

Causes of Death and Prognostic Factors in Multiple Endocrine Neoplasia Type 1: A Prospective Study

Comparison of 106 MEN1/Zollinger-Ellison Syndrome Patients With 1613 Literature MEN1 Patients With or Without Pancreatic Endocrine Tumors

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Abstract: Multiple endocrine neoplasia type 1 (MEN1) is classically characterized by the development of functional or nonfunctional hyperplasia or tumors in endocrine tissues (parathyroid, pancreas, pituitary, adrenal). Because effective treatments have been developed for the hormone excess state, which was a major cause of death in these patients in the past, coupled with the recognition that nonendocrine tumors increasingly develop late in the disease course, the natural history of the disease has changed. An understanding of the current causes of death is important to tailor treatment for these patients and to help identify prognostic factors; however, it is generally lacking.

To add to our understanding, we conducted a detailed analysis of the causes of death and prognostic factors from a prospective long-term National Institutes of Health (NIH) study of 106 MEN1 patients with pancreatic endocrine tumors with Zollinger-Ellison syndrome (MEN1/ZES patients) and compared our results to those from the pooled literature data of 227 patients with MEN1 with pancreatic endocrine tumors (MEN1/PET patients) reported in case reports or small series, and to 1386 patients reported in large MEN1 literature series. In the NIH series over a mean follow-up of 24.5 years, 24 (23%) patients died (14 MEN1-related and 10 non-MEN1-related deaths). Comparing the causes of death with the results from the 227 patients in the pooled literature series, we found that no patients died of acute complications due to acid hypersecretion, and 8%–14% died of other hormone excess causes, which is similar to the results in 10 large MEN1 literature series published since 1995. In the 2 series (the NIH and pooled literature series), two-thirds of patients died from an MEN1-related cause and one-third from a non-MEN1-related cause, which agrees with the mean values reported in 10 large MEN1 series in the literature, although in the literature the causes of death varied widely. In the NIH and pooled literature series, the main causes of MEN1-related deaths were due to the malignant nature of the PETs, followed by the malignant nature of thymic carcinoid tumors. These results differ from the results of a number of the literature series, especially those reported before the 1990s. The causes of non-MEN1-related death for the 2 series, in decreasing frequency, were cardiovascular disease,

other nonendocrine tumors > lung diseases, cerebrovascular diseases. The most frequent non-MEN1-related tumor deaths were colorectal, renal > lung > breast, oropharyngeal. Although both overall and disease-related survival are better than in the past (30-yr survival of NIH series: 82% overall, 88% disease-related), the mean age at death was 55 years, which is younger than expected for the general population.

Detailed analysis of causes of death correlated with clinical, laboratory, and tumor characteristics of patients in the 2 series allowed identification of a number of prognostic factors. Poor prognostic factors included higher fasting gastrin levels, presence of other functional hormonal syndromes, need for >3 parathyroidectomies, presence of liver metastases or distant metastases, aggressive PET growth, large PETs, or the development of new lesions.

The results of this study have helped define the causes of death of MEN1 patients at present, and have enabled us to identify a number of prognostic factors that should be helpful in tailoring treatment for these patients for both short- and long-term management, as well as in directing research efforts to better define the natural history of the disease and the most important factors determining long-term survival at present.

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Abbreviations: BAO = basal acid output, CI = confidence interval, CNS = central nervous system, CT = computed tomography, DRS = disease-related survival, GERD = gastroesophageal reflux disease, GRFoma = growth hormone-releasing factor-secreting tumor, GTE = Groupe d'étude des Tumeurs Endocrines, HPT = hyperparathyroidism, HR = hazard ratio, MAO = maximal acid output, MEN1 = multiple endocrine neoplasia type 1, MEN1/PET = patients with MEN1 with pancreatic endocrine tumors, MEN1/ZES = patients with MEN1 and Zollinger-Ellison syndrome, MRI = magnetic resonance imaging, NET = neuroendocrine tumor, NIH = National Institutes of Health, non-MEN1 related = not related to MEN1, OS = overall survival, PET = pancreatic endocrine tumor, PTH = parathormone, SRS = somatostatin receptor scintigraphy, VIPoma = vasoactive intestinal peptide secreting tumor, ZES = Zollinger-Ellison syndrome.

INTRODUCTION

The autosomal dominant disorder, multiple endocrine neoplasia type 1 (MEN1) has an incidence of 0.22%–0.25% in postmortem studies.^{32,239,418} MEN1 is caused by alterations in the 10 exon Menin gene located on chromosome 11q13, which result in abnormalities (mutations, deletions, truncations, primarily) in the 610 amino acid nuclear protein, menin.^{62,195,419} Although the exact mechanisms by which altered or absent menin causes the clinicopathologic changes characteristic of MEN1 are not known, numerous studies have demonstrated

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that menin is involved in many important cellular processes such as cell cycle regulation, transcriptional control, cell division, and genomic stability.^{16,50,195,419,469}

Patients with MEN1 classically develop adenomas or hyperplasia of multiple endocrine glands, with parathyroid hyperplasia resulting in hyperparathyroidism (HPT) being the most frequent clinical abnormality (90%–100%), followed by pancreatic endocrine tumors (PETs) (functional [20%–70%] or nonfunctional [80%–100%]), pituitary adenomas (functional/nonfunctional [20%–65%]), adrenal tumors (occasionally functional [10%–73%]), and thyroid adenomas (primarily nonfunctional [0–10%]).^{48,102,140,195,228,239,262,279,280,374,388,390,418} It has been recognized recently that MEN1 patients have an increased occurrence of other endocrine and nonendocrine tumors including carcinoid tumors (thymic [0–8%], gastric [7%–35%], bronchial [0–8%], and rarely intestinal); skin tumors (angiofibromas [88%], collagenomas [72%], lipomas [34%], and melanomas); central nervous system (CNS) tumors (meningiomas, ependymomas, schwannomas [0–8%]); and smooth muscle tumors (leiomyomas, leiomyosarcomas [1%–7%]).^{13,46,48,49,74,131,176,209,228,261,274,354,388,393,413,465} In other reports, small numbers of other tumors have also been described, although it is unclear if they are increased in frequency or aggressiveness in MEN1 patients (lymphoma, renal cancer, hematologic disorders [thrombotic thrombocytopenic purpura, myeloma], ovarian tumors, gastrointestinal stromal tumors, seminomas, chondrosarcoma, mesothelioma, thymomas).^{1,77,84,89,150,214,216,256,312,341,410,432}

Whereas there have been many advances in a number of aspects related to MEN1 including molecular understanding, development of molecular screening methods, and treatment of various MEN1-related disorders, the late course of the disease remains unclear, particularly the current causes of death. An understanding of the late course of disease could allow treatments to be tailored to the most significant disorders found to occur (for example, treatment of PETs), and could allow the possible identification of risk factors and prognostic factors that could alter treatment approaches. This is important because the disease has a long course in many cases, and thus there are often opportunities to institute treatments early in the course.

There is a lack of prospective studies evaluating the long-term course and causes of death of MEN1 patients at present. This lack of information is a particular problem at present because there have been numerous widespread treatment changes over the last few years that have altered the late course of MEN1, and have likely altered the causes of death. These changes include the increased ability to control various hormone excess states that were a frequent cause of death in early studies of MEN1 patients,^{15,43,72,73,83,88,158,180,188,224,225,240,254,279,307,353,366,386,399,438,444,458,461,465,466} accounting for up to 73%–91% of all deaths in some early series.^{15,195,224,254,444} These include particularly the ability to treat the gastric acid hypersecretion in Zollinger-Ellison syndrome (ZES), earlier diagnosis and better treatment of insulinomas, and the increased use of somatostatin analogues or other treatments for other hypersecretory states (vasoactive intestinal peptide secreting tumors [VIPomas], etc). This also includes an understanding of the diffuse nature of the parathyroid disease in these patients resulting in HPT, which almost all patients develop early in the disease course, and the development of effective treatment with multigland parathyroidectomies, which prevents the development of nephrolithiasis, and renal failure,^{54,57,78,129,149,150} which not infrequently occurred in earlier series.^{15,32,68,88,129,224,285,438,444,465,466} Similarly, the recognition of the pituitary disease and more aggressive treatments have made this a rare cause of morbidity and death at present compared to in earlier studies.^{49,129,150,222,378,379,465}

Lastly, it is now recognized that MEN1 patients develop neoplasms other than those classically described, such as various carcinoid tumors, CNS tumors, skin tumors, and soft tissue tumors. Of these the carcinoid tumors can be of concern because they can be aggressive and develop later in the disease course.^{34,40,94,131,150,151,253,326,360,465} The thymic carcinoids, which are rarely reported before 1990, are of particular concern, especially in males, because as a group they are the most aggressive tumors that MEN1 patients develop and are an increasing cause of death, later in the disease course.^{111,130,131,151,408,413,414,465} With the effective treatment of hormone excess states, they are becoming increasingly important.

We conducted this study to describe the current course of MEN1 patients late in the disease history, as well as the causes of death at present, and to identify prognostic factors for different causes of death. Unfortunately, to our knowledge there are no reports in the literature of prospective studies of MEN1 patients containing sufficient deaths to allow a direct comparison to the patients in the present study. To allow comparison to existing data in the literature, we compared our results to outcomes reported in 2 other groups of MEN1 patients, as described in the Methods section below. From these comparisons we were able to draw a number of conclusions and to identify a number of prognostic factors that could affect clinical management.

PATIENTS AND METHODS

NIH MEN1/ZES Patients

All patients admitted to the National Institutes of Health (NIH) Digestive Diseases Branch with a diagnosis of a PET with ZES with MEN1 over a 32-year period¹⁴⁰ were evaluated for eligibility for this study. Eligibility requirements included the presence of MEN1 with a PET with ZES and an agreement to participate prospectively in the initial and follow-up evaluations. The present study is part of a prospective study of patients with MEN1 with MEN1/ZES at the NIH approved by the Clinical Research Committee of the National Institute of Diabetes and Digestive and Kidney Diseases.

Diagnostic Criteria

Diagnostic criteria for a PET included functional, pathologic, or imaging evidence for the presence of a PET. Diagnostic criteria for ZES were as previously described^{115,365} and included 1) elevated fasting serum gastrin (>100 pg/mL until 1994, >200 pg/mL since 1994);^{36,135} 2) elevated basal acid output (BAO >15 mEq in unoperated patients, >5 mEq in patients with previous acid reducing surgery;^{200,290,364} 3) positive provocative testing with secretin (an increase of >120 pg/mL postinjection) or with calcium (an increase of >395 pg/mL);^{35,85,122} 4) positive histologic confirmation of gastrinoma; or 5) a combination of these criteria.^{115,200,365} Secretin testing and the calcium provocative test were performed as described previously.^{35,122} With the calcium test, an increase of >395 pg/mL over the average of the pre-injection values was considered a positive response.^{35,85,122} The calcium infusion test was not performed if the patient was hypercalcemic prior to starting the test.

Diagnostic criteria for MEN1 with MEN1/ZES included ZES plus either a family history of MEN1 or evidence of HPT or pituitary disease as previously described.^{31,189,195} Serum gastrin levels were determined by Bioscience Laboratories (New York, NY) until 1994 and subsequently by Mayo Clinic Laboratories (Rochester, MN).^{36,64,115,122} BAO and maximal acid output (MAO) were measured when off all antisecretory

medications as described previously.^{115,282,364} Briefly, patients were not treated with anticholinergic agents for 3 days, oral histamine H₂-receptor antagonists for at least 30 hours, proton pump inhibitors for 1 week, and all intravenous infusions of H₂-receptor antagonists for at least 12 hours.^{282,364} MAO was assessed whenever possible if either pentagastrin or histalog was available by administering either histalog (1.5 mg/kg intramuscularly, Eli Lilly, Indianapolis, IN) or pentagastrin (6 µg/kg subcutaneously, Ayerst Laboratories, New York, NY) as described previously.^{115,282,364} All results were expressed as mEq/h.

Evaluations and Definitions

On the initial evaluation, a family and personal history for endocrinopathies or other illness was obtained as described previously.^{31,195,365} Using a questionnaire, outside records, and correspondence from referring physicians, we thoroughly reviewed the MEN1-related disease. We obtained a detailed record of the diagnosis and treatment of all endocrinopathies, with particular attention to parathyroid, pituitary, and pancreatic disorders. For parathyroid disorders the time of first determination of hypercalcemia, history of renal colic, parathyroidectomy history (time, number, type of operation, result, and time of last calcium and/or parathormone [PTH] assessment) were obtained. The time of first onset of renal colic or determination that hypercalcemia or HPT was present was taken as the time of establishment of HPT and was used in the study as the time of diagnosis of HPT as described previously.¹⁴⁰ Each patient underwent extensive questioning regarding symptoms compatible with gastric acid hypersecretion including abdominal pain, heartburn, nausea, vomiting, weight loss, diarrhea, and gastrointestinal bleeding.^{140,365} We conducted a complete review of past medical history for other diseases including other gastrointestinal and hepatic disorders present at the time of the initial admission.³⁶⁵ The time of onset of ZES and time of diagnosis of ZES were determined as described previously.^{365,459} The duration of ZES from onset to diagnosis was calculated as the interval from the time of onset to the time of diagnosis of ZES. The time of onset of MEN1 was the time of the first clinical manifestation of MEN1 (renal colic, pituitary disease, symptomatic PET) or the time the disease was first detected by biochemical screening.^{31,140,175} Most of the study period preceded the widespread use of genetic testing, and no patients were initially identified by genetic testing. The time of diagnosis and onset of MEN1 or pituitary disease was determined as described previously.^{31,140,175} To establish the presence of lipomas, melanomas, smooth muscle tumors, thyroid disease, or other PETs prior to evaluation at the NIH, we reviewed the hospital pathology and physician records from pre-NIH evaluations. Family history of MEN1 was considered positive if any sibling, parent, or grandparent had any of the principal manifestations compatible with MEN1 (parathyroid, pituitary, PET).

Patients were admitted for the initial evaluation and then yearly as described previously, except for patients with advanced disease who were admitted more frequently depending on the antitumor treatment protocol (every 3–6 months).^{140,351,382,450,476} On the initial admission and subsequent admissions, all patients had laboratory evaluations including complete blood count, urinalysis, at least 3 fasting serum gastrin levels, tumor imaging studies, biochemistry studies including liver function tests and an upper gastrointestinal endoscopy. Cross-sectional imaging studies (ultrasound,^{242,335} computed tomography scan [CT] with contrast,^{220,335,415,456} and magnetic resonance imaging [MRI]^{121,335,349,415}) were performed to assess tumor location and extent as described previously.^{335,476} If the tumor localization or extent was unclear, selective abdominal angiography

was performed.^{132,269,335} Since 1994, all patients underwent initially and then yearly somatostatin receptor scintigraphy (SRS) using 6 mCi of [¹¹¹In-DTPA-DPhe¹]octreotide with spot views and single photon emission CT imaging at 4 hours and 24 hours postinjection performed as previously described.^{134,137,138,415,416} Liver metastases were established by biopsy in all patients as described previously.^{405,459,476} Bone metastases were assessed using bone scanning, SRS, and MRI of the spine as described.^{133,137,138,476} If imaging results remained uncertain, bone biopsy was performed.¹³³ Gastric acid hypersecretion was controlled in all patients using either histamine receptor antagonists (cimetidine, ranitidine, famotidine) alone or with an anticholinergic agent until 1983, then primarily using proton pump inhibitors (omeprazole, lansoprazole) as described previously.^{123,192,200,266,281,282,283,284,294,350,417} Sufficient antisecretory drug was given to reduce acid secretion to <10 mEq/h in the hour before the next dose of medication or to <5 mEq/h (or to the absence of symptoms) in patients with prior partial gastrectomy²⁶⁶ or severe gastroesophageal reflux disease (GERD).^{266,281,283,284,295}

At the initial NIH evaluation and on subsequent NIH admission all patients underwent detailed clinical, biochemical, and imaging studies to assess the possible presence of MEN1 and, if present, additional studies to assess the extent of MEN1 involvement.^{13,31,131,139,141,175,315} To assess parathyroid function all patients were evaluated for total serum calcium, albumin, plasma, PTH determination using an assay that identified the midportion of PTH (performed at the NIH from 1974 to 1983 and by Bioscience Laboratories from 1983 to 1991). Since 1988 an assay measuring the intact PTH molecule (Nichols Institute, San Juan Capistrano, CA) was performed.^{140,328} Plasma ionized calcium levels were performed in the last 10 years. To assess pituitary disease, serum prolactin, adrenocorticotropin, thyroid stimulating hormone, growth hormone, luteinizing hormone, follicle stimulating hormone, thyroid function studies (T₄, T₃) and urinary cortisol excretion were assessed, as were sella turcica size and pituitary imaging abnormalities using CT and/or MRI of the sella turcica.^{13,133,140} To assess for the presence of a functional PET in addition to fasting gastrin levels, plasma insulin, proinsulin, glucose, adrenocorticotropin, glucagon, pancreatic polypeptide, serotonin, calcitonin and urinary 5-hydroxyindolacetic acid, N-methyl histamine excretion and cortisol excretion were determined.^{24,139,141,267} Prior to surgery in patients with insulinomas and selected patients with gastrinomas, functional localization studies were performed assessing hormonal gradients using either selective venous sampling or hepatic vein sampling after intraarterial injections of either calcium or secretin as described previously.^{64,91,92,293,422} The presence of a PET was also assessed by tumor imaging studies using cross-sectional imaging (ultrasound, CT scan, MRI, and, if results were unclear, angiography) and SRS as described above. Thymic carcinoids were assessed by chest CT scanning, SRS and, since 2000, MRI of the chest as described.¹³¹ Lung/bronchial carcinoids were assessed by chest CT and chest X-ray and, since 2000, by MRI of the chest, and were confirmed by thoracotomy. The presence of gastric carcinoids was assessed by upper gastrointestinal endoscopy using a videoscope GIF 100 endoscope (Olympus America, Inc., Melville, NY) with a 3.7 mm biopsy channel.^{34,139,268,344} Skin lesions associated with MEN1 (collagenoma, angiofibromas, lipomas, melanomas)^{74,195} were investigated in all patients since 2000 as described previously.¹⁴ Other tumors that are found in MEN1 patients (smooth muscle tumors [leiomyomas, leiomyosarcomas, etc], CNS tumors [meningiomas, ependymomas, schwannomas])^{13,42,195,261,418} were sought for using cross-sectional

imaging studies as well as upper and lower gastrointestinal endoscopy as described previously.^{13,131}

Exploratory laparotomy was performed in patients with MEN1 with PET/ZES with an imageable lesion >2.5 cm, who did not have diffuse liver metastases or an intercurrent illness limiting life expectancy.^{189,195,314,315,318,324,380} At exploration all patients had a standard operation consisting of an extensive search for a PET/gastrinoma as described previously.^{7,250,314,315,316} Because of the frequent occurrence of gastrinomas in the duodenum,^{9,195,347,421} which are frequently small and multiple in MEN1,^{9,195,250,347} particular attention was paid preoperatively and intraoperatively to the duodenum by performing an extended Kocher maneuver, intraoperative endoscopic transillumination of the duodenum,¹²⁴ intraoperative ultrasound with a 10-MHz real time transducer³¹⁸ and a 3-cm longitudinal duodenotomy.^{124,195,324,403,421} Parathyroidectomy was performed in all patients with renal colic, nephrolithiasis, reduced bone density, or symptoms due to HPT.^{317,328} Initially, either a 3.5 gland resection or 4 glands with an implant was performed.^{317,328} All lung carcinoids and thymic carcinoids were treated with surgical resection as described previously.¹³¹ Gastric carcinoids were treated by endoscopic resection, except in 3 patients who underwent total gastrectomy because of the extensiveness of the disease and the growth as described previously.³²⁶

In patients with liver metastases, after histologic confirmation no anticancer treatment was given initially, and the growth of the liver metastases was evaluated by repeated imaging studies in 3–6 months as described previously.^{133,351,450} If on recent imaging, no growth was seen, growth was reassessed at 3–6 month intervals. If growth was seen, patients were treated with interferon (5×10^6 units/d),³⁵¹ chemotherapy (streptozotocin, fluorouracil, and doxorubicin),⁴⁵⁰ or octreotide-long-acting release (octreotide-LAR) preparation.³⁸² Patients who initially had metastases that were limited to 1 lobe of liver or that were considered potentially resectable were considered for exploratory laparotomy and partial hepatic resection as described previously.^{58,315,325,327,329} For each patient the number and size of each measurable tumor were determined in transverse sections of an imaging modality and the rate of growth on serial imaging studies was calculated as described previously.^{141,476} The rate of change of the most rapidly growing hepatic or extrahepatic tumor was used to determine the growth category. Patients were stratified in 2 groups based on their tumor growth rate: patients were classified as having an aggressive form of MEN1 if there was >25% increase in tumor volume per month or appearance of new lesion(s) at any follow-up evaluation. Patients were classified as developing liver metastases or any new lesion(s) if during follow-up evaluations a new lesion(s) appeared either in the liver or in other sites.

Causes of Death

Any deaths during follow-up were classified as either MEN1 related or not. MEN1-related deaths were deaths due to an MEN1-associated feature, including endocrinopathy, metastatic neuroendocrine tumor (NET), and MEN1 treatment. MEN1-related deaths were also classified as being ZES related or not. ZES-related deaths were defined as deaths due to the tumor because of metastatic spread of the gastrinoma, tumor-related complications, or acute effects of gastric acid hypersecretion ($n = 0$) as described previously.^{141,476} The causes of MEN1-related deaths (including all ZES-related deaths) were further categorized into the following 5 subgroups: 1) death due to ZES/PET with progressive liver metastases causing progressive inanition or sepsis; 2) death due to the development of a progressive thymic carcinoid tumor; 3) death due to the

development of a non-ZES functional PET; 4) death due to the development of another (nongastrinoma, nonthymic carcinoid tumor) MEN1-associated malignant tumor, and 5) death due to tumor-related embolism. The causes of non-MEN1-related deaths were further categorized into the following 5 subgroups: 1) death due to cardiac causes including myocardial infarction, arrhythmia, or cardiac arrest; 2) death due to the development of an additional non-MEN1-associated malignancy; 3) death due to a cerebrovascular accident; 4) death due to a drug-related cause not related to treatment of advanced metastatic disease; and 5) death due to progressive aplastic anemia.

Genetic Analysis

Sequence analysis of the MEN1 gene was performed since 1998 through our laboratory,¹⁴⁶ the Molecular Diagnosis program of the Children's Research Institute (Children's National Medical Center, Washington, DC), or through GeneDx Inc. (Gaithersburg, MD). The polymerase chain reaction conditions and primers were as previously described.^{146,384}

Literature Review of Causes of Death in MEN1 Patients With or Without PETs

Unfortunately, to our knowledge there are no series in the literature comparable to the current study in which a large number of MEN1/ZES patients have been prospectively followed, so a direct comparison is not possible. Furthermore, there are insufficient patients reported in the literature with MEN1/ZES described with causes of death defined not due to acid hypersecretion. Therefore, in an attempt to allow comparisons between our data and data from the existing literature, we used 2 specific groups from the literature for comparison, realizing that these groups of patients are not completely comparable in all aspects to our population.

