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Prospective Study of Surgery for Primary Hyperparathyroidism (HPT) in Multiple Endocrine Neoplasia-type 1 (MEN1), and Zollinger-Ellison syndrome (ZES): Long-term Outcome of a More Virulent form of HPT

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Abstract

Background—HPT in MEN1 patients with ZES is caused by parathyroid hyperplasia. Surgery for parathyroid hyperplasia is tricky and difficult. Long-term outcome in ZES/MEN1 /HPT is not well known.

Methods—84 consecutive patients (49 F/35 M) with ZES/MEN1 /HPT underwent intial parathyroidectomy (PTX) and were followed at 1−3 yr intervals.

Results—Age at PTX was 36±2 yrs. Mean follow-up was 17±1 yrs. Prior to PTX, mean Ca=2.8 mmol/L (nl<2.5), PTH_i=243 pg/ml (nl <65), and gastrin=6950 pg/ml (nl <100). 61% had nephrolithiasis. Each patient had parathyroid hyperplasia. 58% of patients had four parathyroid glands identified. 9/84 (11%) had 4 glands removed with immediate autograft, 40/84 (47%) 3−3.5 glands, while 35/84 (42%) <3 glands.removed. Persistent/recurrent HPT occurred in 42%/48% of patients with <3 glands, 12%/44% with 3−3.5 glands, and 0%/55% with 4 glands removed. Hypoparathyroidism occurred in 3%, 10% and 22%, respectively. The disease-free interval following surgery was significantly longer if >3 glands were removed. After surgery to correct the HPT, each biochemical parameter of ZES was improved and 20% of patients no longer had laboratory evidence of ZES.

Conclusions—HPT /MEN1/ZES is a severe form of parathyroid hyperplasia with a high rate of nephrolithiasis, persistent and recurrent HPT. Surgery to correct the hypercalcemia significantly ameliorates the ZES. Removal of less than 3 and ½ glands has an unacceptably high incidence of persistent HPT (42%), while 4 gland resection and transplant has an high rate of permanent hypoparathyroidism (22%). >3gland resection has a longer disease-free interval. 3 and ½ gland parathyroidectomy is the surgical procedure of choice for patients with HPT/MEN1/ ZES. Careful long-term follow-up is mandatory as a significant proportion will develop recurrent HPT.

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Introduction

Primary hyperparathyroidism (HPT) is the most common clinical manifestation of Multiple Endocrine Neoplasia Type 1 (MEN-1)[1, 2]. Although there may be asymmetrical enlargement of the parathyroid glands causing the surgeon to mistaken the pathology as adenoma, it is always caused by hyperplasia or multiple abnormal parathyroid glands.[3, 4] Surgery to control the HPT in MEN-1 patients requires either three and one-half gland parathyroidectomy or four-gland excision with autograft.[5-8] Patients have a significant rate of persistent HPT with lesser procedures and a high-rate of recurrent HPT as well.[5, 9-13] Careful long-term follow-up studies of these patients are few and the long-term results of surgery have been infrequently reported. We[14] and others[6, 15-17] have previously focused on the results of initial and reoperations[18] in patients with MEN-1 and HPT. This study focuses on a more unique subgroup, those with MEN-1, HPT and ZES. Few previous studies have focused solely on this subgroup, even though ZES occurs in 30−70% of all patients with MEN1. [19]

Zollinger-Ellison syndrome (ZES) is the most common functional pancreatic neuroendocrine syndrome associated with MEN-1.[20, 21] It is generally caused by multiple endocrine tumors either within the pancreas or duodenum. Surgery to remove these tumors is seldom curative.[20, 22] Further, in small numbers of cases some groups[23, 42-47, 57-60] ,but not others[46-49, 59, 61] , have reported an improvement in the laboratory parameters of ZES when surgery is performed to correct the hypercalcemia in MEN-1 patients with HPT and ZES.[23] However, since patients with HPT, ZES and MEN-1 are even more rare than those with MEN-1 and HPT without ZES, no previous study has carefully examined the precise nature of the parathyroid disease in these patients.

This study carefully characterizes the primary hyperparathyroidism in patients with HPT, ZES and MEN-1. It reports the long-term results of initial surgery for the HPT in terms of correction of hypercalcemia and the parameters of ZES. The results suggest that the HPT in MEN-1 patients with ZES and HPT is more severe than previously reported in routine MEN1/HPT patients and that correction of the hypercalcemia dramatically effects the laboratory parameters of ZES.

