs. However, in recent studies of patients with sporadic PETs (primarily with sporadic ZES), two distinctive clinical courses of the PET are reported, with the PET demonstrating an aggressive growth pattern in a subset of patients and a benign clinical course in the remaining larger group of patients (14, 15, 18). Furthermore, even in patients with hepatic metastases due to a sporadic malignant PET, tumor growth in a subset of the patients is aggressive, whereas in the majority tumor growth is indolent (19, 47). Whether a similar phenomenon occurs in MEN1 patients with PETs was unclear before this study. The determination of whether in a subset of patients with MEN1 the PETs pursue an aggressive or a nonaggressive growth pattern is clinically important for a number of reasons. This distinction could allow identification of a subgroup of patients with MEN1 and PETs in whom more frequent and comprehensive follow-up evaluations would be indicated. Because of the expense of repeat imaging studies, especially somatostatin receptor scintigraphy, which can cost $2000–3000/examination (31), this identification of a high risk group could result in a considerable decrease in expense. Furthermore, identification of a high risk group might justify more aggressive treatment, such as early tumor resection or more extensive resection. Lastly, if different disease growth patterns existed, the rate of tumor growth would be an important variable in any antitumor treatment protocol, a factor that is not considered at present (19, 48).

In this study we show for the first time that gastrinomas in 14% of patients with MEN1 and ZES show aggressive growth. Furthermore, our studies show that the presence

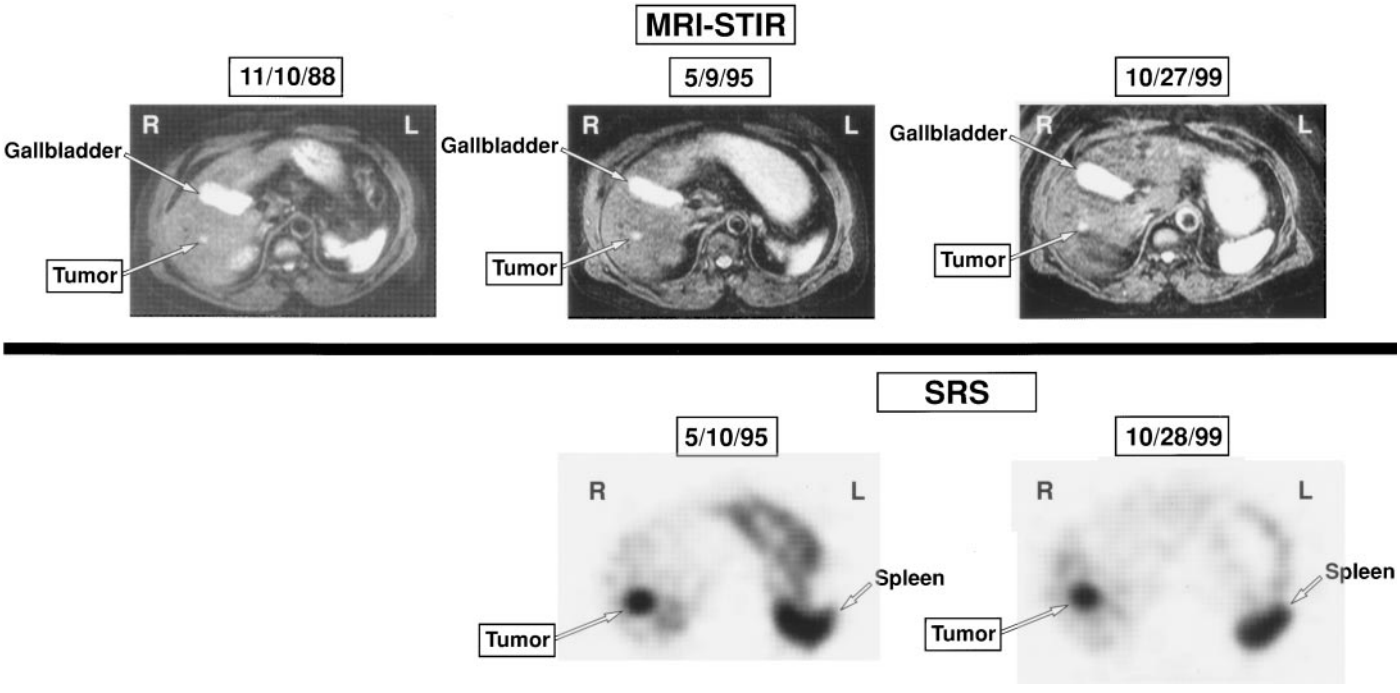

FIG. 3. A patient with ZES and MEN1 with nonaggressive disease and liver metastases. The patient (NIH 122873) developed a right hepatic lobe lesion in November, 1988 (*upper left panel*), which remained unchanged in size for 11 yr (*top panels*). SRS was first performed in May 1995, demonstrating the right hepatic lobe lesion, and no change occurred over the next 4 yr (*bottom panels*). The patient has a history of pituitary disease, hyperparathyroidism, and gastric carcinoid tumors. Surgery was not performed because of advanced age and associated medical conditions.