First, we compared our results to the results of a pooled summary of a literature search for any case report or small series of MEN1 patients (<7 deaths) where the patients had a PET of any kind, the cause of death was reported, and the cause of death was not peptic ulcer related. This group was similar to our NIH population in that all had MEN1, all had PETs, and 67% had ZES; however, not all patients had ZES. The search for these patients included primarily reports since 1980, when effective medical/surgical treatments for the gastric acid hypersecretion of MEN1 patients with ZES became widely available and in general use. Specifically, we excluded patients in a series or report where the long-term survival was limited due to death from the complications of uncontrolled acid peptic disease. Especially in many early series of patients treated before 1980,^{43,60,158,225,260,265,275,307,332,366,399,404,438,445,458} this was the major cause of death, and thus few patients had long-term follow-up, which is not the case at present. In the mid-1970s adequate medical antisecretory treatments with either H₂-histamine receptor antagonists or proton pump inhibitors became generally available,^{15,69,73,108,135,192,224,254,278,282,287,444,483} and this, in addition to the use of total gastrectomy in selected patients, has led to the current situation where few patients die of acid peptic-related disease. Because the current natural history and causes of death are thought to differ markedly from these early reports,^{54,57,78,88,150,217,367,378,379,448,465} we did not include patients from the early reports.

Second, we compared our results with results of larger MEN1 series in the literature that reported the cause of death of ≥ 10 patients who died from any cause other than a peptic ulcer-related cause. These patients were similar to our NIH patients in that all had MEN1; however, they were different in that not all had PETs or ZES: 60% had a PET and 54% had ZES. This group resembled the general population of

MEN1 patients reported in large series with or without ZES. Comparing our results with this group allowed identification of similarities and differences from series more typical of a general population of MEN1 patients with advanced disease.

To accomplish these comparisons, we searched MEDLINE (National Library of Medicine, Bethesda, MD) using the key words MEN1 or multiple endocrine neoplasia combined with gastrinoma, pancreatic endocrine tumor, glucagonoma, Zollinger-Ellison syndrome, thymic carcinoid, HPT, death, survival, and pituitary tumor, either alone or in combination. We reviewed the bibliographies of all papers to identify papers, book chapters, and other reports not referenced in MEDLINE. All papers were reviewed and relevant data entered into an Excel spreadsheet (Microsoft, Redmond, WA) that was used for all analyses and comparisons. The Japanese literature was also carefully reviewed, both using MEDLINE and reviewing symposium proceedings, books, and abstracts of scientific meetings. We found 10 reports that appeared only in Japanese; for these, the titles and data were translated into English.

For the first comparison with small series or case reports of patients with MEN1 with PETs (MEN1/PET patients) with at least 1 reported death not peptic ulcer disease related, we identified 108 separate reports containing 227 patients; 62 reports contained a single case^{4-6,25,28,32,68,70,82,86,97,109,111,112,119,125,142,156,162,165,202,206,207,213,216,229,236,249,264,296,297,300,301,304-306,311,313,333,334,358,359,361,369,381,386,387,391,393,396,398,409,411,414,426,430,438,449,460,462,464,467,468} and 40 contained >1 case (mean, 4.3 cases/report).^{21,22,30,40,41,46,94,113,120,153,166,180,203,223,226,230,238,244,246,247,303,346,353,362,372,375,389,398,406,407,413,425,427,431,440,443,458,461,466,475}

For the second comparison we found 18 series that reported the non-peptic cause of death in ≥ 7 MEN1 patients with or without a PET.^{15,54,57,78,88,129,150,217,224,226,254,289,367,378,379,444,448,465}

Statistical Analysis

All data were entered into Excel spreadsheets and analyzed using Statistica MAC (Statsoft, Tulsa, OK) and Statview (SAS Institute, Inc., Cary, NC). Statistical analysis was performed using the Student *t* test for paired and unpaired values, the Mann-Whitney *U* test, the Fisher exact test, the chi-square test, and ANOVA. For a post hoc test the Bonferroni/Dunn test was used. *P* values < 0.05 were considered significant. All continuous variables are reported as mean \pm SEM. Survival curves were plotted in the form of Kaplan-Meier, and 95% confidence intervals (CI) were calculated using Statview (SAS Institute, Inc., Cary, NC).

RESULTS

General Characteristics of the NIH and Literature Patients

We studied 106 NIH patients with PETs with MEN1 prospectively and compared their causes of death with those of 227 MEN1/PET patients pooled from case reports or small series in the literature, who died of non-acid related causes. The general characteristics of the NIH MEN1/ZES patients are shown in Table 1, and the characteristics of those who died during follow-up (*n* = 24) are compared to those of the MEN1/PET patients from the pooled literature. For the 106 NIH patients, the main features of MEN1 during the course of the 32-year follow-up were that 106/106 (100%) of the patients had MEN1 with a PET, 100% had ZES, 94% had HPT, and 58% had pituitary disease, primarily prolactinomas. There was a slight preponderance of males (59%), and 30% of patients had no family history of MEN1. During the course of their disease, with repeated evaluations, almost one-half of the

patients (46%) were found to have adrenal abnormalities, primarily nonfunctioning adenomas, and 51% had skin tumors, which are increasingly described in MEN1 patients (especially angiofibromas and collagenomas).^{14,59,74,89,313,336,370} One-third developed a carcinoid tumor, with the most common site a gastric carcinoid followed by bronchial carcinoids (10%) primarily in females and thymic carcinoids in males (6%), as reported in other series.^{98,131,190,195,465} Smooth muscle tumors (5%), thyroid disease (11%), and other functional PETs (primarily insulinomas) were not uncommon (10%), as were CNS tumors (meningiomas, ependymomas, schwannomas) (7%), as previously described.^{13,73,95,102,111,131,140,142,195,209,261,414,418,451}

Most of the NIH patients had the onset of MEN1 in the third decade (mean age, 29.3 yr) with the development of signs and symptoms of HPT, although about 40% presented with symptoms of ZES, as reported in other studies.^{31,140,378,387,444} However, there was an average delay of almost 9 years in establishing the diagnosis of MEN1 (mean, 38.2 yr) (see Table 1). Patients were followed to their last evaluation or death for an average of almost 25 years (average, 24.4 yr) and for 15.5 years from their diagnosis. Patients had an average age of 53.9 years at the last follow-up; however, this varied widely from age 27 to 80.6 years at the last visit.

For the NIH MEN1/ZES patients, 24 of the 106 (23%) patients died during follow-up, which averaged 15.5 ± 0.9 years (range, 1–44 yr) from diagnosis of MEN1 (Figure 1). The general characteristics of the 24 deceased patients were similar to those of all the NIH patients (see Table 1). These 24 NIH MEN1/ZES patients had both similarities to and differences from the 227 MEN1/PET patients from the pooled literature. They were similar in all having a PET, in having a high frequency of HPT (95%–96%), in the rates of thymic carcinoids (12.5%–13.3%), and in the frequency of non-ZES functional PETs (21%–23%), CNS tumors (0.5%–4.2%), or smooth muscle tumors (0–0.9%), and some skin tumors (melanomas, lipomas) (0.5%–4.6%). The patients were also similar in the high frequency of a family history of MEN1, in having a slight male predominance (58–61%), and in their mean age at last follow-up (51.6–55.1 yr).

In contrast, the 24 NIH MEN1/ZES patients who died during follow-up differed from the 227 deceased MEN1/PET pooled literature patients in the following ways: the NIH patients had a 3-fold higher frequency of pituitary disease; a 5-fold higher frequency of adrenal abnormalities; a higher incidence of ZES (100% vs 67%); a 2-fold higher frequency of any carcinoids found, with an 8-fold higher frequency for gastric carcinoids and 6-fold higher frequency for bronchial carcinoids; a higher frequency of the common skin tumors found in MEN1 (collagenomas, angiofibromas); and a 12-fold higher frequency of thyroid disease (see Table 1). The deceased NIH patients also had a younger age of onset of MEN1 than the pooled literature patients (27.2 vs 36.4 yr) and were younger at the diagnosis of MEN1 (37.1 vs 45.8 yr). Many of these differences were likely due to the regular systematic follow-up visits the NIH patients underwent (mean, 15 visits) and also the more recent appreciation of the presence of various features of MEN1 (such as smooth muscle tumors, adrenal disease, skin tumors, carcinoid tumors),^{14,42,74,131,140,195,261,280,414,418} that were not routinely sought for in older studies.

The characteristics of the 106 NIH MEN1/ZES patients and the 227 MEN1/PET patients from the pooled literature who died from a reported cause were both similar to and different from the characteristics of patients from the 15 larger literature series of all MEN1 patients whose survival data were also compared. Results were similar in all 3 groups regarding the

TABLE 1. MEN1 Disease Characteristics of All 106 NIH MEN1/ZES Patients With PETs and 24 Who Died Compared With 227 MEN1/PET Patients From the Pooled Literature Who Died During Follow-Up

Characteristic	Percentage			p ⁽²⁾
	NIH MEN1/ZES All Cases (n=106)	NIH MEN1/ZES Died (n=24)	Pooled Literature-MEN1/ PET Died (n=227) ⁽¹⁾	
I. MEN1 features				
PET present	100%	100%	100%	
HPT	96%	96%	95%	0.88
Pituitary disease	58%	62%	21%	<0.00001
Adrenal abnormality ⁽³⁾	45%	50%	7.3%	<0.00001
Carcinoid (any)	32%	38%	19%	0.036
Gastric	19%	25%	3.3%	<0.00001
Bronchial	10%	8.3%	1.4%	0.027
Thymic	6%	12.5%	13.3%	0.91
ZES	100%	100%	67%	0.0009
Other functional PET ⁽⁴⁾	10%	21%	23%	0.82
CNS tumor ⁽⁵⁾	7%	4.2%	0.5%	0.18
Skin tumors	51%	33%	2.8%	<0.00001
Collagenoma	32%	12.5%	0%	<0.00001
Angiofibroma	32%	16.7%	0%	<0.00001
Melanoma	3%	4.2%	0.46%	0.061
Lipoma	7%	4.2%	2.3%	0.59
Smooth muscle tumor ⁽⁶⁾	5%	0%	0.9%	0.63
Thyroid disease	11%	12.5%	0.92%	0.0001
II. Age at various MEN1 features				
Age (yr) mean ± SEM, [range]				
At onset MEN1 ⁽⁷⁾	29.3 ± 1.1	27.2 ± 2.2	36.4 ± 2.3	>0.30
[range]	[10.1 – 60.6]	[10.1 – 51.3]	[22 – 65]	
At diagnosis of MEN1 ⁽⁷⁾	38.2 ± 1.2	37.1 ± 3.0	45.8 ± 1.1	>0.30
[range]	[12.6 – 72.8]	[12.6 – 61.1]	[22 – 77]	
At last follow-up/death ⁽⁸⁾	53.9 ± 1.2	55.1 ± 2.8	51.6 ± 1.2	>0.30
[range]	[27.0 – 80.6]	[27.0 – 79.6]	[27.0 – 88.1]	
III. MEN1 demographic features				
Family history MEN1	72%	88%	87%	0.95
Sex (male)	41%	58%	61%	0.24

Abbreviations: Lit = literature.

⁽¹⁾The 227 patients with MEN1 and PETs from the literature were identified as described in the Methods section.

⁽²⁾P value comparing 24 NIH MEN1/ZES patients who died during follow-up with 227 literature patients.

⁽³⁾Adrenal abnormality refers to presence of an abnormality detected on imaging studies (NIH [n = 45], lit [n = 9]), and/or clinically adrenal Cushing syndrome (NIH [n = 3], lit [n = 1]), or pheochromocytoma (NIH [n = 2], lit [n = 1]).

⁽⁴⁾Other functional PET includes insulinoma (NIH [n = 10], lit [n = 27]), glucagonoma (NIH [n = 1], lit [n = 8]), carcinoid syndrome (NIH [n = 1], lit [n = 1]), GRFoma ([lit = 1]), SSoma ([lit = 1]), ACTHoma ([lit = 1]), and VIPoma ([lit = 3]).

⁽⁵⁾CNS tumor includes meningiomas (NIH [n = 4]), ependymomas (NIH [n = 1], lit [n = 2]), schwannomas (NIH [n = 1]), and neurolemmoma (NIH [n = 1]).

⁽⁶⁾Smooth muscle tumor includes leiomyomas (NIH [n = 1], lit [n = 1]), and leiomyosarcomas (NIH [n = 2]).

⁽⁷⁾Onset of MEN1 was time of first symptom compatible with MEN1 or time of detection at screening if asymptomatic, and time of diagnosis was time patient first told had MEN1.

⁽⁸⁾Age was for last follow-up in 82 patients and for death in 24 patients [NIH].

high percentage of patients with HPT and the high frequency of PETs, which averaged 74% ± 5% (range, 36%–100%) in the larger series (see Table 12). The occurrence of ZES varied widely in the larger MEN1 literature series (range, 23%–100%; mean, 47% ± 4%); the percentage was lower in a number of these large series than in the pooled literature series and in the NIH patients.

Causes of Death in the 24 NIH MEN1/ZES Patients and the 227 Patients With MEN1/PET From the Pooled Literature

During the mean 15.5 years of follow-up from MEN1 diagnosis (24.1 yr from onset), 24 (23%) of the 106 NIH patients died (see Figure 1). In 14 patients (13% total, 58% of total

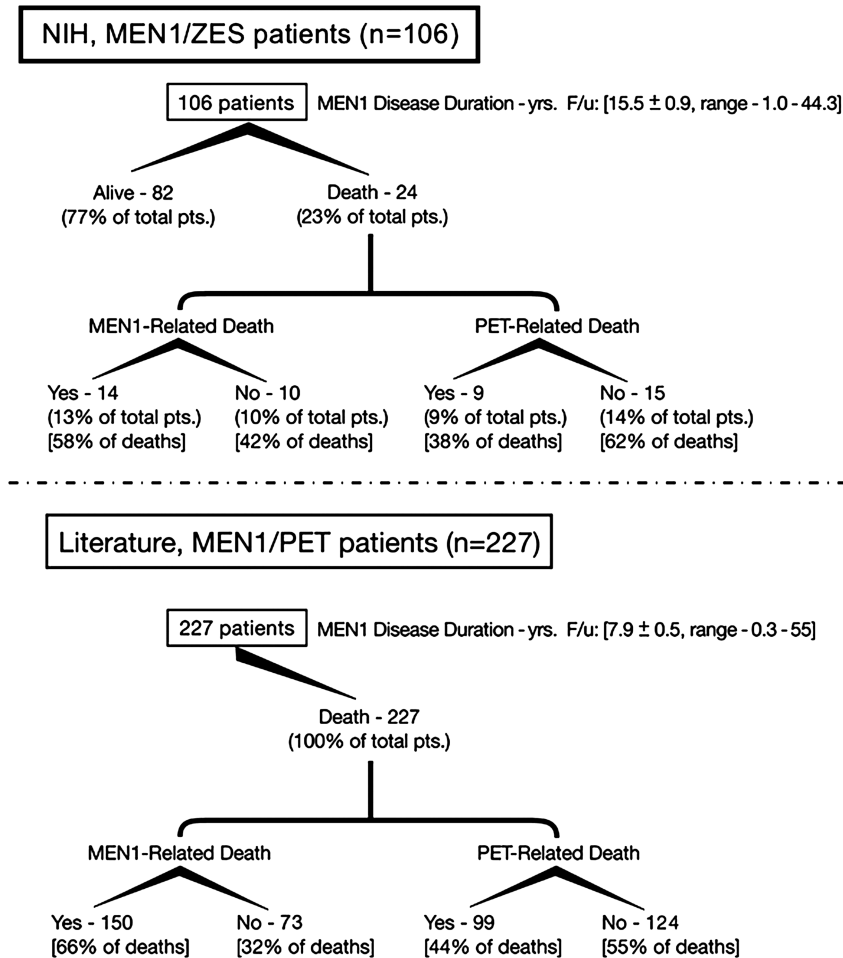


FIGURE 1. Schematic diagram of causes of death in the 2 study groups. The top panel shows the results of the 106 prospectively studied NIH MEN1/ZES patients followed for a mean of 15.5 years from the time of diagnosis of MEN1. During this time 24 patients died; 14 deaths were due to MEN1-related causes and 10 patients died of non-MEN1-related causes. The deaths were stratified as to whether they were (n = 9) or were not (n = 15) directly due to a PET causing the death. In the bottom panel a similar diagram is shown for the 227 MEN1/PET patients from the pooled literature from case reports and small series (<7 cases).

deaths) the deaths were determined to be MEN1-related, and in 9 patients (9% of total patients, 38% of deaths) the deaths were due to a malignant PET. In no patient was death related to the acute complications of peptic ulcer disease due to uncontrolled gastric acid hypersecretion, as was commonly reported in the past.^{15,43,72,73,83,88,158,174,180,224,225,240,254,307,353,366,386,399,438,444,458,461,465,466} This demonstrates the effectiveness of long-term medical management of the acid hypersecretion as reported in a number of studies,^{69,123,136,172,192,201,268,278,279,284,287,350} because no patient underwent a total gastrectomy during follow-up at the NIH for control of the gastric acid hypersecretion. In the NIH patients all the MEN1-related deaths were due to a NET in some manner (carcinoid, PET, other endocrine tumor), and in 79% it was due to the malignant nature of the NET. In 5 patients the MEN1-related death was due to a malignant non-PET, which included 1 case of meningioma, 3 of thymic carcinoid, and 1 case of the gastrinoma causing long-standing GERD that was inadequately controlled, leading to the development of Barrett esophagus with high-grade dysplasia and esophageal cancer. A hormone excess state caused death in 2/14 patients (14%), due to an uncontrolled malignant insulinoma in 1 patient and in the 1 patient with the long-standing

GERD which likely led to the development of Barrett esophagus and the development of terminal esophageal cancer. In the NIH patients a PET-related death occurred in 71% of patients, which in 64% was due to the malignant nature of the gastrinoma and in 1 case was due to a malignant insulinoma. In the NIH patients 3/14 (21%) deaths were due to carcinoid tumors and none to gastric or lung carcinoids, demonstrating the particularly aggressive behavior of thymic carcinoids, as reported in a number of studies.^{111,131,151,414,465} In the NIH patients there were no deaths related to pituitary disease, and, in contrast to a number of older studies,^{88,224,438,444,465} there were no deaths due to HPT-related disease, because the HPT was effectively treated by parathyroidectomy in all patients.^{104,195,317,328}

When the cause of death results from the 24 NIH MEN1/ZES deceased patients are compared to the results of the 227 MEN1/PET patients from the pooled literature, the proportion dying from an MEN1-related cause was not different (68% vs 66%, p = 0.38) (see Figure 1, Table 2). The pooled literature results were similar to the NIH causes of MEN1-related death in that there were no significant differences in the percentage of deaths in all of the categories analyzed including death due to any NET, to the presence of a malignant NET, to a NET

TABLE 2. Causes of Death of MEN1/PET Patients (NIH Series and Pooled Literature Review)

Cause of Death	Number (%) ⁽¹⁾		P
	NIH	Pooled Literature ⁽¹⁾	
MEN1-related death⁽²⁾	14	150	
Specific cause MEN1-related deaths			
Any NET-related death ⁽³⁾	14 (100%)	150 (100%)	
Any malignant NET	11 (79%)	124 (83%)	0.70
Malignant non-PET NET ⁽⁴⁾	5 (36%)	34 (23%)	0.27
Any NET hormone excess state ⁽⁵⁾	2 (14%)	26 (17%)	0.77
NET-related not due to progressive mets/hormone excess ⁽⁶⁾	1 (7%)	6 (4%)	0.47
PET-related MEN1 death ⁽⁷⁾	10 (71%)	99 (66%)	0.90
Due to malignant PET	9 (64%)	87 (58%)	0.65
Due to malignant gastrinoma	8 (57%)	46 (31%)	0.14
Other malignant PET due to MEN1 ⁽⁸⁾	1 (7%)	43 (29%)	0.25
F-PET hormone excess state ⁽⁵⁾	2 (14%)	12 (8%)	0.42
Pituitary related	0 (0%)	4 (3%)	0.54
HPT related	0 (0%)	14 (9%)	0.34
Carcinoid tumor related	3 (21%)	30 (20%)	0.90
Thymic carcinoid	3 (21%)	28 (19%)	0.80
Non-MEN1-related death⁽²⁾	10 (100%)	73 (100%)	
Cardiac	4 (40%)	12 (16%)	0.079
Additional non-MEN1 malignancy ⁽⁹⁾	3 (30%)	18 (25%)	0.72
Cerebrovascular	1 (10%)	8 (11%)	0.93
Drug related ⁽¹⁰⁾	1 (10%)	0 (0%)	0.007
Hematologic ⁽¹¹⁾	1 (10%)	2 (3%)	0.25
Suicide	0 (0%)	1 (1%)	0.094
Accident	0 (0%)	4 (6%)	0.44
Unknown specific cause⁽¹²⁾	0	22	0.11

Abbreviations: See Table 1. F-PET = functional PET.

⁽¹⁾The number of total patients dying of the indicated cause is shown as well as the percentage of patients with an MEN1- or non-MEN1-related death who died of the indicated cause. Note the literature cases total more than 227 because some causes were specified as related or not related to MEN1 but the exact cause was not specified. (See footnote 12.)

⁽²⁾Deaths were classified as MEN1-related or not depending on their principal cause as defined in Methods.

⁽³⁾Death due to any NET includes death due to malignancy, functionality or related to the presence of any NET due to MEN1.

⁽⁴⁾Non-PET, MEN1-related malignancy causing death included malignant CNS tumors [meningioma,¹³ n = 1, NIH; lit = 2, ependymomas]; esophageal cancer with Barrett esophagus with dysplasia secondary to poor control of GERD in the past¹⁷⁵ [n = 1, NIH]; thymic carcinoids [n = 3, NIH; lit = 28]; lung carcinoid [n = 1, lit]; spindle cell sarcoma of pituitary [n = 1, lit], melanoma [n = 1, lit], parathyroid cancer [n = 1, lit], pheochromocytoma [n = 1, lit], renal failure due to HPT untreated [n = 2, lit].

⁽⁵⁾Functional PET syndromes causing death include uncontrolled insulinoma [n = 1, NIH; n = 8, lit]; patient dying of esophageal cancer secondary to uncontrolled GERD and development of Barrett esophagus with dysplasia [n = 1, NIH]¹⁷⁵; VIPoma [n = 1, lit]; ZES patients operated for acid died of non-acid postoperative problems [n = 2, lit].

⁽⁶⁾This includes death from a tumor-related pulmonary embolus associated with progressive tumor [n = 1, NIH]; death from postoperative complications [n = 3, lit], and death due to pituitary disease complications [n = 3, lit].

⁽⁷⁾PET-related, MEN1 deaths were deaths due to either a malignant PET, its hypersecretion and F-PET syndrome or its presence in a way as defined in Methods and previously.^{141,476}

⁽⁸⁾Due to other functional PET (nongastrinoma) included death from progressive insulinoma and refractory hypoglycemia [n = 1, NIH, n = 3, lit]; malignant glucagonomas [n = 5, lit], malignant NF-PETs [n = 15, lit]; malignant nongastrinoma PETs, type not specified [n = 20, lit].

⁽⁹⁾Additional malignancy [non-MEN1]-related deaths include death due to squamous cell cancer of the oro-naso-pharynx [n = 1, NIH], lung cancer [n = 6, lit]; breast cancer [n = 1, NIH]; colon [n = 1, lit]; hepatocellular cancer [n = 1, lit]; gastric [n = 1, lit], prostate [n = 2, lit] urinary bladder cancer [n = 1, NIH].