Methods

Since 1980 at the National Institutes of Health (NIH), 84 consecutive patients with ZES[23, 24, 25] HPT and MEN1 were included in this analysis.[26] All patients had the diagnosis of HPT confirmed by biochemical studies and signs and symptoms of primary hyperparathyroidism were especially noted.[19, 23, 27] Elevated serum levels of calcium and intact parathyroid hormone were measured to substantiate the diagnosis of HPT in all patients. 24 hour urinary levels of calcium excretion were also elevated. The diagnosis of ZES was based on acid secretory studies, measurement of fasting serum level of gastrin as well as the results of secretin and calcium provocative tests.[24, 25, 28-31] Basal and maximal acid output (BAO, MAO) were determined for each patient using methods described previously.[27] Doses of oral gastric antisecretory drug were determined as described previously.[27] A detailed past history of disease was taken at first admission including symptoms related to ZES and past medical/surgical procedures as described previously[26] . Time from onset of the disease to exploration was determined for all patients. The time of diagnosis of ZES was the time the diagnosis was first established by appropriate laboratory studies or when a physician established the diagnosis based on clinical presentation.

All patients had the diagnosis of Multiple Endocrine Neoplasia type 1 (MEN1). MEN1 was established by careful personal and family history, the presence of other tumors associated with MEN1[19, 32], and assessing plasma hormone levels (PTH [intact, mid-molecule], prolactin,

insulin, proinsulin, glucagon), serum calcium (ionized, total) and glucose that may be abnormal in MEN1, All patients had primary hyperparathyroidism as diagnosed by elevated serum levels of calcium and parathyroid hormone. Surgery for primary hyperparathyroidism in patients with MEN1, HPT and ZES was done over a 35 year period between 1970 and 2005. The operating surgeon had the choice for the type of surgery that was performed. Some of the operations were done at other institutions and the exact protocol was not followed. Operations wre performed with the intent to identify all four parathyroid glands, and most consisted of either subtotal (three or 3.5 glands resected) parathyroidectomy [7,14] or a 4 gland parathyroidectomy with transplant[23] of 20 2×1 mm fragments of parathyroid tissue into the non-dominant forearm. The cervical thymus was routinely excised in order to excise any supernumary fragments of parathyroid tissue. Intraoperative parathyroid hormone level determinations were not done.[33] Thirty-nine of the patients had surgery performed initially at the NIH and 45 at outside institutions. For these latter patients the results of this surgery were carefully recorded paying special attention to the number of glands remove as well as total number identified and the preoperative biochemical and hormonal data. In that setting the surgeon may have failed to recognize the extent of HPT or the presence of MEN1 and may have removed less than 3 glands. For the outside surgical MEN1/ZES patients initially 29 patients had <3 glands removed, and 16 patients had 3−3.5 glands removed.

Postoperatively, NIH patients underwent evaluation for HPT and ZES immediately after surgery, within 3 to 6 months post-resection, and then every year thereafter. Yearly evaluations included measuring serum levels of calcium and PTH, acid secretory studies, fasting gastrin determinations, secretin provocative test, and assessment of other endocrine status (pituitary, adrenal function). Disease-free or cure is defined as a normal serum level of calcium and parathyroid hormone.[29, 34-36] Persistent disease is defined as elevated serum levels of calcium and PTH immediately postoperatively. Recurrent disease is defined as an elevated serum level of calcium and PTH after a postoperative period of at least 6 months or more of normocalcemia.

The Fisher's exact test and the Mann-Whitney test were used for two-group comparisons.[26] All continuous variables were reported as mean ± standard error of the mean. The probabilities of disease-free survival were calculated and plotted according to the Kaplan-Meier method and compared using the exact log rank test and the method of Rothman to determine the confidence intervals.[37] Comparisons with the literature were performed using the normal distribution and calculating means plus 2 SD's to define the limits for $p<0.05$.