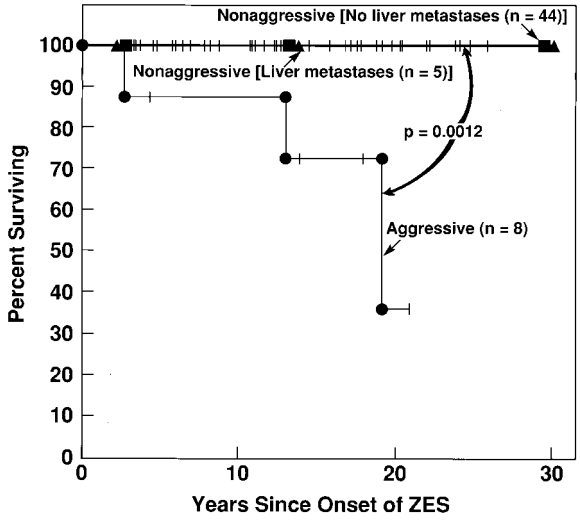

FIG. 4. Survival of patients with ZES and MEN1 with or without aggressive disease. Disease-related survival is shown. Survival is from the onset of ZES. During the follow-up period, three of eight patients (38%) with aggressive disease died compared with no patients with nonaggressive disease with (n = 5) or without (n = 44) liver metastases.

of liver metastases is not synonymous with aggressive tumor growth. Liver metastases were present at some time during the study in 23% of the patients; however, aggressive tumor growth was seen in 62% of the patients with liver metastases. In all of the patients with aggressively growing tumors, liver metastases were present. These results are very similar to reports in patients with sporadic malignant PETs, including gastrinomas, in which the PET demonstrated aggressive growth in a subset of the patients (14, 15, 18, 49) [*i.e.* 25–30% in one study (15)]. Furthermore, in two studies (13, 19) tumor growth was reported in 70–74% of patients with malignant sporadic PETs with liver metastases (13, 19), and aggressive tumor growth occurred in only 40% of the patients (19). In various series in the literature involving patients with MEN1 and PET, 6–30% are reported to develop liver metastases (11, 24, 37, 39, 50–52), and 0–30% die from metastases from a PET (11, 24, 37, 39, 50, 52, 53). In our study the 14% of patients showing aggressive PET growth may be an underestimation, because 72% of patients underwent exploratory laparotomy. If larger PETs were not resected from these patients, a higher proportion of patients may have developed liver metastases, because a correlation between primary tumor size and the incidence of liver metastases has been shown in a number of studies (6, 15). Whereas the aggressiveness in MEN1 patients of thymic carcinoid tumors in men (7, 54) and bronchial carcinoids in females has been emphasized (7), and an occasional study describes a patient with a PET showing aggressive growth (5, 24, 53, 55), the present study is the first to systematically study this group of patients and show that it is not a rare occurrence.

In our study there were three tumor-related deaths, with each patient having liver metastases, and the tumors in each patient demonstrated aggressive growth. Therefore, 5% of the total study group (*i.e.* 3 of 57 patients), 23% of the patients (3 of 13 patients) with liver metastases and 38% (3 of 8 patients) with aggressive disease, died of tumor progression in this study. This result has similarities with