⁽¹⁰⁾Drug-related death was due to cocaine overdose [n = 1, NIH].

⁽¹¹⁾Hematologic causes of death include progressive aplastic anemia [n = 1, NIH], leukemia [n = 1, lit] and thrombotic thrombocytopenia purpura [n = 1, lit].

⁽¹²⁾In the 22 cases of unknown cause of death in the literature, 18 cases were specified as related or not related to MEN1 but the exact cause was not specified.

hormone excess state, to a PET, to a malignant PET, to functional PET syndrome, to pituitary disease, to HPT-related disease, or to the presence of a thymic carcinoid or other carcinoid tumor.

For the NIH MEN1/ZES patients, 10/24 (42% of deaths) were due to non-MEN1-related causes. The most common cause of non-MEN1 death was cardiac (4/10, 40% of non-MEN1

deaths) due to myocardial infarction, arrhythmia, or cardiac arrest (see Table 2) followed by death due to a non-MEN1-related malignancy (3/10, 30% of non-MEN1 deaths) which included 1 death due to squamous cell cancer of the oronasopharynx, 1 from breast cancer, and 1 from urinary bladder cancer. Three additional non-MEN1-related deaths included 1 death from a hematologic cause (aplastic anemia), 1 from a cerebrovascular accident, and 1 from a drug overdose (cocaine). The proportion of non-MEN1-related deaths in the 227 pooled literature patients did not differ from that in the NIH MEN1/ZES patients (32% vs 42%, respectively; $p = 0.38$). Similarly, there were no differences in the proportion of the pooled literature patients who died of various non-MEN1-related causes, including an additional non-MEN1 malignancy, cerebrovascular disease, hematologic disorders, suicide, or accidental death. There was a significant difference in that 1 patient in the NIH series died of a drug overdose (cocaine), whereas no such death was reported in the 227 literature patients (10% vs 0 of non-MEN1 deaths, $p = 0.007$).

The cause of death in all 24 deaths in the NIH patients could be determined, but in 22/227 (9.7%) deaths in the pooled literature, the exact cause of death was not reported. However, in 18 cases the report specified whether the death was an MEN1-related or non-MEN1-related death, therefore in only 4/227 (1.7%) cases in the pooled literature was it unknown whether the death was MEN1 related or not MEN1 related (see Table 2).

Disease, Laboratory, and Tumoral Features in NIH MEN1/PET Patients by Survival Status

Because it is currently unknown whether the presence of MEN1 could be contributing even to the deaths that we have characterized as non-MEN1 related, to analyze for possible prognostic factors for survival we first compared various characteristics of the NIH MEN1/ZES patients who were still alive to those of the deceased NIH patients (see Tables 3–6). For general disease features of the NIH patients, there were no significant differences between patients who died and those who were alive at last follow-up in terms of sex, race, age at first visit to NIH, age at last follow-up, or duration of follow-up from onset of MEN1 or from first visit (Table 3).

In various studies of patients with ZES a number of specific disease-related features have been reported to have prognostic significance, including disease duration,⁴⁷⁶ extent of hypergastrinemia,^{191,292,397,405,459,476,484} BAO,^{191,476} presence of peptic ulcer disease or its complications,^{108,117,191,199,200,483} previous gastric acid reducing surgery,⁴⁷⁶ and antisecretory drug used.⁴⁷⁶ We compared each of these features in NIH patients by survival status (Table 4). There was no significant difference between the alive and deceased NIH patients in the duration of ZES to last follow-up, the increment in gastrin during the secretin test (delta secretin), the duration or type of antisecretory treatment, peptic ulcer disease history, or occurrence of bleeding or other peptic ulcer disease complications. In contrast, deceased patients were more likely than alive patients to have had a very high fasting gastrin level (>20-fold elevated, $p = 0.022$), a longer delay in diagnosis (8.1 vs 4.9 yr, respectively, $p = 0.039$), a prior gastric acid reducing surgical procedure (33% vs 12%, $p = 0.026$), to have taken histamine H₂-receptor antagonists for a longer time ($p = 0.064$), to have a history of heartburn/GERD ($p = 0.065$), and to have a higher MAO ($p = 0.059$).

In various studies a number of features of MEN1 patients have been reported to have prognostic significance, including age at MEN1 onset/diagnosis,^{46,150,383} disease duration,^{78,141}

TABLE 3. General Disease Features of NIH MEN1/ZES Patients by Survival Status

Disease Feature	Number (%)		P
	Alive	Dead ⁽⁵⁾	
No. of patients	82	24	
Male	52 (63%) ⁽⁴⁾	14 (58%) ⁽⁴⁾	NS
Race			
White	63 (77%)	20 (83%)	NS
Black	9 (11%)	2 (8%)	
Hispanic	8 (10%)	2 (8%)	
Other ⁽¹⁾	2 (2%)	0 (0%)	
Age at first visit to NIH (yr)			
Mean ± SEM	41.2 ± 1.1	41.1 ± 1.8	0.64
[range]	[21.8–70.8]	[11–61]	
Age at last follow-up (yr) ⁽²⁾			
Mean ± SEM	53.5 ± 1.4	55.1 ± 2.8	0.53
[range]	[27.7–80.6]	[27.0–79.6]	
Duration of follow-up			
Onset of MEN1 to last follow-up/death (yr) ⁽³⁾			
Mean ± SEM	23.4 ± 1.3	27.8 ± 2.5	0.095
[range]	[3.6–59.3]	[10.2–51.3]	
First NIH visit to last follow-up/death (yr)			
Mean ± SEM	12.1 ± 0.8	13.8 ± 1.9	0.52
[range]	[0.1–34]	[2.5–34.2]	

⁽¹⁾Two patients were from the Philippines.

⁽²⁾Age at last follow-up or death.

⁽³⁾Onset of MEN1 was time of first symptoms compatible with MEN1 or time of detection at screening if asymptomatic.^{31,140}

⁽⁴⁾Numbers in parentheses are the percentage of the patients with the indicated feature that were alive or dead.

⁽⁵⁾Number of patients who died of any cause during follow-up.

presence of a family history;^{46,150} presence of any PET including gastrinoma, glucagonoma, insulinoma, VIPoma, somatostatinoma, and nonfunctional;^{71,88,150,217,233,234,389,465} presence of adrenal disease;^{150,228,388,390,465} presence of lung,^{368,465} gastric,^{141,326} or thymic carcinoid tumors;^{111,131,150,151,413,414,465} and severity and control of HPT.^{46,88,224,226,328,444,465} We compared each of these features in NIH patients by survival status (Table 5). Deceased patients, compared to alive patients, more frequently had >3 parathyroidectomies ($p = 0.008$) to control the HPT, suggesting they may have had more severe HPT; more frequently had a gastrinoma with another functional syndrome such as carcinoid syndrome or Cushing syndrome/disease ($p = 0.0033$); and more frequently had gastrinomas with another functional PET, particularly insulinomas ($p = 0.031$). Deceased patients tended to have a positive family history of MEN1 more frequently than alive patients (88% vs 67%, $p = 0.052$) and they were less likely to have had a cutaneous manifestation of MEN1 detected ($p = 0.051$). There was no significant difference between the 2 patient groups in their age at MEN1 onset or diagnosis or age at onset of HPT or first parathyroidectomy; in the duration of follow-up from time of MEN1 diagnosis, from onset of HPT to last follow-up, or from onset of HPT to first parathyroidectomy; in the number of parathyroid glands removed; presence of renal colic; or any other feature of MEN1 including frequency of pituitary disease, HPT, adrenal disease,

TABLE 4. Clinical and Laboratory ZES Features in the NIH MEN1/ZES Patients by Survival Status

Disease Feature	Number (%) ⁽¹⁰⁾		P
	Alive	Dead ⁽¹¹⁾	
No. of patients	82	24	
Age ZES onset (yr) ⁽¹⁾			
Mean ± SEM	34.1 ± 1.1	35.4 ± 2.3	0.70
[range]	[12.1–60.6]	[0.04–23.0]	
Duration ZES onset to diagnosis (yr) ⁽¹⁾			
Mean ± SEM	4.9 ± 0.6	8.1 ± 1.4	0.039
[range]	[0.01–26.2]	[0.04–23.16]	
Duration ZES onset to last follow-up (yr)			
Mean ± SEM	19.1 ± 1.1	21.2 ± 1.9	0.28
[range]	[3.6–46.4]	[8.0–42.5]	
BAO (mEq/h) ⁽²⁾			
Mean ± SEM	41.1 ± 3.4	54.3 ± 8.7	0.16
[range]	[4.3–112]	[13.5–144]	
MAO (mEq/h) ⁽²⁾			
Mean ± SEM	57.6 ± 4.6	75.4 ± 8.1	0.059
[range]	[15–133]	[29.4–144]	
Fasting serum gastrin (pg/mL) ⁽³⁾			
Median	720	1412	
Mean ± SEM	15,215 ± 7198	3807 ± 1412	0.20
[range]	[52–550,000]	[180–22,000]	
>20-fold increased	19 (24%) ⁽⁴⁾	11 (50%) ⁽⁴⁾	0.022
Δ secretin–serum gastrin (pg/mL) ⁽⁵⁾			
Median	1380	570	
Mean ± SEM	28,729 ± 13,145	1846 ± 781	0.29
[range]	[0–700,000]	[137–25,000]	
Antisecretory drug			
H2R taken ⁽⁶⁾	44 (54%)	18 (75%) ⁽¹⁰⁾	0.064
PPI taken ⁽⁶⁾	70 (85%)	19 (79%)	
Duration total treatment (yr)	14.0 ± 0.9	14.7 ± 1.7	
Duration PPI treatment (yr)	9.9 ± 0.5	9.9 ± 1.2	
Prior gastric acid surgery ⁽⁷⁾	11 (13%)	8 (33%)	0.0261
Present ZES symptom ⁽⁸⁾			
Pain	53 (65%)	17 (71%)	NS
Diarrhea	54 (66%)	18 (75%)	NS
Pain/diarrhea	34 (41%)	14 (58%)	0.142
Heartburn/GERD	37 (45%)	16 (67%)	0.065
Peptic ulcer history	45 (55%)	17 (71%)	0.16
ZES complication			
Bleeding	15 (18%)	5 (21%)	NS
Other ⁽⁹⁾	14 (17%)	7 (29%)	0.19

Abbreviations: See previous tables. H2R = Histamine H₂-receptor antagonist, PPI = proton pump inhibitor, Δ secretin–serum gastrin = increase in fasting gastrin during the secretin test.

⁽¹⁾Onset of ZES was the time of continuous symptoms compatible with gastric acid hypersecretion as defined in Methods.³⁶⁵

⁽²⁾BAO data are from 82 patients (65 alive, 17 dead) and MAO from 53 patients (38 alive, 15 dead) who had not had previous gastric acid reducing surgery.³⁶⁴

⁽³⁾Fasting serum gastrin concentration is the average of at least 3 separate values during the initial evaluation at NIH.³⁶

⁽⁴⁾Initial fasting gastrin levels prior to any treatment were available from 78 of the patients still alive and 22 of the deceased patients.

⁽⁵⁾The Δ secretin–serum gastrin is the increase in serum gastrin (in pg/mL) postbolus injection of secretin determined as described in Methods and previously.³⁵

⁽⁶⁾H2R treatment includes use of cimetidine, metiamide, ranitidine, famotidine, and PPI treatment includes use of omeprazole, lansoprazole, esomeprazole.^{69,135,282}

⁽⁷⁾Previous gastric surgery includes patients with prior vagotomies (n = 13), Billroth I or II gastrectomies (n = 7), or total gastrectomies (n = 7).

⁽⁸⁾Initial symptom of ZES at presentation determined as described in Methods and in reference 365.

⁽⁹⁾Other complications include intestinal perforation (n = 8), pyloric obstruction (n = 6), esophageal stricture (n = 11).

⁽¹⁰⁾Numbers in parentheses are the percentage of the patients with the indicated feature that were alive or dead.

⁽¹¹⁾Number patients died of any cause during follow-up.

TABLE 5. Clinical and Laboratory MEN1 Features in NIH MEN1/ZES Patients by Survival Status

Disease Feature	Number (%) ⁽¹²⁾		P
	Alive	Dead ⁽¹³⁾	
No. of patients	82	24	
Age at MEN1 onset (yr) ⁽¹⁾			
Mean ± SEM	30.0 ± 1.3	27.2 ± 2.2	0.29
[range]	[12.1–60.6]	[10.2–51.3]	
Age at MEN1 diagnosis (yr) ⁽²⁾			
Mean ± SEM	38.6 ± 1.4	37.0 ± 3.0	0.80
[range]	[15–72.8]	[12.6–61.1]	
Duration of follow-up (yr)			
Time from diagnosis of MEN1 to death/last follow-up			
Mean ± SEM	15.1 ± 1.4	17.2 ± 2.3	>0.4
[range]	[1.0–43.0]	[3.6–44.3]	
Time from onset HPT to last follow-up/death ⁽³⁾			
Mean ± SEM	19.8 ± 1.4	24.1 ± 2.9	0.17
[range]	[1.0–59.5]	[3.6–56.4]	
MEN1 family history	55 (67%)	21 (88%)	0.052
MEN1 feature present			
HPT	80 (98%)	23 (96%)	0.65
Pituitary disease ⁽⁴⁾	47 (57%)	15 (62%)	0.65
Adrenal disease	34 (41%)	12 (50%)	0.46
Any carcinoid	29 (35%)	9 (38%)	0.85
Gastric ⁽⁵⁾	14 (17%)	6 (25%)	0.38
Lung ⁽⁵⁾	9 (11%)	2 (8%)	0.71
Thymic ⁽⁵⁾	3 (4%)	3 (12%)	0.098
Skin disease ⁽⁶⁾	46 (56%)	8 (33%)	0.051
Thyroid disease	9 (11%)	3 (12%)	
Other functional PET ⁽⁷⁾	5 (6%)	5 (21%)	0.031
Other functional syndrome ⁽⁸⁾	14 (17%)	11 (46%)	0.0033
Other ⁽⁹⁾	14 (17%)	1 (4%)	0.109
MEN1 feature present first			
HPT 1st	36 (44%)	13 (54%)	0.38
ZES 1st	36 (44%)	6 (25%)	0.094
Pituitary disease 1st	8 (10%)	4 (17%)	0.34
ZES and HPT 1st ⁽¹⁰⁾	2 (2%)	1 (4%)	0.64
Time (yr) from HPT onset to ZES diagnosis ⁽²⁾			
Mean ± SEM	8.0 ± 0.8	12.3 ± 2.3	<0.05
[range]	[0–36.0]	[0.01–34.3]	
PTX (amount removed, total) ⁽¹¹⁾			
<3 glands	28 (34%)	8 (33%)	0.91
3–3.5 glands	32 (39%)	8 (33%)	0.61
>3.5 glands	5 (6%)	4 (17%)	0.10
PTX (number) ⁽¹¹⁾			
0	16 (20%)	4 (17%)	0.75
1	32 (39%)	8 (33%)	0.61
2–3	31 (38%)	8 (33%)	0.68
>3	2 (2%)	4 (17%)	0.008
HPT features			
Renal colic present	41 (50%)	14 (58%)	0.47
Age HPT onset			
Mean ± SEM	33.6 ± 1.4	31.1 ± 2.4	>0.3
[range]	[12.8–72.8]	[13.2–51.3]	
Age first PTX			0.54
Mean ± SEM	35.6 ± 1.2	38.1 ± 3.0	
[range]	[15.1–57.4]	[20.3–61.7]	

TABLE 5. (Continued)

Disease Feature	Number (%) ⁽¹²⁾		P
	Alive	Dead ⁽¹³⁾	
Yr HPT onset to first PTX			0.62
Mean ± SEM	4.4 ± 0.7	7.5 ± 2.2	
[range]	[0.1–26.0]	[0.1–34.7]	

Abbreviations: See previous tables. PTX = parathyroidectomy.

⁽¹⁾Onset of MEN1 was the time of first symptoms compatible with MEN1 or time of detection at screening if asymptomatic as defined previously and in Methods.¹⁴⁰

⁽²⁾Diagnosis of MEN1 or ZES was the first time the patient was informed he/she had MEN1 or ZES respectively.^{31,135,140}

⁽³⁾Onset of hyperparathyroidism was time of the first symptom occurrence or biochemical result compatible with its presence as defined as described previously and in Methods.^{140,328}

⁽⁴⁾Pituitary disease included 49 patients with prolactinomas, 10 with nonfunctional tumors, 7 with Cushing disease and one with acromegaly diagnosed as described previously and in Methods.^{140,267}

⁽⁵⁾Gastric, lung and thymic carcinoids were identified by upper gastrointestinal endoscopy, conventional imaging studies and SRS diagnosed as described previously and in Methods.^{34,131,139,140,268}

⁽⁶⁾Skin disease included 36 patients with angiofibromas, 34 with collagenomas, 12 with other skin tumors including 7 lipomas, 3 melanomas and 1 patient with café au lait spots determined as described previously and in Methods.^{14,140}

⁽⁷⁾Other functional PETs included 10 patients with insulinomas, 1 with glucagonoma, and 1 causing carcinoid syndrome.

⁽⁸⁾Other functional syndromes included the 10 patients with other functional PETs in footnote #7, ten patients with Cushing disease, 3 patients with Cushing syndrome, a patient with pheochromocytoma and 1 with acromegaly.

⁽⁹⁾Other included 4 patients with meningiomas,¹³ 1 with an ependymoma, 2 with neurolemmona/schwannoma, 1 with an appendiceal carcinoid, 4 with leiomyomas/leiomyosarcomas, and 2 with angiofibromas.

⁽¹⁰⁾ZES and MEN1 present feature means three patients presented with the onset of both HPT and ZES symptoms at same time.

⁽¹¹⁾PTX total amount removed refers to the number of parathyroid glands removed during the indicated number of parathyroidectomies.

⁽¹²⁾Numbers in parentheses are the percentages of the patients with the indicated feature that were alive or dead.

⁽¹³⁾Number patients died of any cause during follow-up; 14 died an MEN1-related death (Figure 1).

any carcinoid tumor, any MEN1-related skin disorders, or the initial MEN1 presenting feature.

Numerous studies, but not all, report that various PET tumoral features and their treatment, such as PET size, extent, location, growth rate, distant metastases, PET resection, and duration of the PET may all have prognostic significance for either survival or for the development of liver metastases, which is the most important determinant of survival,^{54,141,191,288,338,340,434,459,476} in both patients with sporadic PETs^{90,118,133,141,252,288,320,398,405,459,476} and in a few studies of patients with MEN1.^{54,88,141,150,195,217,233,234,433,434} We compared each of these tumoral variables in NIH patients by survival status (Table 6). Large primary tumor size (>3 cm) (p = 0.022), presence of liver metastases initially (p = 0.011), development of bone metastases (p = 0.0002), development of liver metastases (p = 0.0010), presence of a PET on initial imaging (p = 0.0322), and aggressive tumor growth (p < 0.00001) were all more frequent in the deceased patients than in those still alive at last follow-up. In

contrast, the location of the primary gastrinoma (duodenal vs pancreatic), the presence of lymph node metastases, the age when liver metastases were found, whether a PET resection was performed or not, the age a PET resection was performed,

TABLE 6. Tumoral Features in NIH MEN1/ZES Patients by Survival Status

Disease Feature	Number (%) ⁽¹²⁾		P
	Alive	Dead ⁽¹³⁾	
No. of patients	82	24	
Primary gastrinoma location ⁽¹⁾			
Duodenum	43 (52%)	13 (54%)	0.58
Pancreas	12 (15%)	3 (12%)	
Unknown ⁽¹⁾	33 (40%)	11 (46%)	
Pancreatic PET present ⁽²⁾			
Yes	48 (58%)	16 (67%)	0.47
No	34 (42%)	8 (33%)	
Primary tumor size (cm) ⁽³⁾			
Mean ± SEM	2.9 ± 0.2	3.7 ± 0.5	0.072
[range]	[0.4–12.0]	[1.5–9.0]	
≤1 cm ⁽³⁾	20 (24%)	2 (8%)	0.086
1.1–3 cm	44 (54%)	11 (46%)	
>3 cm	18 (22%)	11 (46%)	0.022
Tumor extent			
Localized ⁽⁴⁾	63 (77%)	12 (50%)	0.0029
Distant metastases ⁽⁵⁾	19 (23%)	12 (50%)	0.011
Liver metastases	19 (23%)	12 (50%)	0.011
Bone metastases	3 (4%)	7 (29%)	0.0002
Lymph node metastases ⁽⁶⁾			
Yes	40 (49%)	8 (33%)	
No	11 (13%)	7 (29%)	0.057
Unknown ⁽⁶⁾	31 (38%)	9 (38%)	
Age liver metastases found			
Mean ± SEM	41.6 ± 1.3	42.3 ± 3.1	0.97
[range]	[24.0–61.8]	[17.4–62.4]	
No. lesions initially imaged ⁽⁷⁾			
0	15 (18%)	1 (4%)	0.032
1	27 (33%)	11 (38%)	
2	18 (22%)	5 (21%)	
>2	22 (27%)	7 (29%)	
PET resection ⁽⁸⁾			
Yes	51 (62%)	17 (71%)	0.44
No	31 (38%)	7 (29%)	
Age tumor resection (yr)			
Mean ± SEM	41.6 ± 1.3	42.3 ± 3.1	
[range]	[24.0–61.8]	[17.4–62.4]	0.72
Yrs MEN1 onset to resection ⁽⁹⁾			
Mean ± SEM	11.5 ± 1.3	12.6 ± 2.7	0.98
[range]	[0.1–39.2]	[1.0–35.4]	
Yrs ZES onset to resection ⁽⁹⁾			
Mean ± SEM	7.6 ± 1.0	9.3 ± 1.8	0.59
[range]	[0.8–29.4]	[0.1–25.0]	
Developed new lesions ⁽¹⁰⁾			
Any lesion	27 (33%)	12 (50%)	0.124
Liver metastases	14 (17%)	12 (50%)	0.0010
Aggressive disease ⁽¹¹⁾			
Yes	13 (16%)	16 (67%)	<0.00001

TABLE 6. (Continued)

Disease Feature	Number (%) ⁽¹²⁾		P
	Alive	Dead ⁽¹³⁾	
No	69 (84%)	8 (33%)	

Abbreviations: See previous tables.

⁽¹⁾Primary gastrinoma location was determined by surgery, imaging or endoscopy in 62 patients as described in methods and previously.^{141, 189,315} Three patients had both a duodenal and pancreatic gastrinoma.

⁽²⁾Primary pancreatic PET was identified using either surgery, endoscopy or imaging with cross sectional imaging studies and SRS.^{7,138, 140,220,315}

⁽³⁾Diameter of largest primary PET identified by surgery, endoscopy or imaging.

⁽⁴⁾Localized refers to no liver, bone or other distant metastases present.¹⁴⁰

⁽⁵⁾Distant metastases include those in liver, bone, and other distant sites determined using cross section imaging, SRS and bone scanning as described in Methods and previously.^{135,405}

⁽⁶⁾Lymph node metastases were determined at surgery in 44 patients and distinguished from a lymph node gastrinoma primary as described in Methods and previously.^{12,314} Unknown refers to results in 38 patients without surgery.