Results

84 patients with MEN1, primary hyperparathyroidism, and ZES were studied (Table 1). 49 were female (58%). The mean age of onset of the MEN1 was 27 years, HPT 31 years and the ZES 33 years (Tables 1 and 2). Each patient had elevated serum levels of ionized calcium, total calcium and PTH with a mean level of 1.52 mmol/L (nl 1.17−1.31 mmol/L), 2.81 mmol/L (nl 2−2.5 mmol/L) and 2.43-fold normal, respectively (Table 2). Urinary levels of calcium excretion were also elevated with a mean level of 8.6 mmol for 24 hours. 62% had kidney stones. Bone density studies were done in 56 patients (67%) and 25 had decreased bone density (46%) (Table 2). Each patient had MEN1, and 81% had a family history consistent with MEN1, 63% had pituitary tumor and 34% carcinoid of either the bronchus (14%) or the thymus (7%) (Table 1). Each had concomitant ZES with elevated fasting levels of gastrin (8-fold increase over normal) and elevated basal acid output 38 mEq/h and maximal acid output 57 mEq/h (Tables 1 and 2). 79% had upper abdominal pain and indigestion, 65% had diarrhea and 48% had gastro-esophageal reflux symptoms. 56% had a peptic ulcer on endoscopy, while 20% had prior gastric surgery.

It was a mean of 9 years from the onset of MEN1 and 5 years from the onset of HPT to the time of initial neck surgery for HPT (Table 2). At the initial operation for HPT, 35 patients (42%) had less than 3 glands removed, 40 (47%) had between 3 and 3.5 removed, while 9 had a four gland resection with transplant (11%) (Table 3). The mean number of parathyroid glands removed was 2.8. The pathologist diagnosed parathyroid hyperplasia on every parathyroid gland that was removed. The mean follow-up after parathyroid surgery was 7.2 years and 34 (40%) were disease-free, 33 (39%) hypercalcemic, 17 (20%) hypocalcemic and 44% had an elevated PTH level. If less than 3 parathyroid glands were removed at the initial operation as occurred in 35 patients, the incidence of hypoparathyroidism was 3% and the nearly everyone developed either recurrent (46%) or persistent (43%) hypercalcemia for a total of 92%. If between 3 (n=4 patients) and 3.5 glands (n=36 patients) were removed, hypoparathyroidism was 10% and persistent (12%) or recurrent (44%) hyperparathyroidism for a total of 57%. If 4 or more glands were removed, persistent HPT was 0% and recurrent was 22%. Overall, in the 84 patients studied with 16 years follow-up, 24% had persistent disease and 46 had recurrent HPT, while 7% were hypoparathyroid (Table 4). The parathyroid disease-free survival for all patients from the original surgical procedure for HPT was 50% at 10 years (Figure 1 **Upper Left Panel**). If either 3 and ½ parathyroid glands or 4 glands were removed surgically, the disease-free survival was significantly improved (Figure 1 **Lower Left Panel**). In patients with recurrent HPT, the recurrence rate was 50% at ten years (Figure 1 **Upper Right Panel)** and there was no difference in time to recurrence between greater and less than 3 glands removed at the initial surgery (Figure 1 **Lower Right Panel)**.

Fasting serum levels of gastrin did not affect the parameters of HPT including ZES onset, age at first surgery for HPT, and surgical parameters (Table 5). However, when the biochemical parameters of HPT are corrected with surgery, the biochemical parameters of ZES are dramatically improved (Figure 2). When HPT was corrected surgically, serum levels of gastrin, BAO and delta gastrin level with secretin each significantly improved. Those who underwent parathyroid surgery without correction of hypercalcemia had significantly less changes in their biochemical parameters of ZES post PTX (Figure 2). Specifically, the means±SEM decrease in fasting serum gastrin in the patients with successful PTX was 70 ± 3% versus 35 ± 25% in patients with an unsuccessful PTX, which was significantly different (p=0.023). Furthermore, in a recent study we sampled fasting serum gastrin on serial days from ZES patients and showed with our assays intra- and inter-assay variations that a significant decrease occurred ($p<0.05$) only with changes greater than 60% (abou-saif . add referenceCancer 98:249−261, 2003). In our study 28% of the patients with an unsuccessful PTX showed such a change on post PTX follow-up, whereas 74% of the patients with a successful PTX showed such a change, which was significantly different (p=0.030). The biochemical parameters decreased to such a degree in a number of patients after successful PTX that 20% of patients with MEN1, HPT and ZES no longer had any biochemical evidence of ZES following surgery to treat HPT without removing any pancreatic or duodenal neuroendocrine tumor.