studies in patients with sporadic PETs (13–15). In one recent study (19) involving 19 patients with metastatic gastrinomas to the liver, 0% of the patients with tumors showing no or slow growth (58% of all patients) died during follow-up, whereas 60% of the patients with rapidly growing tumors died. Similarly, in a study of 54 patients with metastatic PETs (13), 63% of patients with tumors demonstrating growth died compared with 17% without tumor growth ($P < 0.007$). These results suggest that if clinical, laboratory, or tumoral characteristics could be determined that would allow identification of MEN1 patients with PETs that will develop aggressive growth, they would be important clinically because their use would allow closer surveillance and more aggressive treatment to be directed at this subset of patients. In the present study we found that increased pancreatic tumor size (>3 cm; $P < 0.0001$), the presence of liver metastases ($P < 0.0001$), a markedly increased fasting gastrin level ($P < 0.0001$), the presence of bone metastases ($P = 0.0019$), and the presence of gastric carcinoid tumors ($P = 0.024$) occurred more frequently in patients with aggressive tumor growth (Table 6). Each of these factors, except the presence of gastric carcinoid tumors, has been shown to be associated with aggressive tumor growth or poor prognosis in patients with sporadic PETs (6, 13–17, 20, 35, 42, 48). Furthermore, in previous retrospective studies in MEN1 patients with PETs, the presence of liver metastases (6), a large primary pancreatic PET (≥3 cm) (6, 24), and an elevated fasting gastrin level (11, 24) are reported in some studies to be associated with decreased survival.

Similar to previous studies of sporadic PETs (13–15, 19), in the present study in patients with MEN1 and aggressive growth of the PET, survival was decreased. Therefore, if the prognostic factors listed in Table 6 can be used to reliably identify patients whose tumors will develop aggressive growth, the conclusions of this study have important clinical implications. In the subset of patients who will develop more aggressive tumors, more aggressive antitumor treatments (surgery, somatostatin analogs, hepatic artery embolization, or chemo-embolization) can be used selectively to possibly increase survival. Although unproven in a prospective study, aggressive cytoreductive surgery in patients with primarily sporadic PETs and carcinoid tumors is reported to be beneficial and frequently extend survival (48, 56, 57). Whether this approach in patients with aggressive PETs with MEN1 would have similar results is at present unclear. At least one study (6) that retrospectively analyzed the effect of surgical exploration in patients with large pancreatic PETs with MEN1 concluded that surgery did not prevent the development of hepatic metastases and extend survival. However, a recent study (58) in patients with primarily sporadic gastrinomas provided evidence that early surgical resection of the primary tumor decreased the probability of developing hepatic metastases. A second possibility would be to consider treating patients with aggressively growing PETs with MEN1 with a long-acting somatostatin analog (octreotide, lanreotide). Recent studies (47, 59–61) demonstrate that these analogs have a tumoristatic effect in 50–80% of patients with sporadic PETs and can induce apoptosis in these tumors (62). Whether similar results would be obtained in patients with MEN1 with aggressively growing PETs is unknown. A third possibility is to consider hepatic artery embolization or chemo-embolization for rapidly growing tumors restricted to the liver (42, 48, 63).

In conclusion, the present study demonstrates that in 57 patients with gastrinomas and MEN1 prospectively followed for a mean of 8 yr (0.45–27 yr), 23% have or develop liver metastases, and 14% have a gastrinoma showing aggressive growth. Aggressive tumor growth, but not liver metastases without aggressive tumor growth, is associated with significantly decreased survival ($P = 0.0012$). A number of clinical, laboratory, and tumor characteristics are identified that are associated with aggressive tumor growth (Table 6). The availability of these characteristics possibly coupled with genetic testing results that suggest some germline mutations may be associated with more aggressive PETs (64) may allow the early identification of patients who will develop aggressive PET growth. This would allow earlier institution of more aggressive antitumor treatments as well as more detailed molecular analysis of this subgroup of tumors to attempt to identify pathogenetic mechanisms that distinguish them.

TABLE 6. Factors predictive of aggressive growth of gastrinomas in patients with MEN1

Clinical	
Age at MEN1 diagnosis (yr), <35	($P = 0.021$)
Age at ZES onset (yr), ≤27	($P = 0.043$)
Age at ZES diagnosis (yr), ≤33	($P = 0.032$)
Duration of ZES before diagnosis (yr), <2.1	($P = 0.021$)
Laboratory	
Fasting gastrin levels, ≥10,000 pg/ml	($P < 0.0001$)
Tumor characteristics	
Pancreatic tumor size, >3 cm	($P < 0.0001$)[a]
Presence of liver metastases	($P < 0.00001$)
Presence of bone metastases	($P = 0.0019$)
Presence of gastric carcinoid	($P = 0.024$)

[a] Data from 41 patients who underwent abdominal exploration.

Acknowledgments

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The main topics are: Steroid receptors, structure, gene expression, and mechanism of action; non-genomic effect of steroid hormones; steroid membrane receptors; steroids and cancer; steroids in the central and peripheral nervous systems; steroids and the menopause; enzyme modulators; steroid hormones, phyto- and xeno-estrogens, and the environment; steroids and sport.

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