⁽⁷⁾Refers to the number of possible primary PETs or localized lesions seen on initial imaging studies.^{7,315}

⁽⁸⁾Number of patients who underwent attempted PET resection as described previously.^{250,315,324}

⁽⁹⁾Onset of MEN1 and ZES were determined as described in Table legends 1–3 and Methods.

⁽¹⁰⁾Refers to the development of new lesions on follow-up imaging studies determined as described in Methods.

⁽¹¹⁾Aggressive growth during follow-up was determined from serial imaging studies as defined and described in Methods and previously.^{141,382,405}

⁽¹²⁾Numbers in parentheses are the percentage of the patients with the indicated feature that were alive or dead.

⁽¹³⁾Number of patients who died of any cause during follow-up; 14 died an MEN1-related death (Figure 1).

or the duration from ZES onset to the tumor of a PET resection did not differ between the 2 groups of patients.

Clinical and Tumoral Features in NIH MEN1/ZES Patients Who Died From MEN1-Related and non-MEN1-Related Causes

To investigate further prognostic factors that might be associated with an MEN1-related death, we compared various clinical, laboratory, and tumoral features of MEN1 and ZES for the NIH MEN1/ZES patients classified as having either an MEN1-related death or a non-MEN1-related death. We compared the clinical and laboratory features of MEN1 or ZES and tumoral features that were compared in the NIH patients by survival status in Tables 5 and 6 in patients who had either an MEN1-related death or a non-MEN1-related death (Tables 7 and 8). We found no significant differences for any of the 34 clinical or laboratory characteristics compared. In particular, there was no significant difference in fasting gastrin level, duration, or other features of various MEN1-related manifestations, many of which have been reported to have prognostic significance in some studies.^{46,54,71,141,151,152,414,465} In contrast, for a number of the tumoral features in the NIH patients, there was a significant difference between patients who did or did

not have an MEN1-related death. Specifically, of the 42 tumor features compared, those significantly associated with an MEN1 disease-related death included an increased primary tumor size ($p = 0.0203$), particularly >3 cm ($p = 0.0042$); the presence of liver metastases ($p = 0.0180$), bone metastases ($p = 0.0180$), or any distant metastases ($p = 0.0180$); the number of PET lesions initially imaged, particularly if ≥ 2 were seen ($p = 0.0180$); a younger age of developing liver metastases ($p = 0.028$); the development of any new lesions during follow-up ($p = 0.0180$); the development of liver metastases during follow-up ($p = 0.0180$); or the presence of tumors demonstrating aggressive growth ($p = 0.0001$). Whether a previous PET resection occurred has been reported to be an important tumor feature in some studies of NIH MEN1/ZES patients^{22,150,195,217,217,234} and to have prognostic significance; however, we did not find it to be important in the current study as a prognostic factor for an MEN1-related death ($p = 0.30$). Similarly, in contrast to sporadic ZES, a number of tumoral features reported to have prognostic value for disease-related death^{118,191,201,279,287,320,459,476} were not found to be associated with an MEN1/ZES-related death in the current study, including the presence of a pancreatic PET rather than a duodenal PET ($p = 0.47$); the presence of any pancreatic PET ($p = 0.44$); the failure to undergo a PET resection ($p = 0.30$); or the presence of lymph node metastases ($p = 0.56$).

MEN1 and Tumoral Features in 227 MEN1/PET Patients From the Pooled Literature Who Died From MEN1-Related and non-MEN1-Related Causes

We carried out a similar analysis to identify possible prognostic factors determining an MEN1-related death in the 227 MEN1/PET patients from the pooled literature (Table 9). For various MEN1 features there was no significant difference between the percentage of patients who died from an MEN1-related or unrelated cause, including HPT (95% vs 96%, respectively); pituitary disease (23% vs 20%); adrenal abnormality (8.9% vs 8.7%); ZES (66% vs 75%); another functional PET (22% vs 17%); a nonfunctional PET (29% vs 18%); or a CNS, skin, or smooth muscle tumor (0–3.5%). In contrast, MEN1/PET patients from the pooled literature with an MEN1-related death more frequently had a carcinoid tumor (26% vs 9%, $p = 0.0048$), and in particular a thymic carcinoid tumor (22% vs 3.3%, $p = 0.006$) but not a gastric, lung, or intestinal carcinoid. Almost reaching significance was the presence of PETs other than gastrinomas in patients with an MEN1-related death (47% vs 33%, $p = 0.058$), whereas thyroid disease showed a trend toward higher occurrence in patients with a non-MEN1-related death (0 vs 2.95%, $p = 0.050$).

The pooled literature MEN1/PET patients with an MEN1-related death died at a younger age than those with a non-MEN1-related death (51.1 ± 1.2 vs 53.0 ± 2.1 yr), with 51% dying before age 46 years compared to 29% of patients with non-MEN1-related deaths ($p = 0.002$) (see Table 9). In contrast, there was no difference in the age at diagnosis of MEN1 (44.9 ± 1.2 vs 49.0 ± 2.4 yr), with 79%–83% of both groups aged >45 years at diagnosis; nor in the age of onset of ZES (43.9 ± 1.2 vs 46.6 ± 2.2 yr), with 50%–66% aged >44 years at the time of diagnosis. Similarly, there was no difference in sex frequency in patients dying from an MEN1-related- or non-MEN1-related cause (60%–62% male); however, a family history of MEN1 was significantly more frequent in patients dying from an MEN1-related cause than in patients with a non-MEN1-related cause of death (91% vs 77%, $p = 0.019$), as was the occurrence of liver metastases (72% vs 20%, $p < 0.0001$).

Effect of Different MEN1 Gene Mutations on Total and MEN1 Disease-Related Survival for 106 NIH MEN1/ZES Patients

Although in most studies no genotype-phenotype correlations are reported in MEN1 patients with the different manifestations or tumor features,^{143,419,420,457} in a few studies the presence or absence of certain MEN1 gene mutations (that is, exon 2 or nonsense/frameshift mutations in exon 2, 9, 10)^{22,217} is reported to have prognostic significance. To explore this possibility in the 106 NIH MEN1/ZES patients, we correlated the presence or absence of various types and locations of MEN1 gene mutations with both total survival and MEN1 disease-related survival (Table 10). For the 89 patients who underwent MEN1 gene testing, the location of the MEN1 gene mutation (exon 2, 8, or exon 9) did not have prognostic significance nor did the presence of a mutation that was not predicted to inactivate menin (missense, nonframeshift changes). However, inactivating mutations overall showed a trend to being more frequent in patients who died of any cause ($p = 0.084$), and were borderline more frequent in patients dying from a disease-related cause ($p = 0.047$) both in all patients and in those with only familial MEN1 ($p = 0.047$). The presence of frameshift mutations showed a similar result.

Total Survival and MEN1 Disease-Related Survival for 106 NIH MEN1/ZES Patients

To assess the total survival as well as the MEN1 disease-related survival for the 106 prospectively studied NIH MEN1/ZES patients, we analyzed both types of survival in the form of Kaplan-Meier plots (Figure 2), using time from onset of MEN1 (24.5 ± 1.2 yr; range, 3.6–59.3 yr) or time from diagnosis of MEN1 (15.5 ± 0.9 yr; range, 0.96–44.3 yr). The 5-year survival was excellent (97%–100%) for each of the 4 categories assessed in the NIH patients (that is, total survival from MEN1 onset or diagnosis, and MEN1 disease-related survival from MEN1 onset or diagnosis) (Table 11). The total survival curve for the NIH MEN1/ZES patients for time from MEN1 onset was not significantly different from the MEN1 disease-related survival (hazard ratios [HR] for onset or diagnosis, 1.7; 95% CI, 0.9–3.2) (see Figure 2, panel A). The median total survival time from time of MEN1 onset was 42.8 yr (95% CI, 25–69 yr), whereas for MEN1 disease-related survival, the median survival time was >50 years. For the NIH patients, the median total survival from time of diagnosis was 36.5 yr (95% CI, 11–73 yr); it was similar for MEN1-disease related survival (see Figure 2, panel B). The 20-year disease-related survival for NIH patients, from either diagnosis or onset of MEN1, remained excellent with values of 80% and 93%, respectively, whereas the 20-year total survival was 67.5% and 90%, respectively.

In contrast, when a similar survival analysis was performed for the 227 MEN1/PET patients from the pooled literature, both the total survival and the disease-related survival were much poorer, with 5-year survivals of 60% and 68%, respectively, and 20-year survivals of 5% and 15%, respectively (see Figure 2, panel C; Table 11). The median survival times were also shorter for the pooled literature data than for the NIH data, with a mean of 6.1 years (95% CI, 5.7–7.0 yr) for the total survival for pooled literature patients and 8 years (95% CI, 7.5–9.3 yr) for disease-related survival, which were significantly different ($p = 0.0011$).

DISCUSSION

Classically, patients with MEN1 develop adenomas or hyperplasia of multiple endocrine glands, with HPT due to parathyroid hyperplasia the most frequent abnormality, followed by

functional or nonfunctional PETs, pituitary adenomas, adrenal tumors, and thyroid adenomas, as discussed above in the Introduction. It has been increasingly recognized that these patients develop additional tumors including carcinoid tumors (thymic, gastric, bronchial, and rarely intestinal); characteristic tumors of the skin (angiofibromas, collagenomas, lipomas, melanomas); CNS tumors (meningiomas, ependymomas, schwannomas); and smooth muscle tumors (leiomyomas, leiomyosarcomas). (See Introduction for details.)

TABLE 7. Clinical MEN1 and ZES Features in Deceased NIH MEN1/ZES Patients With or Without MEN1-Related Death

Disease Feature	No. (%) ⁽¹¹⁾		P
	Yes	No	
No. of patients	14	10	
Male	7 (50%)	7 (70%)	0.29
Age (yr)			
MEN1 onset	28.4 ± 2.7	25.4 ± 3.7	0.32
MEN1 diagnosis	36.4 ± 3.5	37.8 ± 5.4	0.81
ZES onset	35.5 ± 2.2	35.1 ± 5.7	0.91
HPT onset	32.8 ± 3.3	28.9 ± 3.5	0.46
1 st PTX	37.3 ± 3.8	39.0 ± 5.0	0.73
Age death	54.6 ± 3.0	55.8 ± 5.5	0.60
Duration (yr)			
Onset MEN1 to death	26.1 ± 3.1	30.3 ± 4.3	0.41
MEN1 diagnosis to death	18.2 ± 3.2	15.8 ± 3.2	0.86
ZES onset to death	20.3 ± 2.6	22.6 ± 2.8	0.48
ZES onset to diagnosis	7.4 ± 1.9	9.0 ± 2.4	0.55
Initial Lab studies			
Fasting serum gastrin (pg/mL)			
Median	610	2000	0.38
Mean ± SEM	4704 ± 1843	2411 ± 662	
[range]	[180–22000]	[650–6398]	
BAO (mEq/h) ⁽¹⁾	41.9 ± 7.6	65.3 ± 14.4	0.44
MAO (mEq/h) ⁽¹⁾	71.2 ± 8.1	78.2 ± 12.6	0.95
Δ secretin–serum gastrin (pg/mL) ⁽²⁾	2366 ± 1474	1268 ± 315	0.33
Antisecretory drug			
H2R taken ⁽³⁾	9 (64%)	9 (90%)	0.17
PPI taken ⁽³⁾	10 (71%)	9 (90%)	0.29
Prior gastric acid surgery ⁽⁴⁾	5 (36%)	3 (30%)	0.56
ZES complication			
Bleeding	4 (29%)	1 (10%)	0.29
Other ⁽⁵⁾	5 (36%)	2 (20%)	0.36
Renal colic present	7 (50%)	7 (70%)	0.29
Family history MEN1	12 (86%)	9 (90%)	0.63
MEN1 feature present			
HPT	13 (93%)	10 (100%)	0.58
Pituitary disease ⁽⁶⁾	8 (57%)	7 (70%)	0.42
Adrenal disease	6 (43%)	6 (60%)	0.34
Any carcinoid	6 (43%)	3 (30%)	0.42
Gastric	4 (28%)	2 (20%)	0.51
Lung	1 (7%)	1 (10%)	0.67
Thymic	3 (21%)	0 (0%)	0.18
Skin disease ⁽⁷⁾	7 (50%)	1 (10%)	0.051
Thyroid disease	1 (7%)	2 (20%)	0.37

TABLE 7. (Continued)

Disease Feature	No. (%) ⁽¹¹⁾		P
	Yes	No	
Other functional PET ⁽⁸⁾	4 (28%)	1 (8%)	0.28
Other functional syndrome ⁽⁹⁾	7 (50%)	4 (8%)	0.47
Other ⁽¹⁰⁾	1 (7%)	0 (8%)	0.58

Abbreviations: See Table 5 and 6 legends.

⁽¹⁾BAO data are from 17 patients (8 MEN1 death, 9 non-MEN1 death) and MAO from 15 patients (6 MEN1 death, 9 non-MEN1 death) who had not had previous gastric acid reducing surgery.^{200,364}

⁽²⁾The Δ secretin–serum gastrin is the increase in serum gastrin (in pg/mL) post bolus injection of secretin determined as described in Methods and previously with an increased >120 pg/mL considered positive.³⁵

⁽³⁾H2R treatment include use of cimetidine, metiamide, ranitidine, famotidine and PPI treatment include use of omeprazole, lansoprazole, esomeprazole.^{69,135,282}

⁽⁴⁾Previous gastric surgery includes patients with prior vagotomies (n=6), Billroth I or II gastrectomies (n = 5), or total gastrectomies (n = 3).

⁽⁵⁾Other complications include intestinal perforation (n = 2), pyloric obstruction (n = 2), esophageal stricture (n = 5).

⁽⁶⁾Pituitary disease included 11 patients with prolactinomas, 2 with nonfunctional tumors, 2 with Cushing disease diagnosed as described previously and in Methods.^{140,267}

⁽⁷⁾Skin disease included 4 patients with angiofibromas, 3 with collagenomas, and 3 with other skin tumors including 2 lipomas, and 1 melanomas determined as described previously and in Methods.^{14,140}

⁽⁸⁾Other functional PETs included 4 patients with insulinomas and 1 with glucagonoma.

⁽⁹⁾Other functional syndromes included the 5 patients with other functional PETs in footnote #8, 4 patients with Cushing disease, 1 patients with Cushing syndrome, and 1 patient with a pheochromocytoma.

⁽¹⁰⁾Other included 1 patient with a meningioma.¹³

⁽¹¹⁾Number in parentheses is the percentage of the patients with the indicated feature that did or did not have an MEN1-related death.

Although many aspects of MEN1 have been well studied, one of the most important clinical areas, that affects many aspects of the management of these patients, is a clearer understanding of the natural history of the late course of the disease.^{140,141,276} At present there is little prospective information available, particularly related to causes of death and prognostic factors that are important to identify various disease courses of patients in the late stages of MEN1.¹⁹⁵ This lack of information has occurred for a number of reasons, including a number of changes over the last few years that have markedly altered the natural history of MEN1, and likely the causes of death.

First, most studies in the literature are retrospective; many contain only small numbers of cases, which limits analyses; and most of the larger studies contained pooled data from different centers, leading to data variation and the frequent use of historical records or retrospective data to determine causes of death; and therefore they have limitations.

Second, in various studies where 20%–70% (mean 54%, 18 series) of the MEN1 patients developed ZES,^{15,49,63,73,102,152,189,208,212,261,264,298,348,387,418,436,436,444} the most common functional PET seen in patients with MEN1,^{140,195,261,418} the uncontrolled gastric acid hypersecretion, which is characteristic of ZES,^{200,201,279,364} was a leading cause of early death.^{15,43,72,73,83,88,158,180,224,225,240,254,307,353,366,386,399,438,444,}

TABLE 8. Various MEN1 Clinical and Tumoral Features in Deceased NIH MEN1/ZES Patients With or Without an MEN1-Related Death

Disease Feature	No. (%) ⁽⁹⁾		P
	Yes	No	
No. of patients	14	10	
MEN1 feature present first			
HPT 1st	6 (43%)	2 (20%)	0.23
ZES 1st	4 (29%)	7 (70%)	0.22
Pituitary disease 1st	3 (21%)	1 (10%)	0.44
Both HPT/ZES	1 (7%)	0 (0%)	0.58
PTX (amount removed-total)			
<3 glands	3 (21%)	5 (50%)	0.15
3–3.5 glands	5 (36%)	3 (30%)	0.15
>3.5 glands	3 (21%)	1 (10%)	0.44
PTX (number)			
0	3 (21%)	1 (10%)	0.44
1	4 (29%)	5 (50%)	0.26
2–3	5 (36%)	3 (30%)	0.56
>3	2 (14%)	0 (0%)	0.33
Primary gastrinoma location ⁽¹⁾			
Duodenum	7 (50%)	6 (60%)	0.47
Pancreas	1 (7%)	2 (20%)	0.37
Unknown ⁽¹⁾	7 (50%)	2 (20%)	0.14
Pancreatic PET present ⁽²⁾			
Yes	10 (71%)	6 (60%)	0.44
No	4 (29%)	4 (40%)	
Primary tumor size (cm)			
Mean ± SEM	4.5 ± 0.6	2.3 ± 0.3	0.0203
[range]	[1.5–9.0]	[1.5–3.5]	
≤1 cm	0 (0%)	2 (20%)	0.16
1.1–3 cm	4 (29%)	7 (70%)	
>3 cm	10 (71%)	1 (10%)	0.0042
Tumor extent			
Localized ⁽³⁾	4 (29%)	2 (20%)	0.51
Distant metastases ⁽⁴⁾	10 (71%)	2 (30%)	0.0180
Liver metastases	10 (71%)	2 (20%)	0.0180
Bone metastases	7 (29%)	0 (0%)	0.0099
Lymph node metastases ⁽⁵⁾			
Yes	5 (36%)	3 (30%)	0.56
No	4 (29%)	3 (30%)	
Unknown ⁽⁵⁾	5 (36%)	4 (40%)	
Age liver metastases found			
Mean ± SEM	49.9 ± 2.5	56.8 ± 5.3	0.028
[range]	[35.6–64.2]	[51.5–62.1]	
Number lesions initially imaged ⁽⁶⁾			
0	0 (0%)	1 (10%)	0.42
1	4 (29%)	7 (70%)	0.22
2	4 (29%)	1 (10%)	0.28
>2	6 (43%)	1 (10%)	0.097
PET resection			
Yes	11 (79%)	6 (60%)	0.30
No	3 (21%)	4 (40%)	
Age tumor resection (yr)			
Mean ± SEM	39.5 ± 3.3	47.4 ± 6.2	
[range]	[17.4–53.2]	[22.7–62.4]	0.16

(continued on next page)

TABLE 8. (Continued)

Disease Feature	No. (%) ⁽⁹⁾		P
	Yes	No	
Yr MEN1 onset to resection			
Mean ± SEM	10.4 ± 2.6	16.4 ± 5.9	0.19
[range]	[1.0–25.4]	[1.9–35.4]	
Yr ZES onset to resection			
Mean ± SEM	8.6 ± 2.1	10.4 ± 3.8	0.61
[range]	[0.1–19.7]	[1.0–25.1]	
Developed new lesions ⁽⁷⁾			
Any lesion	10 (71%)	2 (20%)	0.0180
Liver metastases	10 (71%)	2 (20%)	0.0180
Aggressive disease ⁽⁸⁾			
Yes	14 (100%)	2 (20%)	0.0001
No	0 (0%)	8 (80%)	

Abbreviations: See Table 4–6 legends.

⁽¹⁾Primary gastrinoma location was determined by surgery, imaging or endoscopy in 62 patients as described in methods and previously.^{141,189,315} Three patients had both a duodenal and pancreatic gastrinoma.

⁽²⁾Primary pancreatic PET (gastrinoma, nonfunctional PET, other) was identified using either surgery, endoscopy, or imaging with cross-sectional imaging studies and SRS.^{7,138,140,220,315}

⁽³⁾Localized refers to no liver, bone, or other distant metastases present.¹⁴⁰

⁽⁴⁾Distant metastases include those in liver, bone, and other distant sites including lymph nodes determined using cross-sectional imaging, SRS, and bone scanning as described in Methods and previously.^{133,405}

⁽⁵⁾Lymph node metastases were determined at surgery in 8 patients and distinguished from a lymph node gastrinoma primary as described in Methods and previously.^{123,314} Unknown refer to results in 9 patients without surgery.

⁽⁶⁾Refers to the number of possible primary PETs or localized lesions seen on initial imaging studies.^{7,315}

⁽⁷⁾Refers to the development of new lesions on follow-up imaging studies determined as described in Methods.

⁽⁸⁾Aggressive growth during follow-up was determined from serial imaging studies as defined and described in Methods and previously.^{141,382,405}

⁽⁹⁾Numbers in parentheses are the percentage of the patients with the indicated feature that were alive or dead.

458,461,465,466 Gastric acid hypersecretion accounted for up to 73%–91% of all deaths in some early series.^{15,195,224,254,444}

At present the situation is entirely different, with the development of effective means to treat the gastric acid hypersecretion; first surgically with total gastrectomy described in the 1950–1960s,^{108,424,483} followed by increasingly effective medical therapy, first with histamine H₂-receptor antagonists^{69,135,178,193,197,266,272,278,295} and later with H⁺, K⁺ ATPase inhibitors (proton pump inhibitors).^{123,171,189,192,227,270,278,284} Proton pump inhibitors are the drugs of choice controlling the acid hypersecretion in almost every ZES patient, both acutely and long-term,^{123,171,189,192,227,266,270,278,281,284,295,350} because tachyphylaxis does not develop.^{123,171,189,192,227,270,278,281,284} The availability of proton pump inhibitors has almost completely eliminated the lethal complications of peptic ulcer disease (perforation, bleeding, penetration) in MEN1/ZES patients which were so frequent in older studies.^{15,17,43,72,73,83,88,107,129,140,158,180,189,195,224,225,240,254,307,310,353,366,386,399,438,444,458,461,462,465,466,474} and therefore their

use has changed the natural history of MEN1 in regard to times and causes of death. To our knowledge, at present there are no prospective studies of the natural history of MEN1 and the causes of death that reflect these changes in the control of acid hypersecretion.

Third, in other older studies, uncontrolled HPT, leading to nephrolithiasis and renal failure^{3,245,465} was not an uncommon course of death.^{15,32,68,88,129,224,285,438,444,465,466} With the increased understanding of the diffuseness of the parathyroid disease (hyperplasia affecting all glands) requiring either a 3.5-gland parathyroidectomy or 4-gland parathyroidectomy with a parathyroid

implant to effectively control the HPT long-term,^{11,42,44,104,169,211,328,330,352,376} renal failure due to uncontrolled HPT is now a rarely reported cause of death (Table 12).^{54,57,78,129,149,150}

Fourth, it has become increasingly apparent that MEN1 patients develop a number of tumors that are different from the classical endocrine tumors or hyperplasia originally described. These include both other endocrine tumors (carcinoids of thymus, stomach, lung, rarely intestinal) and nonendocrine tumors (CNS tumors [meningiomas, schwannomas, ependymomas], skin tumors [angiofibromas, collagenomas, lipomas, melanomas], and smooth muscle tumors [leiomyomas, leiomyosarcomas]).^{13,14,34,56,66,74,111,131,151,176,195,228,261,274,368,388,390,393,413,428,465} Of these, particularly thymic carcinoids, which occur primarily in males, occur characteristically later in the MEN1 course (mean age, 42–46 yr), are generally very aggressive, and hence are increasingly a cause of death.^{111,130,131,151,408,413,414,465} Similarly, in some studies lung carcinoid tumors as well as gastric carcinoids/NETs also can pursue an aggressive course.^{34,40,94,150,253,326,360,465} The fact that MEN1 patients are living longer¹⁵⁰ is raising the likelihood that a number of these more newly described tumor types in MEN1 patients will play an increasing role in long-term survival as most occur later in the course of patients with MEN1,^{13,131,195,261,280,326,418} and their effect has generally not been evaluated.