Laboratory, clinical and operative findings were analyzed in an attempt to determine factors that may predict the long-term disease-free survival of HPT in patients with HPT, ZES and MEN1 (Table 6). The diagnosis of ZES as the initial manifestation of MEN1 is associated with a decreased probability of HPT being present at last follow-up (9% vs 43%, p=0.0006). If a germline mutation in the Menin gene was detected, there is an increased probability that HPT is present at last follow-up (100% vs 79%, p=0.0069). If HPT was diagnosed greater than 28.5 years of age, there was a decreased likelihood of recurrence (39% vs 61%,) (p=0.045). Finally, if serum calcium levels were increased greater than 110% normal, there was a 78% chance of HPT at last follow-up versus 28% in those with lesser elevations (p=0.0020) (Table 6).

Discussion

Even though up to 70% of all patients with MEN1 develop ZES in some studies[19, 38] and almost one-half of the patients in an average of 14 series[19]; few, if any, prior studies have focused on parathyroid surgery only in MEN1 patients with HPT and ZES (MEN1/HPT/ZES). These patients have a number of unique features from patients with MEN1/HPT without ZES. First, in previous studies of parathyroid surgery in MEN1 patients the percentage of patients with ZES was not distinguished, was low in percentage of all patients in the study, as well as in the total number of MEN1/ZES included in all these series (i.e., 5 series, mean 14 ±4 patients, 26 ±4 % of total)[1, 6, 14, 39, 40]. Second, MEN1/HPT patients in these other surgical series were often detected by screening for MEN1 and hence the MEN1/HPT was usually detected at a different time in the natural history of the disease than most MEN1/HPT/ZES patients [19, 41]. Third, up to 30% of MEN1/ZES patients present with symptoms of the ZES and the HPT may only be recognized later[19, 28]. Therefore, the timing of the initial PTX as well as its place in the natural history of the MEN1 may differ substantially from patients without ZES. Fourth, the occurrence of the ZES may have an effect on the timing of the PTX in an MEN1 patient, because previous studies in small numbers of patients show, in some studies [23, 42-45], but not others[44, 46-49], the PTX with correction of the hypercalcemia, may have an ameliorating effect on the acid secretion, responsiveness to anti-secretetory drugs, fasting gastrin levels and secretin provocative testing . The current study includes a large number of MEN1/HPT/ZES patients (n=84) who were prospectively studied.

A number of our results support the conclusion that the primary hyperparathyroidism in patients with MEN1/HPT/ZES is more severe and more difficult to treat than reported in MEN1/HPT patients. First, a higher percentage of our patients had a history of neprolithiasis at the time of the initial PTX than reported in the literature in MEN1/HPT patients (62%- our study vs 40 ±6%, P<0.05, 7 series)[10, 14, 16, 40, 50-52]. This finding suggests our patients had more aggressive disease at the time of surgery. Second, in our patients the average serum intact PTH level at the initial PTX was increased to a greater extent than reported in the MEN/HPT patients in the literature (our patients-2.4 fold increase vs 1.67 ± 0.38-fold in the literature (n=8 series), p<0.05)[1, 9, 39, 40, 53-55]. These results further support the conclusion that our patients had a more severe form of HPT at the time of the initial PTX. Third, our patients had a mean lower age at the initial PTX than reported in the literature for series of MEN1/HPT patients (ours-36 yrs vs 40.5 ± 1.8 yrs, p<0.05)(10 series)[1, 6, 7, 10, 14, 50, 53, 54, 56]. These results demonstrated that the increased severity of the HPT seen in our patients was not due to a later time of presentation in the natural history of the MEN1 of the patients, but instead due to an increased severity of the HPT itself. Fourth, our surgical results demonstrate our recurrence rate after subtotal parathyroidectomy (3−3.5 glands) was 2.6-fold higher than that reported in the literature for MEN1/HPT patients (our patients-44% vs literature-16.8%, p<0.00001, 15 series, Table 7). Finally, bone density was decreased in 47% of patients which is also consistent with more severe HPT.

To attempt to identify clinical or laboratory factors that might be predictive for which patients demonstrate more aggressive HPT with a higher recurrence rate, we correlated a number of these factors with the surgical outcome. Four factors that were particularly important and three favoring a higher recurrence rate were; the occurrence of ZES as the initial symptom, the presence of higher calcium levels pre-PTX and the presence of a germline MEN1 mutation; whereas a lower recurrence rate was favored by older age of detection of HPT (>28.5 yrs old). In one study[54] an important predictor of whether the PTX would control the HPT long-term was the absence of a family history of MEN1. Because a family history is associated with a germline MEN1 mutation detected[19], this is consistent with our findings. A second study [27] also shows that patients[19] with a positive family history had a more severe form of HPT which

is consistent with our findings. These results suggest these factors will be important on recurrence rates post-PTX in future studies.

The effect of PTX on the behavior of the gastrinoma in patients with MEN1/HPT/ZES including fasting gastrin levels, basal acid ouput and secretin provocative testing is controversial in the literature[44]. Whereas some previous studies on small numbers of cases[23, 42-47, 57-60] report that PTX in MEN1/HPT/ZES patients can markedly decrease the fasting gastrin levels, basal acid output and/or secretin-stimulated gastrin response, a number of other studies report either no effect or a minimal effect on these measures of gastrinoma function[46-49, 59, 61]. Our study convincingly demonstrates the marked ameliorating effect of a successful PTX on these parameters, because we were able to study a larger number of patients and correlate the changes in gastrinoma function with the outcome of the PTX. (Figure 2). In fact, some patients (20%) with MEN1/HPT/ZES no longer had biochemical evidence of ZES with surgery not directed at the pancreatic neuroendocrine tumor, but to remove only the abnormal parathyroid glands. These data are similar to what we previously reported in 1987[23]; however, in that study a higher proportion of patients were cured. The prior study had fewer patients with shorter follow-up which may explain the increase in cure-rate. These findings are even more important when we remember that surgery to remove the gastrinoma in MEN1 patients seldom affects the parameters of ZES[19, 20, 26, 62]. In fact, ZES in these patients is seldom cured by surgery to remove the gastrinoma because the tumors are often multiple within the duodenum and pancreas, as well as frequently associated with lymph node metastases[21, 62-64]. This further supports the strategy that parathyroid surgery should be performed first prior to any abdominal surgery for ZES.

Previously it is reported that the HPT in patients with MEN1 is always hyperplasia and the operation of choice is either 3 and ½ gland parathyroidectomy or four gland parathyroidectomy with transplant.[11-13, 16, 17] The current study corroborates the presence of multiple gland disease in MEN1/HPT/ZES patients and the need for extirpation of at least 3 or more glands. In fact, when this was accomplished patients had a longer disease-free interval, but not a lower incidence of recurrent hypercalcemia (Figure 1). Recurrent HPT is explained by the pathophysiology of the HPT in these patients, while persistent HPT is explained by the extent of the surgery. Recurrent HPT depends on the subsequent growth of residual abnormal parathyroid glands, while persistent HPT is more common if less than 3 glands are excised. From our results the four-gland resection and transplant is not recommended because there was a high graft failure rate and therefore an unacceptable rate of hypoparathyroidism. Furthermore, most studies of MEN1/HPT patients[5, 6, 33, 53, 65, 66] demonstrate a low rate (0 −13% of patients), whereas a few studies report a high rate (50−66%)[67, 68] of autonomous hyperfunction with time in the transplanted parathyroid glands resulting in recurrent hyperparathyroidism. We found in the MEN1/HPT/ZES patients this was not an infrequent outcome, occurring in 44% of our patients with a 4-gland resection and an implant. This finding supports the contention that the parathyroid disease in patients with MEN1/HPT/ZES is severe. Recurrent HPT due to the graft has previously been felt to make re-operation easier [39]; however, forearm re-operations have been more difficult than previously anticipated (personal observation). Large amounts of forearm muscle may need to excised in order to remove the embedded abnormal parathyroid tissue. Therefore, it appears best to leave a small amount of parathyroid tissue within the neck and mark it with a clip so that, if necessary, it can subsequently be found and either excised or trimmed.

In summary, our studies support the conclusion that patients with MEN-1 HPT and ZES represent a unique subgroup of patients with a more virulent form of primary hyperparathyroidism. In these patients there is no ideal surgical procedure to control the hypercalcemia and ameliorate the symptoms. This is because the HPT is caused by diffuse hyperplasia of all the parathyroid glands even though at times it may be asymmetric. Currently,

the three and one half gland parathyroidectomy is recommended as the best surgical procedure. It is associated with a prolonged disease-free interval in many patients and a low incidence of hypoparathyroidism. Furthermore, three and one half gland resection corrects the hypercalcemia and impacts favorably on the biochemical parameters of ZES. However, our study demonstrates these patients need particularly careful follow-up as they have a high recurrence rate.