Fifth, genetic diagnosis and family screening are being used increasingly to diagnose patients with MEN1 and have resulted in its earlier diagnosis.^{42,150,215,246,309} This earlier diagnosis combined with increasingly effective treatments of the

TABLE 9. MEN1 Features in 227 Deceased Literature MEN1/PET Patients With or Without MEN1-Related Death

Characteristic	Percentage ⁽³⁾		P
	Death due to MEN1-Related Cause ⁽⁴⁾		
	Yes (n=150)	No (n=73) ⁽⁷⁾	
I. MEN1 features			
HPT	95%	96%	0.90
Pituitary disease	23%	20%	0.69
Adrenal abnormality ⁽¹⁾	8.9%	8.7%	0.99
Carcinoid (any) ⁽¹⁾	26%	9%	0.0048
Thymic	22%	3.3%	0.0006
Other ⁽²⁾	5.3%	6.6%	0.72
ZES	66%	75%	0.23
Other PETs ⁽¹⁾	47%	33%	0.058
Other functional PET ⁽¹⁾	22%	17%	0.48
NF-PET	29%	18%	0.12
CNS tumor ⁽¹⁾	1.5%	0%	0.31
Skin tumors ⁽¹⁾	3.5%	1.4%	0.40
Smooth muscle tumor ⁽¹⁾	0.7%	1.5%	0.58
Thyroid disease	0%	2.9%	0.050
II. Age at various MEN1 features (yr)			
At diagnosis of MEN1>45 ⁽⁵⁾	79%	83%	0.61
At onset of ZES>44 ⁽⁶⁾	66%	50%	0.13
At last follow-up/death>51 ⁽⁶⁾	76%	35%	<0.0001
III. Duration (yr)⁽⁶⁾			
Time MEN1 diagnosis to last follow-up/death>8	36%	42%	0.41
IV. MEN1 demographic features			
Family history MEN1	91%	77%	0.019
Male	62%	60%	0.84
V. Tumor extent			
Liver metastases present	72%	20%	<0.00001

Abbreviations: See Table 1 and 2 legend. NF-PET-nonfunctional pancreatic endocrine tumor.

⁽¹⁾Type of adrenal abnormality, carcinoid tumor, other PET, other functional PET, CNS tumor, skin tumor or smooth muscle tumor are specified in legend of Table 1.

⁽²⁾Other carcinoids refers to 7 patients with gastric, 3 with lung, and 1 with intestinal carcinoids.

⁽³⁾Percentage of the reported patients with or without an MEN-1 related death that had the indicated MEN1 characteristic.

⁽⁴⁾The 227 patients with MEN1 and PETs from the literature were identified as described in the Methods.

various hormone excess states, HPT, and PETs,⁴⁶⁶ will likely have important effects on the natural history and causes of death, which will no doubt be different from older reports.

To address the issue of the largely unclear course of MEN1 patients late in their disease history at present, as well as the causes of death at present, and to attempt to identify prognostic factors for different causes of death, we conducted the present study of the long-term courses of 106 MEN1 patients with PETs who were prospectively followed over a 24 ± 1.2 year period (range, 3.6–59.3 yr) from MEN1 onset. As stated above in the previous sections, we compared these results with the results of a literature review of patients who had MEN1 with a PET who died of non-gastric acid related cause. To compare our results with a typical general population of MEN1 patients with advanced disease, we compared our series results to those of MEN1 patients reported in series with >10 cases of MEN1 patients with follow-up data (see Tables 12 and 13). In this group 60% had a PET and 54% had ZES, which are similar to the percentages reported in most large series of MEN1 patients.^{140,167,182,189,254}

The current study has none of the limitations reported in previous studies outlined above. It involves a large number (n = 106) of patients with MEN1/ZES. The patients were prospectively studied and reassessed at regular intervals using a standardized protocol. All patients received standard treatments to control hormone excess states and to deal with potentially malignant tumors or with advanced malignant disease; therefore the results are representative of the current acceptable treatment of these patients. Specifically, gastric acid hypersecretion in all patients with active ZES was controlled, no complications of peptic disease developed, and no patients died from a peptic ulcer disease-related complication. Other hormone excess states due to other PETs or NETs were treated with either surgery or medical therapy (octreotide, interferon, other medical therapies).^{194,196,221} Hyperparathyroidism was treated by multi-gland parathyroidectomies as outlined previously,^{104,211,317,328} and no patients developed renal failure due to nephrolithiasis. Other NETs such as thymic, gastric, or lung carcinoid tumors were treated as described previously.^{131,326,368} Lastly, the cause of death could be established in all patients who died during

TABLE 10. MEN1 Gene Sequencing Results With Overall Survival and With Presence or Absence of an MEN1 Disease-Related Death

Survival all patients	No. (%) ⁽¹⁾		P
	Alive	Dead	
I. Disease feature			
A. All patients⁽¹⁾			
Any mutation present	71 (100%)	18 (100%)	
All non-inactivating mutations ⁽²⁾	51 (72%)	16 (88%)	0.11
Missense mutation present	15 (21%)	3 (17%)	0.48
Any inactivating mutations ⁽³⁾	8 (11%)	3 (17%)	0.39
Nonsense	36 (51%)	13 (72%)	0.084
Frameshift insertion/deletion	9 (13%)	3 (17%)	0.45
Any mutation in exon 2	27 (38%)	10 (56%)	0.14
MEN1 nonsense/frameshift mutation in exon 2,9,10 ⁽⁴⁾	21 (30%)	7 (39%)	0.21
	26 (37%) ⁽¹²⁾	8 (44%) ⁽¹²⁾	0.36
B. Familial MEN1 patients only			
Number familial patients	55 (100%)	17 (100%)	
MEN1 nonsense/frameshift mutation in exon 2,9,10 ⁽⁴⁾	24 (44%) ⁽¹²⁾	8 (47%)	0.35
Inactivating mutation ⁽¹⁾	35 (64%) ⁽¹²⁾	13 (76%)	0.25
Mutation in exon 2	21 (38%) ⁽¹²⁾	7 (41%)	0.52
II. Disease-related death	Yes	No	
A. All patients⁽¹⁾			
No. of patients	11 (100%)	7 (100%)	
Any mutation present	11 (100%)	5 (71%)	0.14
All non-inactivating mutations \	1 (9%)	2 (28%)	0.33
Missense mutation present	1(9%)	2 (28%)	0.33
Any inactivating mutations ⁽¹⁾	10 (91%)	3 (43%)	0.047
Nonsense	2 (18%)	1 (14%)	0.58
Frameshift insertion/deletion	9 (82%)	2 (28%)	0.039
Any mutation in exon 2	5 (45%)	2 (28%)	0.42
MEN1 nonsense/frameshift mutation in exon 2,9,10 ⁽⁴⁾	6 (55%)	2 (28%)	0.28
B. Familial MEN1 patients only			
Familial MEN1 only	11 (100%) ⁽¹²⁾	7 (100%) ⁽¹²⁾	
MEN1 nonsense/frameshift mutation in exon 2,9,10 ⁽⁴⁾	6 (54%)	2 (28%)	0.28
Inactivating mutations ⁽¹⁾	10 (91%)	3 (43%)	0.047
Mutation in exon 2	5 (45%)	2 (28%)	0.42

⁽¹⁾Eighty-nine of the 106 MEN1/ZES patients underwent MEN1 gene testing as described in Methods; 66/89 (74%) had a mutation found on MEN1 gene testing with 61/66 (2%) of patients with a family history having a mutation and 6/23 (26%) without a family history having a mutation.

⁽²⁾Non-inactivation mutations included missense mutations. In-frame changes and other mutations that did not result in a protein that was predicted to be inactive.

⁽³⁾Inactivating mutations were due to nonsense mutations, frameshift mutations including deletions and insertions.

⁽⁴⁾Refers to the percentage of patients that had a truncating nonsense or frameshift mutation in the N- or C-terminal region of the MEN1 gene (exons 2,9,10). Results are expressed as the percentage of patients with indicated mutation of the total sequenced in the MEN1 related or unrelated death group.¹⁴⁶

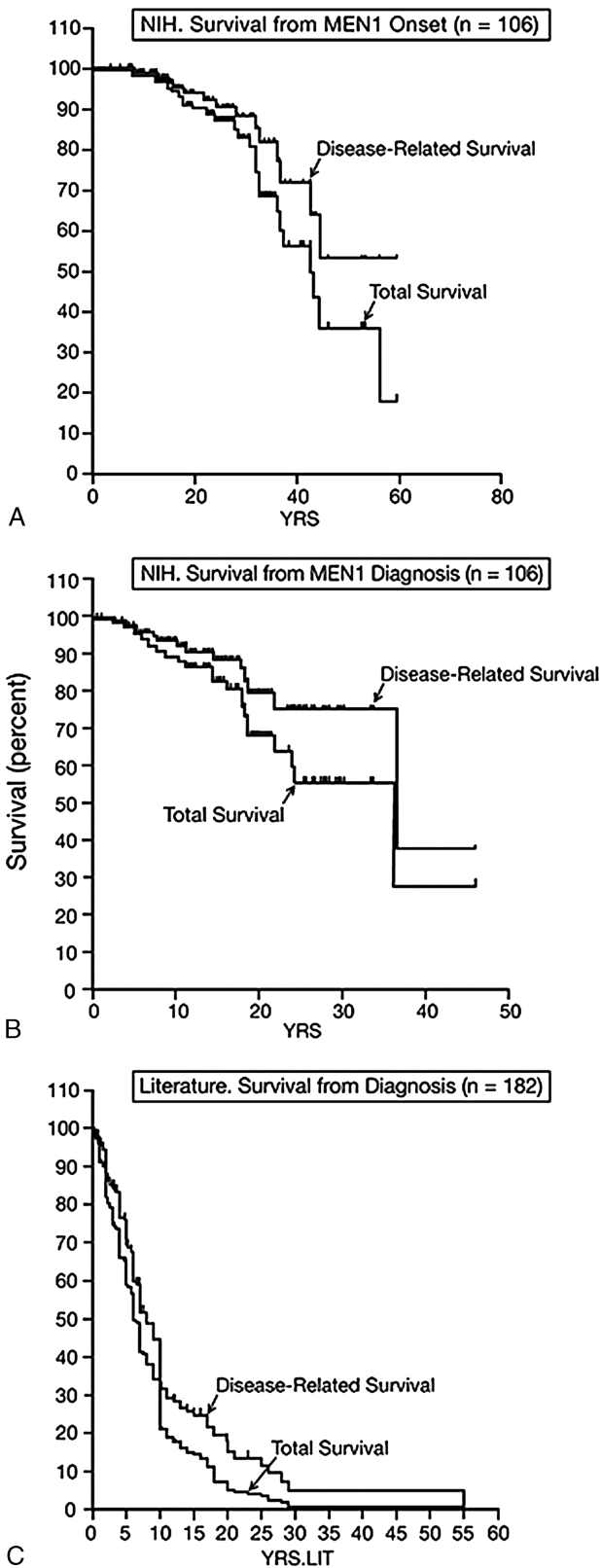
follow-up and was classified as MEN1 related or non-MEN1 related using the criteria outlined in the Methods section.

Survival Data

Whether patients with MEN1 have premature death with shortened survival is controversial in some previous studies.^{78,88,101,129,465} In 2 studies^{88,101} the survival of patients with MEN1 did not differ from that of unaffected individuals; however, 3 other studies^{78,129,465} concluded that MEN1 patients had premature death with shortened survival. In one of the latter studies,¹²⁹ the mean age at death of female MEN1 patients was 47 years and of male patients was 55 years, which was significantly younger than the age at death of Dutch control non-MEN1 female patients (75.6 yr, $p = 0.032$), or of control non-MEN1 male patients (70.1 yr, $p = 0.001$). A second series

reporting premature death⁷⁸ was a large, retrospective study of 228 MEN1 patients from the Mayo Clinic whose mean age at diagnosis of MEN1 was similar to that of our 106 NIH MEN1/ZES patients (39.2 vs 38.3 yr, respectively). In that study⁷⁸ the expected survival at 20 years from age of diagnosis of the MEN1 for a matched control group was 80%, compared with 64% for their MEN1 patients, which was significantly less ($p < 0.001$) than their controls. The survival of their MEN1 patients is similar to the overall survival of our 106 MEN1/ZES patients prospectively followed, which was 67.5% at 20 years from diagnosis, suggesting that our patients also had a premature death.

However, in the current prospective study a number of results suggest that these patients are living longer than reported in many previous series. First, during the long follow-up (mean,



15.5 yr from MEN1 diagnosis; 24.5 yr from MEN1 onset), 23% of the 106 NIH MEN1/ZES patients died, which is comparable to the 28% ± 3% reported in 12 of the general MEN1 series in the literature that reported mortality percentages (1386 patients, see Table 12). However, the deaths in the NIH MEN1/ZES patients occurred over more than twice as long a follow-up period as the follow-up period reported in the literature cases (15.5 [NIH] vs 7.7 ± 1.0 yr from diagnosis of MEN1, n = 6 series]. Similarly for the 227 MEN1/PET deceased patients from the pooled literature, whose data came from 108 separate reports, they represented 18.8% ± 1.9% (data: 36 reports) of the total MEN1 patients being followed in these reports. However, similar to the 12 general MEN1 literature series, the percentage of patients that died in the pooled literature series occurred over less than half of the follow-up time (6.9 ± 1.3 yr) of the NIH series.

Second, if one compares the data from different series, the mean age at death of MEN1 patients varies markedly. In our 106 NIH MEN1/ZES patients, the mean age of patients who died was 55.1 ± 2.8 years. This age is older than that reported in a number of series in the literature, with mean ages of death of 31.7 years,¹⁵ 43.3,⁴⁴⁴ 45.1,²⁵⁴ 47,⁸⁸ 50.3,^{46,57} 50.9,⁴⁶⁵ and 51 years.¹²⁹ However, it is similar to the ages reported in other studies, which have reported mean ages of death of 53.2 years,⁵⁴ 55 years, males/47 years, females,¹²⁹ 60,⁴⁴⁸ and 55 years.⁸⁸

Third, in terms of survival calculated using the Kaplan-Meier method, the 106 NIH MEN1/ZES patients had a much better overall survival at 5, 10, 20, and 30 years postdiagnosis than the 227 pooled MEN1/PET literature patients (at 5 yr, 97.3% vs 60%, respectively; at 10 yr, 89% vs 21%; at 20 yr, 67.5% vs 5%; at 30 yr, 55% vs 0%; p < 0.01). Similarly the NIH MEN1/ZES patients' survival was significantly better than the average of 22 series in the literature,^{54,57,78,94,106,153,166,181,217,233,276,289,303,311,367,424,425,440,481,482} which had mean 5- and 10-year survival rates of 89% ± 1.9% and 78% ± 3.6%, respectively, compared to 97% (95% CI, 92%–100%) and 89% (95% CI, 81%–94%) (p < 0.05), respectively, in the NIH MEN1/ZES patients. If a similar comparison is made for just the MEN1/ZES patients, the survival of the NIH MEN1/ZES patients was also significantly better (p < 0.05) than that of 10 series of MEN1/ZES patients in the literature,^{54,106,166,181,217,276,303,311,367,424,440,481,482} which reported mean 5- and 10-year overall survival rates of 88% ± 2.9% and 80% ± 4.2%, respectively, compared to 97% (95% CI, 92%–100%) and 89% (95% CI, 81%–94%), respectively, for the NIH MEN1/ZES patients.

MEN1-Related Survival

During the follow-up period (mean, 15.5 yr from MEN1 diagnosis, 24.5 yr from MEN1 onset), 24 of the 106 (23%) NIH MEN1/ZES patients died; 14 of the 106 patients (13% of the total patients; 58% of deaths) died from an MEN1-related cause. This is similar to the results for the 227 MEN1/PET patients from the pooled literature series, in which 66% of the deaths were due to an MEN1-related cause. In contrast, in the various larger series of MEN1 patients in the literature (see Table 12), the percentage of deaths due to an MEN1-related

FIGURE 2. Total and disease-related survival for the 2 groups of MEN1/PET patients studied. In the top 2 panels survival data for the 106 NIH MEN1/ZES patients are shown in Kaplan and Meier plots. The top panel shows disease-related and total survival from the time of MEN1 onset and the middle panel from the time of MEN1 diagnosis. The bottom panel shows total survival and disease-related survival from the time of MEN1 diagnosis for the 227 MEN1/PET patients from the pooled literature review of case reports and small series.

TABLE 11. Survival in MEN1/PET Patients From NIH and the Literature

	Survival Percentage [95 % CI] ⁽¹⁾					
	5 yr	10 yr	20 yr	30 yr	40 yr	50 yr
A. NIH patients (n=106)⁽²⁾						
I. Survival from MEN1⁽²⁾ onset						
Total survival	100 [93–100]	100 [93–100]	90 [82–95]	82 [71–90]	56 [40–71]	37.8 [18–56]
Disease-related survival	100 [92–100]	99 [92–100]	93 [87–97]	88 [78–94]	72 [52–85]	53 [32–80]
II. Survival from MEN1 diagnosis						
Total survival	97 [92–100]	89 [81–94]	67.5 [53–79]	55 [38–70]	28 [7–47]	
Disease-related survival	97.3 [93–100]	93 [85–97]	80 [65–88]	75 [59–86]	37.8 [2–78]	
B. Pooled literature patients (n=173)						
I. Survival from MEN1⁽³⁾						
Total survival	60 [52–71]	21 [15–27]	5 [2–9]	0 [0–3]		
Disease-related survival	68 [64–72]	31 [27–35]	14 [11–22]	4.5 [1–11.5]		

Abbreviations: See Table 1 and 2 legends.

⁽¹⁾Percentage survival calculated from data from 106 NIH MEN1/ZES and 173 literature MEN1/PET patients from survival curves shown in Figure 2.

⁽²⁾For the NIH MEN1/ZES patients during the follow-up (24.5 ± 1.2 [range, 3.6–59.3 yr] from onset of MEN1, 15.5 ± 0.9 [range, 0.96–44.3 yr] years from diagnosis), 24 NIH patients died from any cause (Figure 1) and 14 died from an MEN1-related disease cause (Figure 1).

⁽³⁾For the literature MEN1/PET patients during the follow-up (8.2 ± 0.6 [range-0.25–55 yr]), 126/173 (73%) patients died from an MEN1-related cause.

cause varied considerably, although the mean of 68 ± 6 for 14 series reviewed was similar to our results. In 5 of the large MEN1 series in the literature the percentage of MEN1-related deaths was less than in our NIH patients and the 227 pooled literature series (28%–47%).^{54,78,88,378,379,448,465} In 3 of the large series it was similar to our results (67%),^{129,150,371} and in 8 of the large series it was a higher percentage (75%–100%) than in our series.^{15,57,217,224,226,251,254,289,367,444} Our results are consistent with the results of 5 large series of MEN1 patients published in the last 10 years, which reported that $60\% \pm 9\%$ (range, 28%–81%) died from an MEN1-related cause, consistent with the conclusion that at present approximately two-thirds of MEN1 patients die from an MEN1-related cause. These results are lower than a mean MEN1 mortality rate of $88\% \pm 5\%$ reported in 5 large early MEN1 series from the years 1960–1980,^{15,224,226,254,444,474} with the difference primarily due to the occurrence of acid-related deaths in the earlier series. These data demonstrate that at present, approximately two-thirds of MEN1 patients will have an MEN1-related death.

While there have been a number of studies reporting overall survival in MEN1 patients, as discussed in the previous paragraph, to our knowledge there have been only retrospective studies^{88,217} assessing disease-related survival in MEN1 patients. One study assessed disease-related survival in MEN1 patients as a function of the patient's age,⁸⁸ and the other as a function of follow-up time.²¹⁷ The former study found that MEN1 patients who had an MEN1-related death had a shortened survival, with a mean age at death of 47 years compared to MEN1 patients dying from non-MEN1-related causes (age 60 yr; $p < 0.02$) or non-MEN1 carriers (age 55 yr; $p < 0.05$). However, there was no significant difference between the overall survival and the MEN1-disease related survival (mean age, 47 yr vs 50 yr). In the second study,²¹⁷ the 10-year median MEN1 disease-related survival was 73% (95% CI, 58%–95%), which was not significantly different from the overall survival from diagnosis at 10 years of 73% (95% CI, 58%–89%), with a median overall survival of 19.5 months. Our disease-specific survival rates for 106 NIH MEN1/ZES patients as well as the 227-pooled MEN1/PET literature patients, have similarities

with and differences from the rates of the latter study.²¹⁷ Our results are similar, in that there was no significant difference between the overall survival rate and the MEN1-disease specific survival rates, either for time from diagnosis or time from onset of MEN1 (see Figure 2, Table 11). Our results with both patient groups (NIH and pooled literature groups) differ in that our MEN1 disease-related survival for the NIH group was much better than that reported in the above study,²¹⁷ with a 10-year survival rate from diagnosis of 93% (95% CI, 85%–97%) and a 30-year survival rate of 75%, whereas our 10-year and 40-year disease-specific survival rate from onset of MEN1 was 99% and 72%. In contrast, the disease-specific survival rate of the MEN1/PET patients from the pooled literature was much worse than that of the NIH MEN1/ZES patients or of those reported in the above study,²¹⁷ with 10-year survival rates from diagnosis of 31% (95% CI, 27%–35%) compared to 93% in the NIH patients and 75% in the patients in the above study.²¹⁷ Many factors could have contributed to these markedly different MEN1-disease survival rates in these different groups of MEN1 patients, including the differences in study design (retrospective vs prospective); differences in the features of MEN1 patient populations studied; differences in definitions of important variables such as time of diagnosis; and differences in definitions of causes of death. The NIH population has the advantage of being studied prospectively, under a fixed protocol with preset definitions allowing standardization of the results, and thus could be used as a template for further comparative studies.

Causes of MEN1-Related Death

In both our 106 NIH MEN1/ZES patients and the 227 MEN1/PET patients from the pooled literature, all of the MEN1-related deaths were due in some way to a NET, either because of its malignancy, complication of its treatment (post-operative death, etc) or due to the hormone excess state associated with it (for example, PET hormone secretion, HPT) (see Table 2). Of the MEN1-related deaths, 79% and 83% in the 2 groups of patients were due to the malignant nature of the NET, 14%–17% due to a NET hormone excess state, and 4%–7% due to a NET-related problem not due to progressive

metastatic disease or the hormone excess state. The malignant NET deaths (79%–83% of MEN1 deaths) were primarily due to deaths from malignant PETs (57%–58% total MEN1 deaths) or to deaths from thymic carcinoid tumors (19%–21% of MEN1 deaths).