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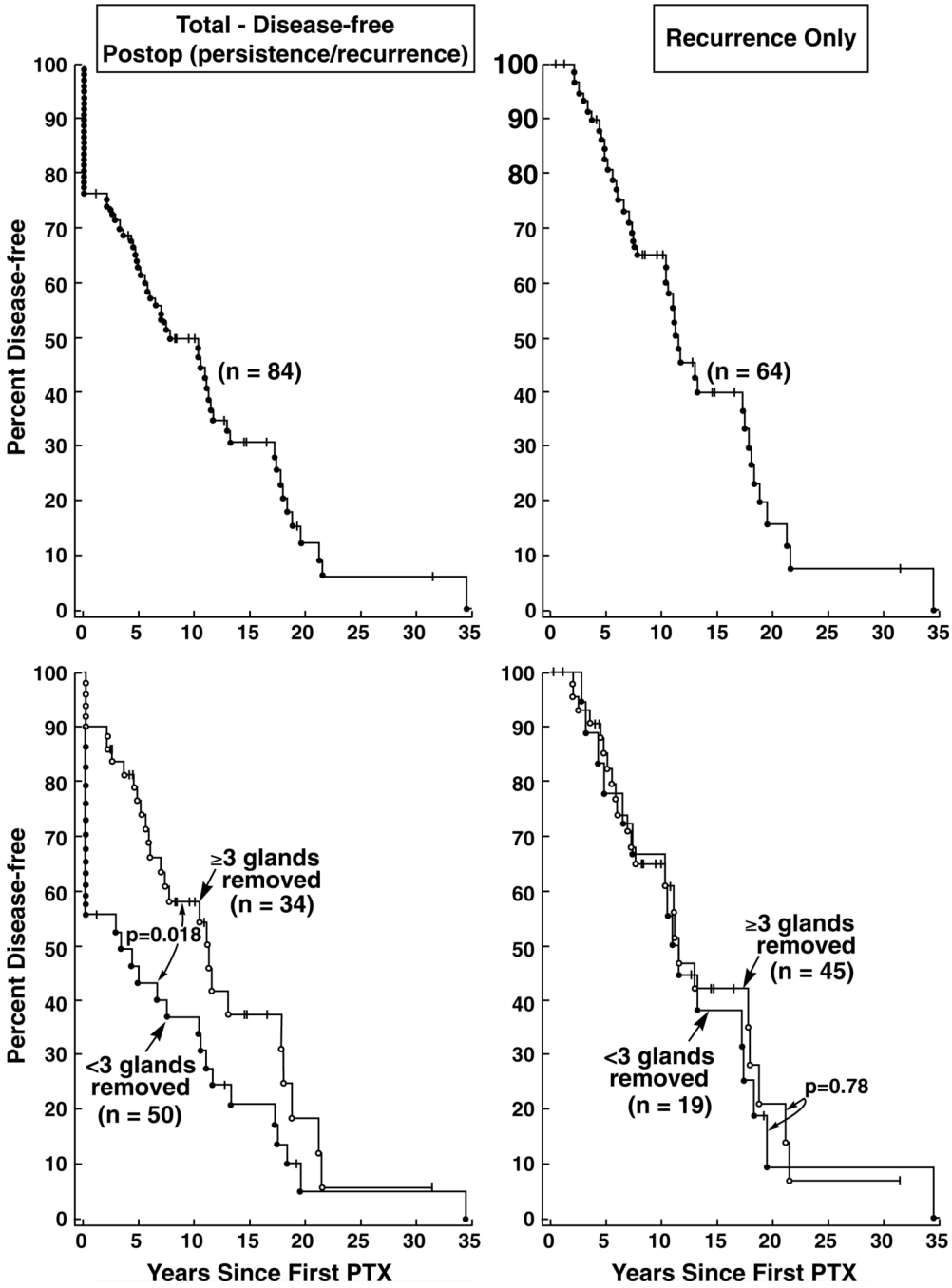

Figure 1.

The disease-free survival (left panels) and recurrence rate (right panels) following initial surgery for hyperparathyroidism in MEN-1 patients with HPT and ZES. The two upper panels show the overall percent who are either free of disease (left panel) or with recurrent HPT (right panel) at follow-up in years. The lower two panels show the same data divided as to whether >3 or <3 glands were removed. It demonstrates that the disease-free survival (but not the recurrence rate) was greater if 3 or more than 3 parathyroid glands were removed compared to <3 glands removed (p=0.018).

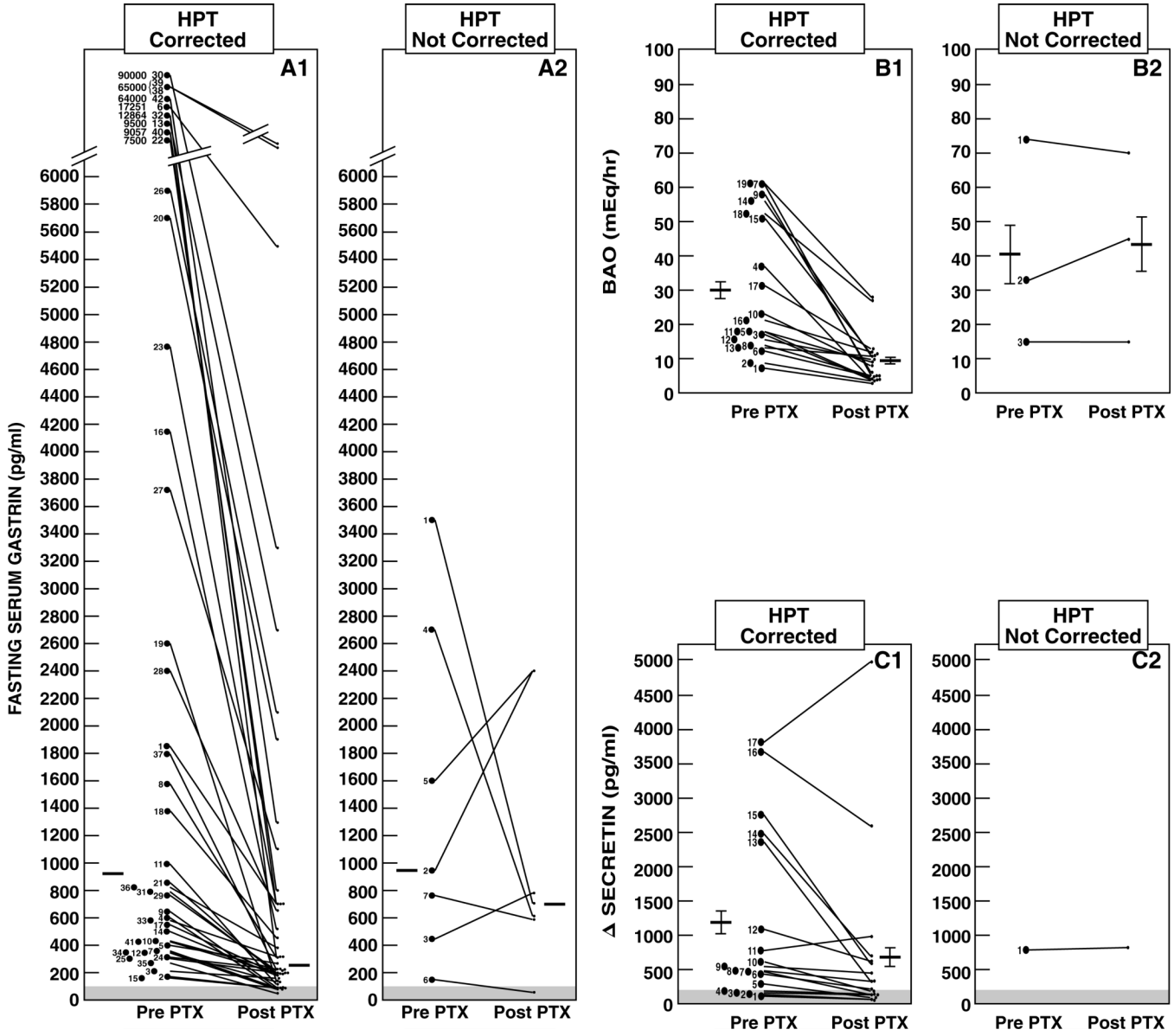

Figure 2.