To compare our data to MEN1 series in the literature, all causes of death were expressed as a percentage of the total deaths, as was done in most of these series (see Table 12). When expressed in this form, our data demonstrated the main single cause of death was due to PETs accounting for 38% (NIH) and 44% (pooled literature series) of the total deaths, followed by death from thymic carcinoid tumors (12%–13%). For 15 large series of MEN1 patients in the literature, the average percentage of death due to a PET-related illness was $53.1 \pm 7\%$ of all deaths; however, this percentage, as well as the exact causes of the PET-related death, varied widely in the individual series, with the total percentage varying from 19% of all deaths^{78,251} to 91% of all deaths.²⁵⁴ In the NIH and pooled literature series, the major cause of a PET-related death was the malignant nature of the PET, responsible for 36% of the total 44% PET-related deaths in the pooled literature series and for all 38% of the PET-related deaths in the NIH patients. In 14 of 15 of the large MEN1 literature series (see Table 12), PET-related illnesses were also the major cause of death (mean, $56\% \pm 7\%$); however, in 1 series²⁵¹ the main cause of death was related to malignant thymic carcinoid tumors (24% of all deaths). Similar to our 2 groups of MEN1 patients (the NIH and pooled literature series), in 8 of the 14 literature MEN1 series where PET-related illnesses were the leading cause of death,^{57,78,88,129,150,217,378,379,448,465} the major cause of the PET-related death was the malignant nature of the PET, averaging $39\% \pm 9\%$ of all deaths (range, 14%–83% of all deaths).

In our 2 series (the NIH and pooled literature series), death due to a malignant PET was most frequently due to a malignant gastrinoma (60% and 100% of cases). This result is similar to that reported in 6 series in the literature^{54,78,224,226,251,289,367,444} where the percentage of malignant gastrinomas responsible for the PET-related malignant deaths could be assessed; however, it differs from results in 4 series^{129,150,378,379,448,465} wherein malignant gastrinomas were responsible for only an average of 16% (range, 0–38%) of the malignant PET deaths. It is unclear from the data available in these latter reports whether this low percentage of malignant gastrinomas contributing to the overall number of malignant PETs is clearly reflective of the actual findings in these patients, because in most of these series the specific nature of the malignant PET is poorly described. Therefore, while our data and most recent literature series clearly establish that the malignant nature of the PET is now the leading cause of death in MEN1 patients, it is not clearly established what type of PET is responsible for this, particularly whether the majority of these malignant PETs are nonfunctional PETs or gastrinomas.

In 6 of the 14 literature series where a PET-related illness was the leading cause of death^{15,54,224,226,254,289,367,444} (see Table 12), the hormone excess state was the leading cause of death, and in each case it was primarily due to uncontrolled gastric acid hypersecretion in patients with ZES. These series generally included patients prior to the widespread availability of effective medical management for the gastric acid hypersecretory state of patients with ZES (in the 1980s). Even though a number of studies have reported that the gastric acid hypersecretion in patients with MEN1/ZES, especially those with uncontrolled HPT, may be difficult to control, compared to patients with sporadic ZES,^{140,189,273,281,317} the data from our NIH patients and from a number of the recent MEN1 literature

studies reviewed in Table 12 support the conclusion that current medical gastric antisecretory treatment in these patients is very effective. Especially compared to earlier series prior to the effective medical treatment of the gastric acid in MEN1/ZES patients, there was a low rate of deaths due to gastric acid hypersecretion in 10 of the MEN1 series since 1990 (3.7 ± 1.3).^{54,57,150,217,251,286,378,379,448,465} This is similar to our results in the 106 NIH MEN1/ZES patients, where 0 patients died due to gastric acid hypersecretion.

Even though gastric acid hypersecretion is now being controlled in almost every MEN1/ZES patient, in contrast to some older studies,¹⁵ other hormone excess states per se are an uncommon cause of death in the current series and in recent series. Specifically, in the NIH patients, only 1/106 (0.9%) patients died from another hormone excess state (insulinoma), and in the 227 MEN1/PET patients from the pooled literature, 2.2% (5/227) died from another non-gastrinoma hormone excess state (8-insulinomas, 1-VIPoma). Even this may be an overestimation because 3 of the 8 insulinoma patients from the pooled literature had malignant insulinomas, and it is unclear whether they died of progression of the malignant disease or of refractory hypoglycemia. Including the 5 patients from the pooled literature series with glucagonomas who died from a MEN1-related cause, all died from progressive metastatic disease. These data support the conclusion that death from the hypersecretion of a PET other than gastrinoma is an uncommon cause of death in MEN1 patients at present. These conclusions are supported by the data from 11 various large literature MEN1 series, where in 8 series, reporting 257 deaths of MEN1 patients,^{57,129,251,254,277,299,371,444} no patients died from insulinoma, and in 3 other series^{54,78,448} comprising 161 deaths of MEN1 patients, only 2 deaths (1.2%) were due to an insulinoma. Furthermore in the Groupe d'étude des Tumeurs Endocrines (GTE) MEN1 series comprising 758 patients, the presence of an insulinoma was not associated with increased mortality, in contrast to the presence of other PETs in MEN1 patients.^{71,150} These data are at some variance with some older studies. Ballard et al,¹⁵ in their sentinel 1964 study of MEN1 where they reviewed findings in an extensive MEN1 kindred as well as 74 additional cases previously reported in the literature, concluded that hypoglycemia suggesting a possible insulinoma was frequent in MEN1 patients, occurring in 36% of cases, and that 5 patients (6%) died of insulinomas, suggesting that it was not an infrequent cause of death. Subsequently most studies show that insulinomas occur less frequently than this in MEN1 patients, occurring in 11.8% of 758 MEN1 patients in the GTE study^{148,150} and in 18% in a recent review of MEN1 cases in a number of series.^{102,174,189,195,212,261,348,418,436}

Both the surgical curability and more effective medical control of the rare MEN1 patient with an insulinoma are contributing to the current low rate of insulinoma as a cause of death in recent MEN1. In recent large series only a small percentage (0–15%) of insulinomas in MEN1 patients are reported to be malignant,^{22,71,82,153,195,205,247,279,330} and the remaining 80%–100% of the MEN1 patients with insulinomas are cured postresection.^{21,22,71,75,82,153,195,247,319,330,425} Short-term medical control with diazoxide, diet, or somatostatin analogues prior to surgery is effective in controlling hypoglycemia in most patients,^{76,81,82,144,196} and therefore uncontrolled hypoglycemia resulting in death is primarily restricted at present to the small percentage with a malignant insulinoma (<1% of all patients) and to an even smaller group comprised of the few patients with malignant insulinomas not controlled by medical therapies (diazoxide, somatostatin analogue, mTOR inhibitors [everolimus, rapamycin])^{76,144,196,221} or more recently by peptide radio-receptor therapy using radiolabeled somatostatin analogues.^{76,144,441}

TABLE 12. MEN1 Characteristics and MEN1-Related Causes of Death, Previous and Present Reports

	Ballard 1964 ¹⁵	Lamers 1978 ^{224,226}	Majewski 1979 ²⁵⁴	Vasen 1989 ⁴⁴⁴	Wilkinson Shepherd, 1991, 1993 378,379,465	Mignon/ Rusniewski 1995,1993 289,367	Doherty 1998 ⁸⁸	Carty 1998 ⁵⁷
I. No. of cases	85	36	22	52	46	45	59	34
II. MEN1 major involvement								
PET (%)	81%	50%	86%	62%	36%	100%	—	74%
ZES (%)	58%	42%	54%	54%	28%	100%	—	47%
Parathyroid (%)	88%	83%	88%	96%	73%	78%	—	82%
Thymic tumor (%)	0%	0%	0%	0%	7%	0%	—	3%
III. Follow-up								
III.A. Time (yr)								
Mean follow-up	—	—	—	—	—	7.9	—	12.1
[range]							—	[1–31]
III.B. Deaths								
III.B.1. Total no. died/no. followed (% followed)	9/15 ⁽¹⁰⁾ (60%)	12/36 (33%)	11/22 (50%)	20/52 (38%)	46/152 (30%)	17/45 (38%)	59/-	7/34 (21%)
III.B.2. Type of death (% total deaths)								
MEN1-related (%)	88%	100%	91%	75%	44%	82%	46%	100%
PET-related (%)	88%	83%	91%	65%	30%	70%	30%	83%
ZES-related (%)	77%	83%	91%	65%	6%	53%	10%	0%
Acid-related (%)	77%	66%	91%	55%	4%	41%	10%	0%
Gastrinoma-related (%)	0%	17%	0%	10%	2%	12%	0% ⁽⁴⁾	0%
Other nonoperative causes ⁽¹⁾	0%	0%	0%	0%	0%	0%	0%	0%
Malignant PET-related (%)	11%	17%	0%	10%	26%	12%	20%	83%
Thymic carcinoid-related (%)	0%	0%	0%	0%	6%	0%	0% ⁽³⁾	0%
Postoperative death (%)	44% ⁽⁵⁾	0%	9%	0% ⁽⁵⁾	0%	41%	0%	0%
HPT-related (%)	0%	12%	0%	10%	13%	12%	0%	0%
Renal failure (%)	0%	12%	0%	10%	13%	0%	5%	0%
Other HPT-related (%) ⁽²⁾	0%	0%	0%	0%	0%	12%	0%	0%
Pituitary disease-related (%)	0%	0%	0%	0%	6.5%	0%	0%	0%
MEN1-lung tumor	0%	0%	0%	0%	2%	0%	0%	0%
Gastric carcinoid	0%	0%	0%	0%	0%	0%	0% ⁽³⁾	0%
Other MEN1-related cause	0%	0%	0%	0%	4% ⁽³⁾	0%	10% ⁽³⁾	17% ⁽³⁾
III.B.3. Mean age at death (yr) [range]	31.6 [15–63]	—	—	44	51	—	55	50 [32–86]
III.B.4. Non-MEN1 deaths (% total deaths)	11% ⁽¹⁰⁾	— ⁽⁹⁾	9%	25%	56%	18%	54%	0%
III.B.5. Unknown cause of deaths (% total deaths)	0%	0%	0%	0%	0%	0%	8%	0%

Abbreviations: PR = present report.

⁽¹⁾Other nonoperative ZES causes of death include in¹⁵⁰ 1 patient with acute pancreatitis, 1 with chemotherapy and 1 with septicemia; in¹²⁹ 9 died sudden unexpected deaths.

⁽²⁾Other HPT-related includes 2 patients with death due to acute hypercalcemia.¹⁵⁰

⁽³⁾Other MEN1 related deaths were 1 due to pheochromocytoma;⁵⁷ 2 to adrenal disease;⁴⁶⁵ 3 deaths to adrenal disease; and 2 to brain tumor;¹⁵⁰ 6 patients with carcinoid tumors not specified;⁸⁸ in the NIH series 1 other MEN1-related death was due to progressive meningioma and in 1 patient it was due to esophageal cancer with Barrett esophagus with dysplasia secondary to poor control of GERD in the past. In the pooled literature review 2 patients died from ependymomas, one with a pheochromocytoma and one with a malignant melanoma.

⁽⁴⁾Twelve deaths (20%) were due to malignant pancreatic endocrine tumors, but number specifically due to gastrinoma was not reported.

⁽⁵⁾In this study⁴⁴⁴ there were 6 deaths (12%) postoperatively in patients with gastrinoma and they are included by authors in the acid-peptic deaths. In one series¹⁵ 44% of patients had a postoperative death all due to peptic ulcer disease complications and thus are also listed in acid-ZES-related death. In this series⁷⁸ there were 10 patients with carcinoids but the specific type was not specified. Three died of carcinoid tumor but type not specified.

Cadiot 1999 ⁵⁴	Dean 2000 ⁷⁸	Geerdink 2003 ¹²⁹	Kouvaraki 2006 ²¹⁷	Vierima 2007 ⁴⁴⁸	Machens 2007 ²⁵¹	Goudet 2010 ¹⁵⁰	Pooled Literature Review ⁽⁸⁾	NIH Series (PR) 2013
77	69	87	55	82	258	758	227	106
100%	47%	—	100%	73%	49%	55%	100%	100%
100%	28%	—	38%	23%		28%	67%	100%
91%	97%	—	—	93%	77%	92%	95%	97%
0%	0% ⁽⁶⁾	—	0%	4%	10	2.5%	13.3%	5.6%
8.5	13.5	—	4.3	7.3		6.3(DX)	7.9(DX)	15.6
[1–30.5]	[0.1–54.3]	—	[0.3–38]	[0–18]		[2.2–33]	[0.3–55]	[1–44.3]
13/77 (17%)	69/233 (30%)	30/87 (34%)	16/55 (29%)	15/82 (18%)	21/258 (8.1%)	101/758 (13%)	227/227 (100%)	24/106 (23%)
46%	28%	67%	81%	47%	76%	67%	66%	58%
31%	19%	33%	62%	40%	19	55%	44%	38%
15%	12%	13%	- ⁽⁷⁾	20%	9.5%	32%	22%	38%
0%	2%	3%	0%	7%	0%	11%	0%	0%
15%	7%	10%	- ⁽⁷⁾	13%	9.5	18%	21%	38%
0%	0%	10%	0%	0%	0%	3%	0.9%	0%
15 %	14%	20%	62%	33%	9.55	55%	36%	38%
0 %	0 % ⁽⁵⁾	13 %	6%	0 %	24%	5 %	12.5%	12%
0%	3%	0%	0%	0%	19%	5%	2.2%	0%
0%	2%	0%	0%	0%	0%	2%	5.3%	0%
0%	0%	0%	0%	0%	0%	0%	4%	0%
0%	2%	0%	0%	0%	0%	0%	1.3%	0%
0%	0%	3%	0%	0%	0%	3%	1.8%	0%
0%	0%		0% ⁽⁶⁾	0%	0% ⁽⁶⁾	5%	0.4%	0%
0%	0 %	10%	0% ⁽⁶⁾	7%	0% ⁽⁶⁾	1%	0.4%	0%
4% ⁽⁵⁾	0%	0%	0%	0%	9.5% ⁽⁶⁾	6% ⁽³⁾	1.7% ⁽³⁾	8% ⁽³⁾
55 [38–79]	52.6	51 [29–80]	—	60 [36–79]		—	51.5 [27–88]	55.1 [27–79.6]
54%	72%	23%	6%	53%	23%	23%	32%	42%
0%	9%	10%	13%	0%	0%	0%	8.8% ⁽¹¹⁾	0%

⁽⁶⁾In 1 series²¹⁷ 3 patients died of foregut carcinoid (13%) and the primary site was not specified. In²⁵¹ 2 patients (9.5% of all deaths) were due to unspecified non-thymic carcinoids (i.e. ?gastric or pulmonary).

⁽⁷⁾In²¹⁷ 9 of the 15 deaths were due to malignant PETs, but type PET not specific;

⁽⁸⁾See Methods for description of pooled literature review.

⁽⁹⁾In²²⁴ only the MEN1-related number and causes of death were reported.

⁽¹⁰⁾In this series¹⁵ the long term survival and/or cause of death is reported in 15 patients and in addition a literature review reveals data on 85 patients of which 33/85 (39%) died from an MEN1 related problem. These included 69% due to PETs, 48% due to ZES, 18% to intractable hypoglycemia, 12% to pituitary disease complications, 6% to uremia, and 3% to diarrhea of unknown case.

⁽¹¹⁾In the literature search 4/227=1.8% did not have stated whether they had an MEN1-related or Non-MEN1 related-death and 16/227=7.0% did not have stated the non-MEN1-related cause of death.

TABLE 13. Non-MEN1-Related Causes of Death, Previous and Present Reports

	Majewski 1979 ²⁵⁴	Vasen 1989 ⁴⁴⁴	Wilkerson 1993 ⁴⁶⁵	Mignon/Rusniewski 1995,1993 ^{289,367}	Doherty 1998 ⁸⁸	Carty 1998 ⁵⁷	Cadiot 1999 ⁵⁴
No. of cases	22	54	46	45	59	34	77
Non-MEN1 deaths							
Total no. died/no. followed (%)	11/22 (50%)	15/52 (29%)	46/152 (30%)	17/45 (38%)	59/-	7/34 (20%)	13/77 (17%)
Non-MEN1 deaths (% total deaths)	9%	25%	56%	185	54%	0%	54%
Type Non-MEN1 deaths (% total deaths)							
Heart disease	0%	0%	27%	0%	15%	0%	0%
Cerebrovascular disease	0%	0%	0%	0%	0%	0%	0%
Lung disease	0%	5% ⁽⁴⁾	0%	0%	6% ⁽⁴⁾	0%	8% ⁽⁴⁾
Other cancers	0%	5%	6%	0%	15%	0%	15%
Type other cancer							
Oral	0%	0%	2%	0%	0%	0%	8% ⁽¹⁾
Esophageal	0%	0%	0%	0%	0%	0%	8%
Breast	0%	0%	0%	0%	2%	0%	0%
Lung (non-NET)	0%	0%	2%	0%	3%	0%	0%
Kidney/bladder	0%	0%	0%	0%	0%	0%	0%
Hematopoietic	0%	0%	0%	0%	0%	0%	0%
Melanoma	0%	0%	0%	0%	2%	0%	0%
Colon/rectum	0%	5%	2%	6%	2%	0%	0%
CNS	0%	0%	0%	0%	2%	0%	0%
Renal	0%	0%	0%	6%	3%	0%	0%
Prostate	0%	0%	0%	0%	0%	0%	0%
GI diseases—not cancer	0%	0%	0%	0%	2% ⁽²⁾	0%	8% ⁽²⁾
Neurologic disease	0%	0%	0%	0%	2% ⁽⁵⁾	0%	0%
Diabetes	0%	0%	0%	0%	5%	0%	0%
Accidents	0%	0%	13%	0%	0%	0%	0%
Suicide	0%	0%	0%	6%	0%	0%	8% ⁽²⁾
Alcoholism	0%	0%	0%	0%	0%	0%	0%
Other	9% ⁽³⁾	0%	0%	6% ⁽³⁾	0%	0%	8% ⁽³⁾
Unknown causes	0%	0%	0%	0%	8%	0%	0%

⁽¹⁾Oral cancer was a case of carcinoma of the tongue in 2 series.^{54,150}

⁽²⁾GI diseases include 1 patient in 2 series with complications of diverticulitis.^{54,88}

⁽³⁾Other includes “old age”⁵⁴ in 1 case; 11 cases in which cause of death not specified;⁷⁸ 1 case³⁶⁷ due to peritonitis of unknown origin; in study⁴⁴⁸ 1 due to Cor pulmonale, 1 to chronic pericarditis, and 1 to mesenteric artery thrombosis; 1 death due to small bowel obstruction;²⁵⁴ 1 case of accidental drug overdose in our series.

⁽⁴⁾Lung diseases include 1 death due to respiratory failure;⁵⁴ 5 to pulmonary embolus in 3 studies;^{88,129,150,448} 1 to emphysema/COPD;⁸⁸ 3 to pneumonia.⁷⁸

⁽⁵⁾Neurologic diseases include Alzheimers in 1 patient;¹⁵⁰ 1 patient with multiple sclerosis;⁸⁸ 1 patient with Lewy body dementia.⁴⁴⁸

⁽⁶⁾See Methods for description of pooled literature review.

⁽⁷⁾One patient in our series died from esophageal cancer secondary to Barrett esophagus likely contributed to by longterm uncontrolled GERD and was counted as an MEN1 related death.

Other functional PET syndromes (not including insulinomas or gastrinomas) were a rare cause of death in our 2 study groups (the NIH group and the patients from the pooled literature series), causing no deaths in the 106 NIH MEN1/ZES patients and 1 death (0.4%) (a VIPoma) in the 227 MEN1/PET patients from the pooled literature. These data are in agreement with the results reported in 13 large literature series^{54,57,78,129,224,251,254,367,371,444,448,474} which contain data of 463 MEN1 patient deaths, where only 2 deaths (0.4%) were reported due to a glucagonoma and 1 death (0.2%) to a growth hormone-releasing factor-secreting tumor (GRFoma). These rare PETs are frequently malignant

when present in MEN1 patients (33%–50% of cases).^{51,125,195,233,334} In the large GTE series comprising 758 MEN1 patients^{150,233} in which glucagonomas/VIPomas/somatostatinomas were present in 3.3% of all patients, their presence was associated with decreased overall survival (HR = 4.29; 95% CI, 1.54–11.9) and with a decreased 10-year survival (54%) compared to patients with gastrinomas or insulinomas (82%–92%), and was similar to patients with only nonfunctional PETs (62%). While these latter data show that the presence of these rare PETs can affect survival in MEN1 patients, in the current series as in most of the recent literature series reviewed above, the low frequency of deaths

Dean 2000 ⁷⁸	Geerdink 2003 ¹²⁹	Kouvaraki 2006 ²¹⁷	Vierima 2007 ⁴⁴⁸	Goudet 2010 ¹⁵⁰	Pooled Literature Review ⁽⁶⁾	NIH Series (PR) 2013
69	87	55	82	758	227	106
69/233 (30%)	30/87 (34%)	16/55 (29%)	15/82 (18%)	104/758 (14%)	227/227 (100%)	24/106 (23%)
72%	23 %	6%	53%	26%	34%	42%
17%	6%	0%	7%	3%	6.1%	17%
0%	0%	0%	0%	0%	3.5%	4%
9% ⁽⁴⁾	3% ⁽⁴⁾	0%	7% ⁽⁴⁾	1% ⁽⁴⁾	5.3%	0%
12%	9%	0%	7%	11%	7.9%	12.5%
0%	0%	0%	0%	1% ⁽¹⁾	0%	4% ⁽⁷⁾
0%	0%	0%	0%	0%	0%	0%
4%	0%	0%	7%	5%	0%	4%
4%	0%	0%	0%	1%	2.6%	0%
0%	3%	0%	0%	1%	0%	4%
0%	0%	0%	0%	1%	0%	4%
0%	6%	0%	0%	0%	0.44%	0%
3%	0%	0%	0%	0%	0.44%	0%
0%	0%	0%	0%	0%	0.88%	0%
0%	0%	6%	6%	0%	0%	0%
0%	0%	0%	0%	0%	0.88%	0%
0%	0%	0%	0%	0%	1.3%	0%
0%	0%	0%	7% ⁽⁵⁾	1% ⁽⁵⁾	0.88%	0%
0%	0%	0%	0%	0%	0.88%	0%
3%	0%	0%	0%	2%	1.8%	0%
0%	0%	0%	7%	0%	0.44%	0%
0%	0%	0%	0%	1%	0%	0%
16% ⁽³⁾	0%	0%	20% ⁽³⁾	0%	2.6% ⁽³⁾	4% ⁽³⁾
13%	0%	6%	0%	0%	7.4%	0%

caused by these rare PETs in the MEN1 patients is likely due to their low rate of occurrence in MEN1, reported as 1.6%–3% for glucagonomas, 1%–3% for VIPomas, and 0.65% to <1% for GRFomas or somatostatinomas.^{102,152,174,189,195,212,233,261,308,348,418,436}

The second largest single cause of MEN1 death in our 2 groups of patients was thymic carcinoid tumors (12% of the NIH MEN1/ZES patients and 12.5% of the pooled literature series). This finding has both similarities and marked differences from the findings in the 15 large MEN1 literature series reviewed in Table 12 and other recent literature series^{111,150,371,373} reporting assessment of thymic carcinoids in MEN1 patients. Our results are similar to 2 series^{129,217} that report

thymic carcinoids as the second leading cause of MEN1 death (6%–13% of all deaths) behind PET-related deaths. However, they differ from 1 study reporting thymic carcinoids as the most frequent cause of MEN1-related deaths (24% compared to 10% for malignant PETs), and from 12 series in which thymic carcinoids either caused no deaths^{15,54,57,78,88,226,254,289,367,394,463} or caused only a small percentage of MEN1-related deaths (5%–6%),^{150,378,379,465} which was much less than seen with malignant PETs. Almost all of these latter series not reporting thymic carcinoids in MEN1 patients were older series, specifically, they include patients followed before 2000. The likely reason that thymic carcinoids were not reported is

because thymic carcinoids were not recognized as part of MEN1 until 1972,³⁶³ and were not recognized as a major cause of death until the 1990s;^{131,378,465} thus they were not specifically sought for or considered as a cause of death in many of these older series. Since the 1990s a number of studies have called attention to the increasing importance of thymic carcinoids as a cause of death in MEN1, particularly in men, because >90% occur in males.^{45,111,131,151,414,465,477,479} These tumors are particularly aggressive, and are associated with a poor prognosis, with more than one-half of patients in some series having metastases at diagnosis, and even more developing them during follow-up, particularly to the bone.^{45,111,131,151,363,414,477,479} The aggressive nature of these tumors is supported by the results of the large, retrospective GTE study composed of 758 MEN1 patients, in which the presence of thymic carcinoids was reported to be associated with a higher risk of death compared with unaffected patients (HR = 4.64; 95% CI, 1.7–12.4]. The malignant nature of the thymic carcinoid itself is responsible for almost all deaths in MEN1 patients with these tumors, because MEN1 patients with thymic carcinoids rarely develop a hormone excess state.^{111,130,131,151,414,470,479} In this sense thymic carcinoids in MEN1 patients differ from those occurring in patients without MEN1 (that is, sporadic thymic carcinoids), because a hormone excess state due to the thymic carcinoid is very infrequent (only 4 cases reported that we know of),^{111,130,408,470} and the hormone excess state was only Cushing syndrome when it occurred, whereas in patients with sporadic thymic carcinoids, a hormone excess state is more frequent (up to 40%) and more varied, with Cushing syndrome, carcinoid syndrome, and acromegaly being reported.^{38,111,131,185,342,392} Our results and those from a number of studies in the literature support the increasing importance of thymic carcinoids as a cause of death in MEN1 patients. In our series they occurred in 6% of all NIH patients, and in various retrospective studies they occurred in 2.6%,¹⁵¹ 3%,^{45,57,151} 4.2%,³⁰⁵ and 4.9%⁴⁷⁹ of all MEN1 patients; however, in our series they accounted for 12% (NIH) and 12.5% (pooled literature series), and in some recent series they account for up to 24%²⁵¹ of all MEN1 deaths, demonstrating their increasingly important role as a cause of death in MEN1 patients.

In addition to PETs and thymic carcinoid tumors, other MEN1 features have been reported to be an important cause of MEN1-related death in a number of studies, particular some older series. Complications of uncontrolled HPT including renal failure and hypercalcemic crises are reported to contribute to MEN1-related deaths in 10%–12% of patients in 3 older series of MEN1 patients^{224,226,378,379,444,465} and in occasional patients in other reports.^{78,150} In more recent series,^{54,57,129,217,251,371,448,474} including all of the NIH patients in the current series, death from complications of uncontrolled HPT were not seen, because of the greater understanding of the hyperplastic nature of the parathyroid disease and the need for partial or total parathyroidectomy to control the HPT.^{42,104,149,168,211,328,330} Pituitary diseases (pituitary apoplexy, tumor invasion) are reported to either be a cause of or contribute to MEN1-related death in 3%–6.5% of patients in a few older series.^{49,129,150,222,378,379,465} Pituitary tumors in MEN1 patients are more aggressive, more frequently multiple and invasive than in patients with sporadic pituitary tumors.^{49,147,435,447} However, in the NIH prospective series as well as in most current series, although pituitary adenomas are frequently present (20%–65% of patients), they are recognized and adequately treated, so they rarely cause death.^{54,57,78,88,195,217,251,448} This latter conclusion is also supported from the findings of the GTE study involving 758 MEN1 patients, where the presence of pituitary disease was not associated with an

increased risk of death in MEN1 patients (HR = 1.17; 95% CI, 0.72–1.90; $p = 0.54$).¹⁵⁰

Adrenal disease is present in 10%–73% of MEN1 patients on imaging studies^{23,48,128,228,374,388,390,453} and is reported to cause MEN1-related deaths in occasional series (0.4%,¹⁵⁰ 4%⁴⁶⁵) and case reports.^{161,385} Adrenal tumors in MEN1 patients are reported to cause a number of functional hormone excess syndromes including Cushing syndrome, hyperaldosteronism, pheochromocytoma, androgen secretion, or feminization.^{8,27,48,57,128,157,228,261,276,385,388,390,436,453} Functional hormone excess states caused by the adrenal tumors are rarely a cause of MEN1-related death, because in most series >90% of the adrenal lesions are not associated with a functional syndrome (except 1 series²²⁸ where 38% with adrenal lesions had Cushing syndrome).^{48,388,390} In various series,^{23,48,128,140,157,374,385,390,453} 0–6% of MEN1 patients develop adrenal cortical carcinomas, which can be aggressive, invasive, and associated with a functional syndrome such as Cushing syndrome, and which can contribute to or cause death in these patients. However, in both our series including the 106 NIH MEN1/ZES patients and the 227 MEN1/PET patients from the pooled literature, no patient died of adrenal disease, similar to what was reported in a number of recent large MEN1 series,^{23,78,129,157,217,448} supporting the conclusion that it is an uncommon cause of death at present in MEN1 patients. This conclusion is also supported by the results from the 758-patient GTE study of MEN1 patients. In that study, those with adrenal tumors had a trend toward an increased risk of death compared to unaffected patients, but it did not reach significance ($p = 0.064$) (HR = 1.72; 95% CI, 0.97–3.06).¹⁵⁰

In addition to thymic carcinoid tumors, patients with MEN1 have an increased incidence of pulmonary [0–8%]^{47,140,190,195,261,368,378} and gastric carcinoid tumors [7%–35%],^{34,140,187,195,232,326,360} which are reported to be an MEN1-related cause of death in a few series in the literature and in some case reports.^{39,150,326,378,379,448,465} In the 106 NIH MEN1/ZES patients, neither gastric nor pulmonary carcinoid tumors caused any MEN1 deaths; however, in the 227 pooled literature series, 1 patient died from a gastric carcinoid (0.4% of all deaths) and 1 patient died from a pulmonary carcinoid (0.4% of all deaths). These data suggest that although these tumors can be malignant and also cause a hormone excess syndrome (carcinoid syndrome),^{40,94,98,190,360,437} they are an uncommon cause of MEN1-related death at present. This conclusion is supported by the results of 15 MEN1 series (see Table 12) and a detailed series on only pulmonary carcinoids in MEN1 patients³⁶⁸ in which pulmonary carcinoids were reported to be a cause of death in a mean of 0.5% ± 0.4% of total deaths (range, 0–5%) and gastric carcinoids in 1.2% ± 0.8% (range, 0–10%), with 11 series reporting no deaths from either gastric or pulmonary carcinoids. This conclusion for bronchial carcinoids was also supported by the GTE study on 758 MEN1 patients, in which the presence of a bronchial carcinoid did not increase the death rate compared to unaffected controls (HR = 1.55; 95% CI, 0.64–3.77; $p = 0.332$).¹⁵⁰

Prognostic Factors for Survival

We attempted to identify prognostic factors for overall survival in the NIH patients, and for survival from an MEN1-related death in both groups of patients in our study (the NIH and the pooled literature groups). We analyzed overall survival in addition to MEN1 disease-related survival for a number of reasons. In the literature almost all studies on prognosis in MEN1 patients report overall survival, and therefore, to allow comparison we also included overall survival. Second, by including overall survival, MEN1's effect on all disease processes leading to death can be

reviewed. This is an important point because at present there is little information on what is now described as non-MEN1-related deaths and it is unknown whether MEN1 patients have increased occurrences of any of the diseases currently included in this category. Although the exact role of menin, the protein altered in patients with MEN1, in causing many of the abnormalities seen in MEN1 patients is not known, it is clear that it is involved in many important cellular processes such as cell cycle regulation, transcriptional control, cell division, and genomic stability, any of which if altered could lead to many different diseases, including various common neoplasms.^{16,50,195,419,469}

For overall survival in the 106 NIH MEN1/ZES patients, none of 5 general disease features analyzed differed between surviving and deceased patients including sex; race; age at first NIH assessment or age at last follow-up; duration of MEN1 to death or last follow-up; or duration of follow-up at NIH. Similarly, for MEN1 disease-related survival for either the NIH patients or the 227 MEN1/PET patients from the pooled literature series, sex; age at diagnosis of MEN1 or onset of ZES; or time to death or last follow-up did not differ between patients with or without an MEN1-related death. However, the age at death was earlier for the pooled literature patients with an MEN1-related death compared to those with a non-MEN1-related death (51 vs 53 yr, $p = 0.002$). These results differ from a number of MEN1 series in the literature where decreased survival was associated with older age,^{46,54,152,217} and in 2 studies males had a decreased survival compared to females.^{54,150} These results also differ from a study⁵⁴ that assessed the presence of liver metastases as a surrogate marker of survival in MEN1 patients, because their presence is a strong negative prognostic factor in MEN1 and in non-MEN1 patients with NETs or PETs,^{21,37,54,103,105,141,191,217,252,291,398,433,459,471,476,481} which reported liver metastases were more frequent in males with MEN1 than females. Our results are similar to those in various studies of MEN1 patients where survival was not affected by age,^{150,152,217} sex,¹⁵² and another study, which also found that MEN1-related deaths occur at an earlier age than deaths due to non-MEN1-related causes in MEN1 patients.⁸⁷ Our results differ from those in some studies of patients with sporadic PETs or sporadic ZES in which a worse prognosis is associated with female sex and shorter disease histories to diagnosis.^{191,459,476} However, our results are similar to most studies of sporadic PETs, which show no effect of sex on survival.^{100,105,258,338,400,429,446,471} Nevertheless, our result showing a lack of sex effect on survival (total or MEN1-disease related) is somewhat surprising, because even though the most common cause of MEN1 death, PETs, occur approximately equally in males and females, the second most common cause of MEN1 death, thymic carcinoids, occur in >90% males, thus this would be expected to lead to a sex effect on survival.^{111,131,148,151,414,465,477,479} A likely factor contributing to our failure to see the sex effect of thymic carcinoids reflected in our survival results is the fact that thymic carcinoids are diagnosed relatively later in the course of MEN1 (mean age, 42–50 yr)^{131,151,204,362,414,479} and these patients may have a prolonged survival, therefore the full effect on mortality may require even longer follow-up than in the current study.

Previous studies have suggested that a number of clinical and laboratory MEN1-related features can be predictive of survival^{146,141,150,152,367,465} (see Tables 4, 5, 7, 9, 10). For the 106 NIH MEN1/ZES patients most non-PET-related features of MEN1 (HPT, pituitary, adrenal, thyroid, carcinoid) were not significantly associated with decreased overall survival, except for the occurrence of functional syndromes other than ZES (either PET-related [$p = 0.031$] or non-PET-related [$p = 0.0033$]), the requirement for a high number of parathyroidectomies (>3)

($p = 0.008$), a higher fasting serum gastrin level (>20-fold increase)($p = 0.022$), or the need for previous gastric acid reducing surgery ($p = 0.0261$). Almost reaching significance for overall survival was the presence of a higher percentage of patients with family history of MEN1 among patients who died of any cause ($p = 0.052$) and the presence of thymic carcinoids ($p = 0.098$). In contrast, the presence or absence of none of these variables correlated with the presence of disease-related survival in the NIH patients. However, in the 227 MEN1/PET patients from the pooled literature, an MEN1 disease-related death was highly correlated with the presence of thymic carcinoid tumor ($p = 0.0006$) and the lack of a family history of MEN1 ($p = 0.019$), and was borderline correlated with the presence of thyroid disease ($p = 0.050$) or PETs other than ZES ($p = 0.058$). These results are consistent with the conclusion that a worse survival prognosis occurs when an MEN1 patient has severe HPT requiring more parathyroidectomies; higher functional expression of gastrinomas resulting in higher gastrin levels, with more severe gastric acid hypersecretion requiring more frequent need for gastric acid reducing surgery prior to the availability of proton pump inhibitors; the presence of additional functional hormone excess states other than ZES, and the presence of a thymic carcinoid tumor. These conclusions are consistent with a number of previous findings in various studies on MEN1 patients and sporadic PET patients. They are consistent with studies that have shown the development of liver metastases, which are associated with decreased survival in patients with PETs such as gastrinomas,^{37,54,103,105,252,291,398,405,459,471,476} more frequently occur in gastrinoma patients with higher gastrin levels,^{19,33,36,46,96,184,191,241,405,459,476} and in some studies with higher BAOs.⁴⁷⁶

Our findings that more resistant HPT is associated with a poorer survival prognosis is consistent with studies that propose that the presence of uncontrolled HPT in these patients increases the risk of developing PETs,⁴⁷ that it may act as a prerequisite for the development of other neoplasms in MEN1,²⁹ and that it may be an important factor in the release of mitogenic factors that are found in the serum of MEN1 patients, including a basic fibroblast growth factor-like substance.^{263,480}

Our results for the prognostic value of various MEN1 clinical and laboratory features show a number of similarities and differences from other series of MEN1 patients. The are similar to almost all other studies in demonstrating that the frequency of occurrence of many of the features of the MEN1 syndrome including HPT; adrenal or pituitary disease; smooth muscle or CNS tumors; bronchial/gastric carcinoids; or dermatologic lesions does not correlate with survival, and thus these are not prognostic factors for survival.^{78,129,150,152,217,251,289,433,444} In contrast, almost all studies, similar to our MEN1/PET pooled literature series, report that the presence of thymic carcinoids carries a worse prognosis, due to the aggressive nature of these tumors.^{111,131,150,151,331,413,414,465} While our NIH MEN1/ZES series showed a trend toward significance for thymic carcinoid patients having a worse prognosis ($p = 0.098$), a number of factors likely contributed to it not reaching full significance as a prognostic factor. These include that we made an early diagnosis of thymic carcinoid because all patients were prospectively followed with regular imaging¹³¹ and their treatment was aggressive, because of the known progressive nature¹³¹ of these tumors, resulting in prolonged survivals. A number of large studies of MEN1 patients report that the presence of any PET (except insulinomas), is associated with decreased survival.^{150,331,389,465} In our study this could not be evaluated because both groups of MEN1 patients (the 106 NIH patients and the 227 patients from the pooled literature series) all had PETs. The characteristics of the PETs as prognostic factors could be

studied and are dealt with in the next section. Our finding in the MEN1/PET patient pooled literature series that a family history of MEN1 carried a better prognosis agreed with the large French GTE study, which reported similar findings.¹⁵⁰ These findings are at odds with the results of a study⁴⁶ that reported that the presence of a first-degree relative with MEN1 was associated with an increased risk of developing a PET,⁴⁶ which was associated with a worse prognosis.

A number of studies of MEN1 patients report that various tumoral aspects, primarily associated with PETs, have prominent prognostic significance. These include the primary PET size^{54,141,217,234,247,315,324,433,434} whether the PET is functional or non-functional,^{150,217} the functional type of PET,^{46,150} whether liver metastases are present or not,^{54,141,152,217,276} and the effect of various treatments, particularly whether the patient underwent surgical resection of the PET or not.^{152,217,433} In the 106 NIH MEN1/ZES patients, each of these variables could be analyzed and assessed for their effect on both overall survival and MEN1-specific survival. In contrast, because of incomplete data, only a few of these variables could be assessed in the 227 MEN1/PET pooled literature patient series. In the NIH series of MEN1/ZES patients, decreased overall survival (OS) ($p = 0.0203$) and disease-related survival (DRS) ($p = 0.022$) occurred in patients with increasing primary PET tumor size; in patients with liver metastases initially (OS, $p = 0.011$; DRS, $p = 0.0180$); bone metastases (OS, $p = 0.0002$; DRS, $p = 0.0099$), but not lymph node metastases (OS, $p = 0.057$; DRS, $p = 0.56$); for patients who develop liver metastases (OS, $p = 0.001$; DRS, $p = 0.0180$) and for patients whose PETs show aggressive growth (OS, $p < 0.00001$; DRS, $p = 0.0001$). Decreased overall survival also was associated with increasing number of PETs ($p = 0.032$); however, for MEN1 disease-related survival this did not reach significance ($p = 0.097$). Conversely, the development of any new lesion was associated with decreased MEN1 disease-related survival ($p = 0.0180$), but its effects on overall survival did not reach significance ($p = 0.124$). A number of these results are consistent with findings reported in other studies of MEN1 patients or patients with sporadic PETs. The presence of liver metastases initially or their development with time was associated with decreased survival in a number of studies of MEN1 patients,^{54,141,217,276} but not in others.¹⁵² These results are also consistent with most studies of patients with sporadic PETs, which report liver metastases are associated with a poor prognosis,^{37,103,105,159,200,252,255,291,338,398,429,459,471,476,481} but some studies report also their development during follow-up and the extent of the liver metastases correlate with decreasing survival.^{191,459,476} The exact primary source of the liver metastases in almost every study of MEN1 patients is not well defined, and it is often unclear whether it is from a PET, thymic carcinoid, or another carcinoid tumor (gastric, pulmonary). The liver metastases in MEN1 patients with a PET, without a thymic carcinoid, are almost always attributed to the PET, although this remains unproven. Furthermore, the exact source of the liver metastases becomes even more of an issue in patients with MEN1 with gastrinomas, because many of these patients also have nonfunctioning PETs in the pancreas on imaging studies, and in most cases it is unclear which PET metastasized. Lastly, the majority of patients with MEN1 that have thymic carcinoids also have PETs (57%–100%),^{111,131,151,414} and which of these is responsible for the liver metastases is usually not resolved. This ambiguity has occurred because until recent many of these different NETs could not be distinguished histologically or immunohistologically and even in more recent studies where numerous methods to distinguish these NETs have been reported,^{177,237,243,395} detailed histologic/immunohistochemical studies were not performed

to resolve the primary site that metastasized. Because of this, the true metastatic rate of many of the MEN1 NETs to the liver remains unclear.

The prognostic significance of distant metastases (beyond liver) to bone, etc, has not been specifically studied in MEN1 patients. Similarly, the presence of local metastases to adjacent lymph nodes on survival in MEN1 patients has not been specifically studied. However, the prognostic effect of each of these metastatic sites has been studied in detail in patients with various sporadic PETs. In the case of local metastases to lymph nodes, studies have reported contradictory results, with most reporting no prognostic effect,^{54,114,145,191,201,252,279,338,377,459} whereas a few other studies have reported a negative effect on survival;^{37,67,219,429,476} however, the impact is much less than seen with the presence of liver metastases. A number of studies report that the presence of distant metastases, especially to bone, is a predictor of decreased survival.^{20,133,191,231,338,476} In 1 study of patients with advanced gastrinomas (sporadic) the presence of bone metastases was associated with a mean survival of only 1.9 years after their detection.⁴⁷⁶ Therefore, our results with MEN1 patients are similar to most studies with sporadic PETs, which report no effect of lymph node metastases on survival, and other studies, which report decreased survival in patients with sporadic PETs who develop distant metastases to bone.

Our finding that aggressive tumoral growth or the development of new lesions during the follow-up is associated with decreased survival is consistent with results of a few studies on MEN1 patients and a number of studies in patients with sporadic PETs. One prospective study of MEN1 patients with gastrinomas¹⁴¹ reported that 15% of patients demonstrated aggressive growth of their PETs and that it was associated with decreased survival. This is a lower percentage than the 25% of patients with sporadic ZES^{459,476} who are reported to develop aggressive tumor growth over time, but nevertheless, it had similar effect on decreasing survival in both groups of patients. Similarly, a number of single cases reports or small series have reported patients with MEN1 whose tumors demonstrate rapid growth^{51,94,160,183,333,354,454} which in most cases leads to decreased survival. Other studies with various sporadic PETs demonstrate that a subset is associated with rapid growth and the development of new lesions, which is associated with a decreased survival.^{100,337,382,405}

In our 227 MEN1/PET pooled literature patients we did not find a difference in survival between patients with or without a gastrinoma, with or without a nonfunctional PET, or with or without another functioning PET. Our results are similar to those in 1 study of MEN1 patients¹⁵⁰ comparing these different PETs wherein MEN1 patients with various PETs (except insulinomas) all had decreased survival rates (hazard ratios, 1.9–4.3). In contrast, our results differ from a number of other previous studies in MEN1 patients, which have reported that different PETs have different effects on survival rate.^{46,195,217} Insulinomas in MEN1 patients are an uncommon cause of death, especially in more recent series, with 20-year survival >90%, in contrast to gastrinomas, nonfunctional PETs, glucagonomas, and other rarer functional PETs with 20-year survivals of 52%–67%.^{21,57,71,78,166,195,217,233,330,345,433} In MEN1 patients insulinomas are rarely malignant (0–15%) and in most series 80%–100% of the MEN1 patients with insulinomas are cured postresection.^{21,22,71,75,82,153,195,247,319,330,425} In contrast >50% of gastrinomas and 20%–50% of nonfunctional PETs and other rarer functional PETs are malignant.^{155,195,217,233,247,250} These results differ from findings in a large Tasmanian MEN1 family⁴⁶ in which it was reported that the presence of hypergastrinemia was associated with a significant increase of enteropancreatic malignancy and decreased survival. At present it is unclear what the basis is for the difference in our data

from the finding in this large kindred and whether it could be due to different PET behaviors in different MEN1 kindreds.

Our prospective study of the 106 NIH MEN1/ZES patients demonstrated that patients with large PETs had decreased total survival and MEN1-DRS. There were not sufficient data on the 227 MEN1/PET patients from the pooled literature to perform a similar analysis. Our results agree with a number of studies,^{54,141,217,234,315,322,324,433,434} but not all^{217,247} studies in the literature on MEN1 patients that have examined this correlation. Most of these studies reported that in MEN1, primary PETs >2–3 cm in diameter are associated with increased development of liver metastases,^{141,217,234,433,434} which in many reports is also shown to be associated with decreased survival. These results in MEN1 patients are in agreement with a number of studies on sporadic PETs which also show a correlation between primary pancreatic tumor size and the development of liver metastases and in some cases an association with decreased survival is shown;^{37,52,103,159,173,252,339,476} however, other studies do not report this association.^{338,429} Our data on the NIH MEN1/ZES patients did not show an association with the presence of a pancreatic PET or the presence of a duodenal gastrinoma with survival. The situation in patients with MEN1 who develop gastrinomas/ZES is confused by the fact that most of the gastrinomas (80%–100%) occur in the duodenum;^{90,154,250,315,348} however, these patients also frequently develop pancreatic PETs, which are nonfunctional in most cases (80%–100%).^{9,90,315,348} The duodenal gastrinomas in the MEN1 patients are characteristically small, and in contrast to the sporadic cases, are invariably multiple.^{9,90,250,348} Similar to those in sporadic ZES, 60%–75% of the gastrinomas in MEN1 patients are now found in the duodenum, with 20%–30% in the pancreas.^{316,321,323,324} Studies on sporadic gastrinomas demonstrate that the duodenal and pancreatic gastrinomas behave differently in that although they are equally malignant with 40%–70% of patients having metastases in adjacent lymph nodes^{21,22,250,315,459} which have not been shown to affect survival,⁴⁵⁹ metastases to the liver are uncommon with the sporadic duodenal gastrinomas, whereas the sporadic pancreatic gastrinomas are aggressive and are associated with a worse prognosis.^{324,459,476} Fewer data are available in MEN1, but a number of studies show that these patients also frequently (30%–70% of cases) have lymph metastases associated with the duodenal gastrinomas; however, they are uncommonly associated with liver metastases and are not associated with decreased survival in MEN1 patients,^{54,247,250,315,321,389} similar to the results in the current study.

Causes of Non-MEN1-Related Death

While a number of studies report the frequency of all deaths that were due to non-MEN1-related deaths, there are relatively few data on the exact non-MEN1-related causes of death, and it has in general not been systematically studied. In most studies the exact causes of the non-MEN1-related deaths are not specifically stated, so it is in general more difficult to compare our data to that in the literature. In our 106 NIH MEN1/ZES patients the cause of death was determined in all cases, with 42% of the 24 deaths due to a non-MEN1-related death, and in the 227 MEN1/PET patients from the pooled literature, 34% of all the deaths (73/227 patients) were due to a non-MEN1-related cause of death. Whereas the mean overall percentage of deaths due to non-MEN1-related causes in the literature from 13 series^{54,57,78,88,129,150,217,251,254,289,378,379,444,448,465} was similar to the data in our 2 series (mean, 33% ± 7%), the percentage of all deaths due to a non-MEN1-related death varied widely in the different series from 0 to 72% of all the deaths reported (Table 13).

In 4 series the percentage of all deaths due to non-MEN1-related deaths was <20%,^{57,217,254,289,367} and in 5 series >50%.^{54,78,88,378,379,444,465} This marked difference is not due to the time of reporting of the series, because the mean percentage of patient deaths reported due to a non-MEN1-related cause for the 4 series reported before the widespread use of proton pump inhibitors (prior to 1995),^{254,289,367,378,379,444,465} and the 9 series reported after their widespread use (after 1995) are similar^{54,57,78,88,129,150,217,251,448} (25 ± 10% vs 36 ± 9% all deaths due to non-MEN1-related death). These data demonstrate that approximately one-third of all deaths in MEN1 patients are due to a non-MEN1-related cause.

In the 106 NIH prospectively followed MEN1 patients the most frequent non-MEN1-related cause of death was heart disease (myocardial infarction, arrhythmia, or cardiac arrest), followed by death due to non-MEN1-related cancers, cerebrovascular disease, and 1 death due to a cocaine overdose (4% of deaths). The order of the main causes of non-MEN1-related deaths in the 227 MEN1/PET patients from the pooled literature was different, with the most common cause being death from other non-MEN1-related cancers. This was followed in descending frequency by death due to a non-MEN1 cause which was not specified in the report, then by heart disease, lung disease (noncarcinoid), cerebrovascular disorders, accidents, other gastrointestinal disorders (non-cancer or MEN1 related), diabetes, neurologic diseases, and suicide. These results have both similarities to and differences from previous reports of the causes of non-MEN1-related death in various large series of MEN1 patients (see Table 13). They are similar in that for the 12 series of MEN1 patients where data on the cause of non-MEN1-related deaths were reported, in 4 series heart disease either was the most frequent or the second most frequent cause of a non-MEN1-related death.^{78,88,129,378,379,465} Similarly, in 8 series the occurrence of non-MEN1-related cancers was either the most frequent or second most frequent cause of death.^{54,88,129,150,217,289,367,444,448} In contrast to these results, 8 studies do not report heart disease^{54,57,150,217,254,289,367,444,448} and 2 studies a non-MEN1-related neoplasm^{57,254} as one of the most frequently seen causes of a non-MEN1-related-death. Two studies of MEN1 patients^{289,367,448} report suicide as a frequent cause of death in their patients. However, it was not a cause of death in any of the 106 NIH MEN1/ZES patients, and it was the cause of only 1 death in the 227 MEN1/PET patients from the pooled literature. Cerebrovascular disease was a non-MEN1 cause of death in 4% of the 106 NIH MEN1/ZES patients (10% total non-MEN1 deaths) and 3.5% of the 227 MEN1/PET patients from the pooled literature (11% of the total non-MEN1 deaths); however, it is not reported as a cause of death in 12 large series of MEN1 patients (see Table 13).^{54,57,78,88,129,150,217,254,289,378,379,444,448,465}

The finding that heart disease was one of the most frequent non-MEN1 causes of death in the MEN1 patients in the 106 NIH MEN1/ZES patients (20% of all non-MEN1 deaths), the 227 MEN1/PET patients from the pooled literature (40% of all non-MEN1 deaths), and in some of the other large series of MEN1 patients (24%–48% of all non-MEN1 deaths)^{78,88,378,379,465} raises the question of whether it is more common in MEN1 patients. Heart disease is a frequent cause of death in non-MEN1 patients, and at present, without matched controls and more MEN1 deaths, it is unclear whether cardiovascular death is more frequent in MEN1 patients with or without PETs. It has been proposed that MEN1 patients may have an increased risk of cardiovascular disease.⁴⁴² Furthermore, MEN1 patients frequently develop a number of diseases, which are associated with an increased risk of cardiovascular disease. These include insulin resistance and impaired glucose metabolism which are

known to be important risk factors for cardiovascular diseases,^{116,163,442} as well as for the development of chronic HPT, which is associated with an increased mortality, mainly due to an overrepresentation of cardiovascular death.^{116,210,259,455} In 3 studies of MEN1 patients^{271,442,452} evidence is provided to support the conclusion that these patients are more frequently insulin resistant compared to their unaffected relatives, that both increased fasting blood glucose levels and diabetes mellitus were more prevalent in MEN1 patients than unaffected family members, that the impaired glucose metabolism was associated with HPT and hypergastrinemia, and that MEN1 patients had decreased insulin sensitivity. Studies in patients with primary HPT report that it can be associated with an increased cardiovascular morbidity and mortality.^{116,210,259,455} Primary HPT is reported to be associated with hypertension, disturbances in the renin-angiotensin-aldosterone system, reduced coronary flow reserve resulting in dysfunction of the coronary micro-circulation, cardiac arrhythmias, as well as changes both functionally and structurally in walls of blood vessels.^{116,210,259,455} Furthermore, HPT has been related to the development of insulin resistance,²⁷¹ and after successful parathyroidectomy, insulin sensitivity has been reported to improve.^{65,126} Therefore, by influencing glucose homeostasis through the development of insulin resistance, HPT could also affect cardiovascular function and play a role in the development of cardiovascular disease. While this is unproven in patients with MEN1, these patients almost invariably have HPT,^{102,140,189,280,418} it can be severe, especially in patients with MEN1 with gastrinomas;^{245,328} it is frequently long-lasting, being present before diagnosis and frequently recurring even if multigland parathyroidectomies are performed.^{11,44,93,104,149,169,179,211,218,257,328,330} These considerations suggest that in future studies of MEN1 patients, the occurrence and mortality of cardiovascular disease should be carefully assessed and compared to a control population to determine whether the presence of the MEN1 is having an effect, and if so, whether any of the above mechanisms seen in primary HPT are contributing.

Classically, MEN1 is associated with tumors and hyperplasia of the pituitary, parathyroid, duodenum and pancreas, thyroid or adrenal; however, over the last few years a wide spectrum of other tumors has been reported with increased frequency in MEN1.^{195,261,418} These include carcinoid tumors in a number of locations (thymic [0–8%], gastric [7%–35%], bronchial [0–8%], and rarely intestinal); dermatologic tumors (angiofibromas [88%], collagenomas [72%], lipomas [34%], melanomas); various tumors of the central and peripheral nervous systems (meningiomas, ependymomas, schwannomas [0–8%]); and smooth muscle tumors (leiomyomas, leiomyosarcomas [1%–7%]).^{6,13,14,34,46,48,49,56,66,74,111,131,151,176,195,209,228,261,274,368,371,388,390,393,413,428,465} These newer tumors show varying degrees of aggressiveness, with thymic carcinoids being highly aggressive, gastric and pulmonary carcinoids less commonly aggressive (metastasize <30% of cases), as are most smooth muscle or CNS tumors, which rarely metastasize, and the skin tumors, which all have a benign course, except for the occasional melanoma. Similar to the classical endocrine tumors in MEN1 patients,^{80,89,131,170,248,261,419,439} with most of the more recently described tumors associated with MEN1 (smooth muscle tumors including some leiomyomas, leiomyosarcomas, gastric carcinoids, pulmonary carcinoids),^{10,26,53,79,89,274,302,336,451} but not all cases (thymic, some angiofibromas, leiomyomas, and angiomylipomas),^{89,131,156,170,414} molecular studies of the tumor provide evidence that these are intrinsic MEN1 tumors. Loss of heterozygosity of the MEN1 gene is found in the tumor, which is compatible with the proposal that the MEN1 gene functions as a tumor suppressor gene.^{195,419} These results of the increased development of

various tumors in MEN1 patients is consistent with recent results exploring the cellular roles of menin, the protein altered in patients with MEN1. The exact cellular basis for the increased occurrence of these various endocrine and nonendocrine tumors in MEN1 patients remains unclear. The frequent occurrence of various nonendocrine neoplasms as a cause of death in our 106 NIH MEN1/ZES patients, the 227 MEN1/PET patients from the pooled literature, as well as in many of the large MEN1 series from the literature raises the possibility that some of these more common neoplasms could be more frequent in MEN1 patients. At present this remains unclear, and because of the small numbers of patients in most of the series, as well as the lack of systematic collection of the data in a prospective fashion in most studies, this question cannot be answered definitively by the data available at present.

In the 106 NIH MEN1/ZES patients there were 4 deaths due to 4 different non-MEN1 tumors (breast, renal, hematologic, oral cancers), which is close to the 3.2 ± 1.1 non-MEN1 tumor deaths per series found in 12 large literature series.^{54,57,78,88,129,150,217,254,289,378,379,444,448,465} In the 227 MEN1/PET patients from the pooled literature there were 18 non-MEN1 tumor related deaths in a frequency that reflected the common tumors in non-MEN1 patients with lung cancer > prostate, CNS tumors > colorectal cancer. From these limited data only a few trends can be pointed out on the frequency of the individual non-MEN1 tumoral causes of death in the MEN1 patients. For the 12 literature series^{54,57,78,88,129,150,217,254,289,378,379,444,448,465} and the 2 other series in the current study (that is, the 106 NIH MEN1/ZES and the 227 MEN1/PET patients from the pooled literature), the non-MEN1 tumor causing death that appeared in the most series was renal cancer and colorectal cancer (each in 6/14 series = 43%), followed by the common neoplasms causing death in non-MEN1 patients (lung cancer = 36%, 5/14 series; breast cancer = 29%, 4/14 series), followed in decreasing frequency by oral cancers (29%, 4/14 series) and then by hematologic, CNS tumors (14%, 2/14 series) followed by prostate/esophageal cancer in 7% of series (1/14 series). Renal neoplasms are reported in a number of MEN1 patients (renal cell cancer, oncocytoma, angiomylipomas),^{53,84,88,89,99,176,186,217,256,289,448} and 2 reports^{84,186} proposed that renal tumors might be a new manifestation of MEN1. Even though renal neoplasms are reported as a cause of non-MEN1-related death equal in frequency to colorectal cancer, which occurs in >3-fold higher frequency than renal cancer in the general population (United States Cancer Statistics, Centers for Disease Control and Prevention), no definite conclusions can be drawn from the data reported above because of the low numbers of cases, lack of systematic reporting, and lack of careful epidemiologic comparison. In future studies it will be important to prospectively assess whether any of the non-MEN1 neoplasms are increased in MEN1 patients, with particular attention to renal and oral cavity neoplasms.

Authors of 1 study have proposed that suicide⁷² might be an important cause of death in MEN1 patients, and authors of another study proposed that cerebrovascular accidents due to MEN1-mediated related effects result in death.² For the 12 literature series^{54,57,78,88,129,150,217,254,289,378,379,444,448,465} and the 2 other series in the current study (the 106 NIH MEN1/ZES patients and the 227 MEN1/PET patients from the pooled literature), suicide as a non-MEN1 cause of death was reported in 28% of the studies (that is, 4/14 studies).^{54,289,367,448} It was not a cause of MEN1 death in any of the 106 NIH MEN1/ZES patients prospectively studied, and it was a non-MEN1 cause of death in 1 of the 227 MEN1/PET patients from the pooled literature (0.44%). These latter data suggest that suicide is a relatively uncommon cause of death in these patients. Cerebrovascular

disease as a cause of non-MEN1-related death was also uncommon. From the 12 literature series and the 2 other series in the current study, only 1 patient in any series died from a cerebrovascular accident.

Conclusions and Summary

From the current analysis of causes of death and identification of prognostic factors in 106 NIH MEN1/ZES patients prospectively studied compared to the results of pooled data from 227 MEN1/PET patients in case reports or small series and to data from large series of MEN1 patients,^{15,53,54,57,78,88,129,150,217,224,226,254,289,378,379,444,448,465} a number of conclusions can be drawn that will be important in the management of these patients; these are summarized in Table 14.

Our analyses demonstrate that in contrast to the past, in our 2 series and in recent large MEN1 literature series, MEN1 patients rarely die of causes related to the hormone excess state per se. Therefore, at present death is uncommonly due to complications of gastric acid hypersecretion, which was so frequent in the past,^{15,43,72,73,83,88,158,180,224,225,240,254,307,353,366,386,399,438,444,458,461,465,466} due to hormone hypersecretion by other PETs such as insulinomas;^{15,306,334,375,466} due to the complications of untreated HPT such as renal failure or hypercalcemic crises;^{15,32,68,88,129,224,359,427,438,440,444,461,465,466} due to untreated pituitary disease (apoplexy, hormone excess state, etc),^{222,447} or to other uncommon hormone excess states (ectopic Cushing from adrenal tumors, other functional PETs, etc).^{165,228,447,468,475}

Analysis of the survival data of both the NIH and pooled literature series of MEN1/PET patients and comparison with the large MEN1 literature series data, supports the conclusion that MEN1 patients even today have a decreased survival compared to the healthy population, with a mean age of death of 55 years. In both the NIH and pooled literature series, two-thirds of all deaths are due to MEN1-related disease, which also agrees with the data from 12 large MEN1 series in the literature.^{15,53,54,57,78,88,129,150,217,224,226,254,289,378,379,444,448,465} The most frequent causes of MEN1-related deaths are from pancreatic endocrine tumors with the malignant behavior of the tumor being the

major factor. Of the different PETs that MEN1 patients develop, gastrinomas account for more than one-half of the PET-related deaths (60%), and in none of the NIH/pooled literature series patients was death due to the complications of the gastric acid hypersecretion these patients develop, instead it was primarily due to the malignant behavior of the gastrinoma.^{199,200,290,364} The second most common cause of an MEN1-related death was thymic carcinoids, which accounted for almost 20% of the MEN1-related deaths in the NIH/pooled literature series, but only 5% of the 12 large MEN1 literature series. This marked difference can be largely attributed to the fact that thymic carcinoids have only been recognized as part of the MEN1 syndrome from the early 1980s, their aggressive nature was appreciated after this, and thus as a cause of death they were only systematically reported in more recent series.^{45,111,131,150,151,251,413,414,465}

In both the NIH/pooled literature series as well as the average of 12 large literature series,^{15,53,54,57,78,88,129,150,217,224,226,254,289,378,379,444,448,465} one-third of the patients died due to non-MEN1-related causes. The most frequent causes of non-MEN1-related death in the NIH/pooled literature series were cardiovascular disease and death due to other non-MEN1 neoplasms, with numerous other causes such as cerebrovascular disease, lung disorders other than lung carcinoid tumors, and accidents making up the remainder. For the other non-MEN1 neoplasms, colorectal and renal cancers as a cause of death were reported in the most series, followed by lung cancer and breast and oral cancers. However, because of low patient numbers and other technical issues with data collection it can not be determined from the available data whether any of these non-MEN1 neoplasms are more frequently seen or have altered behavior in MEN1 patients.

In the NIH and pooled literature series, comparisons of MEN1/PET patients in different survival categories (alive, deceased, MEN1-related death, non-MEN1-related death) allowed us to identify a number of prognostic factors. These include various clinical features (disease duration, presence of non-ZES functional syndromes, parathyroidectomy number, presence of thymic carcinoid, presence of family history, in ZES previous acid reducing surgery); laboratory features (fasting gastrin levels) and various

TABLE 14. Summary and Conclusions

1. In the present report, MEN1 patients rarely died of hormone excess states, as in the past (complications of gastric acid hypersecretion [ZES]; hyperparathyroidism [renal failure]; hypoglycemia [insulinoma]; pituitary disease).
2. In 106 NIH MEN1/ZES patients followed prospectively, 20, 30, and 40 year overall and disease-related-survivals from MEN1 onset were 20 yr=90%, 93%, respectively; 30 yr=82%, 88%; 40 yr=56%, 72%.
3. Comparison with literature data supports the conclusion that both the 106 NIH and 227 MEN1/PET patients from the pooled literature had decreased survival.
4. In both NIH series and review of 12 large literature series, two-thirds of deaths in MEN1 patients were due to an MEN1-related cause.
5. Causes of MEN1-related deaths in decreasing frequency (as % total deaths) in the NIH and pooled literature review were PETs (38%–44%)>thymic carcinoids (12%–13%)>other (8%–16%).
6. In the NIH/pooled literature series PET deaths were primarily due to gastrinomas (22%–38% total deaths) (0% acid related) with the malignant nature of PET most important (36%–38% total). Literature data from 12 large MEN1 series shows a similar pattern (PET deaths [53% total], gastrinoma [35%], malignant PET [26%]).
7. In the NIH/pooled literature series comparisons of characteristics of MEN1/PET patients in different survival categories (alive, deceased, MEN1-related or non-MEN1-related death) identified a number of clinical, laboratory, and tumoral prognostic factors.
8. In the NIH/pooled literature series one-third (34%–42%) of deaths were due to non-MEN1-related causes, which is similar to the mean of 31% for 12 large MEN1 series in the literature.
9. Causes of non-MEN1-related deaths in decreasing frequency (as % total deaths) in the NIH and pooled literature review were cardiovascular (6%–17% total)>other non-MEN1 neoplasms (7.9%–12.9%)> other causes.
10. At present it is not possible to determine whether any specific non-MEN1-related tumor type is more frequent or aggressive in MEN1 patients, because of various technical aspects of the data (low patient numbers, small number of non-MEN1 deaths, cause frequently not specified, not systematically collected, no control data comparing to control population).

tumoral features (PET size, liver metastases, distant metastases, number lesions imaged, growth behavior of tumor).

The above results lead to a number of general conclusions related to the diagnosis and management of MEN1 patients. Even though survival of these patients has certainly improved from older studies, wherein the hormone excess states of various NETs frequently caused premature death,^{15,43,72,73,83,88,158,180,224,225,240,254,306,307,334,353,366,375,386,399,438,444,458,461,465,466}

survival is still shortened compared to the general population and needs to be improved. This will primarily require more systematic and aggressive treatment of various MEN1 aspects, particularly treatment of PETs and carcinoid tumors, which are the principal causes of MEN1-related death. To accomplish this, earlier diagnosis of MEN1 is needed because the mean delay in diagnosis is 4–7 years from the onset of MEN1 (present study),^{55,140,207,357} and aggressive treatment of NETs is needed.

Because malignant PETs were the principal cause of MEN1-related deaths, particular attention should be paid to their early diagnosis and effective treatment. Particularly important are the diagnosis and treatment of gastrinomas, which were responsible for most (60%–65%) of the PET-related deaths. In almost 25% of the NIH patients liver metastases were already present at the time of MEN1 diagnosis and therefore earlier diagnosis is essential to prevent their development if possible. Also important is the effective treatment of both gastrinomas and other PETs. Their treatment remains controversial because studies show that patients with MEN1 with small nonfunctional PETs (<2 cm) have an excellent long-term prognosis, and in the GTE studies their survival did not differ from patients with MEN1 without a pancreatic PET.^{315,433,434} Patients with duodenal gastrinomas with tumors <2 cm also have an excellent long-term survival, with the survival being 100% of patients at 20 years.³¹⁵ This has led to the recommendation that small PETs (<2 cm) in these patients can be followed without resection either by standard imaging studies or by serial endoscopic ultrasound studies.^{18,110,195,221,315,423,433,434} The present study as well as others in the literature in MEN1 and sporadic PETs shows that tumor size is an important prognostic factor for the development of liver metastases, that liver metastases (either their extent, rate of growth, or development), not lymph node metastases is a very important prognostic factor for long-term survival.^{191,315,405,459,476}

One of the central problems that needs to be assessed is the actual source of the liver metastases that these patients develop. The metastases can either be from a gastrinoma if the patient has ZES; from a small occult thymic carcinoid; from a nonfunctional PET; or from a gastric carcinoid, all of which can be aggressive and malignant.^{111,131,151,195,326,368,413,414} There are few data on well-assessed biopsies from MEN1 patients who do develop liver metastases to allow an accurate assessment of the malignant nature of each of these NETs. At present new treatments for certain NETs (PETs especially) have been described such as with the mTOR inhibitor, everolimus,^{198,355,472,473} the tyrosine kinase inhibitor, sunitinib,^{198,356} various liver-directed therapies using embolization, chemoembolization or radiolabeled microspheres,^{61,127,164,343,401} and new chemotherapeutic regimens that are reported to have a high response rate (capecitabine and temozolomide).^{343,402} It will be important in the future that the source of the metastatic disease be established so that it can be treated appropriately and aggressively.

Thymic carcinoid tumors are generally a later feature of MEN1 and occur in most series in >90% in males, so that it is important that guidelines for screening/management for these aggressive tumors, that have been proposed in a number of recent papers, be carefully followed.^{42,111,131,151,196} It has been proposed that the routine use of partial thymectomy (cervical thymectomy)

at the time of parathyroidectomy may reduce the occurrence of thymic carcinoids, and at present this is generally recommended; however, cases of thymic carcinoid have still occurred in MEN1 patients who have previously had this surgery, therefore careful regular follow-up is required.^{45,98,140,151,156,235,412,414,477,479} At present the treatment of advanced metastatic disease in patients with thymic carcinoids is not very effective, therefore the main aim at present is to prevent them if possible (with cervical thymectomy) and for their early diagnosis and aggressive surgical treatment.^{111,131,151}

In one-third of patients with MEN1 there is a non-MEN1 cause of death, and at present it is unclear whether any of these causes are actually increased in frequency in MEN1 patients and therefore actually MEN1-related. Heart disease and non-MEN1-related tumors were the main causes in our patients and in those in the literature in large MEN1 series.^{15,53,54,57,78,88,129,150,217,224,226,254,289,378,379,444,448,465}

In the case of heart disease there are possible MEN1-associated factors that are associated with an increased risk of cardiovascular disease which include HPT and glucose intolerance/diabetes, the latter which is reported to occur with increased frequency in MEN1.^{116,163,271,442,452} Similarly, because of the fundamental role that the menin protein plays in growth-related processes,^{16,50,195,261,419,469,478} it remains possible that other neoplasms currently thought to be non-MEN1 related might be affected either in frequency or severity in MEN1 patients. At present neither of the above possibilities can be adequately addressed because of the lack of control studies that are prospective in nature addressing either the frequency or severity of cardiovascular disease or other non-MEN1 neoplasms in MEN1 patients. These types of studies will be important in the future to manage these patients and extend their lives.

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