Effect of parathyroidectomy on fasting gastrin level, BAO and Δ secretin in MEN1/ZES patients without or without the hypercalcemia corrected postparathyroidectomy. Results are shown from 50 patients of whom HPT was corrected in 43 and not corrected in 7 patients. Panels A1/A2 show the mean fasting gastrin levels pre- and post-PTX in 49 patients. The horizontal line shows the median value pre- and post-PTX which were 925 and 247 pg/mL for the corrected HPT group and 842 and 740 pg/mL for the uncorrected group. Eight patients had gastrin levels return to the normal range (i.e. <100 pg/mL)(shaded area) post PTX. Panels B1/B2 shows the effect on the BAO in 22 patients. The horizontal line is the mean±SEM and for the HPT corrected group (n=19) was 30.2 ± 4.5 and 9.5 ± 1.6 mEq/hr and for the uncorrected HPT group (n=3) was 40.6 ± 17.4 and 43.3 ±15.9 mEq/hr. Panels C1/C2 show results of the Δ secretin in 18 patients. The horizontal line is the mean ± SEM which was 1175 ± 294 and 745 ± 286 for the HPT corrected group Eight patients demonstrated a negative secretin test

post PTX using the criterion of ≥200 pg/mL increase postsecretin (shaded area) and 3 patients using the recently proposed criterion of ≥ 120 pg/mL increase. [24, 25]

Table 1

General characteristics of the MEN1/ZES patients studied

Characteristic	Number (%)
No.of patients	84 (100%)
Female gender	49 (58%)
Age (yrs)	
Onset ZES	32.9 ± 1.0
Onset MEN1	26.7 ± 1.0
MEN1 Diagnosis	36.6 ± 1.3
MEN1 features	
ZES	84 (100%)
HPT	84 (100%)
Pituitary tumor	53 (63%)
Carcinoid tumor *(1)*	29 (34%)
Bronchial	12 (14%)
Thymic	6 (7%)
Family History MEN1	68 (81%)
Presenting MEN1 feature	
ZES	25 (30%)
HPT	49 (58%)
Other *(2)*	10 (12%)
Fasting gastrin (pg/ml)	
Median	999
[range]	[34−550,000]
BAO (mEq/hr) *(3)*	
Mean	38.7 ± 4
[range]	[3−144]
MAO (mEq/hr) *(3)*	
Mean	56.9 ± 5.1
[range]	[15−144]
ZES presenting symptom	
Pain	66 (79%)
Diarrhea	55 (65%)
Esophageal symptoms	40 (48%)
Other *(4)*	51 61%)
Peptic ulcer present	47 (56%)
Previous GI surgery	
Gastric	17 (20%)
PET resection	9 (11%)
Other *(5)*	5 (6%)

Abbreviations: ZES, Zollinger-Ellison syndrome; MEN1, multiple endocrine neoplasia type 1; HPT, hyperparathyroidism; BAO, basal acid output; MAO, maximal acid output; PET, pancreatic endocrine tumor; GI, gastrointestinal.

(1)Includes gastric, thymic bronchial carcinoids.

(2)Includes pituitary disease, detection during screening, insulinoma

(3)Includes data from patients without previous gastric acid reducing surgery (n=64)

(4)Other presenting symptoms include bleeding, nausea, vomiting.

(5)Other GI surgical procedures include oversew of perforated jejunal ulcer, cholecystectomy, esophageal leiomyoma resection, Nissen fundoplication.

Table 2

Characteristics of the primary hyperparathyroidism of the 84 MEN1/ZES patients included in study.

Characteristic	Number (%)
Age (yrs)	
Onset of HPT	30.6 ± 1.1
First PTX	36.0 ± 1.2
Last follow-up	52.5 ± 1.4
Duration (yrs)	
Onset HPT prior to 1st PTX	5.4 ± 0.8
Onset MEN1 prior to 1st PTX	9.3 ± 0.9
Onset HPT to last F/U	21.9 ± 1.4
1st PTX to Last F/U	16.5 ± 1.2
History renal colic	52 (62%)
Onset ZES prior 1st PTX	27 (32%)
Mean Preoperative Lab values (1st PTX)	
Total calcium (mmol/L) *(1)*	2.81 ± 0.07
Ionized calcium (mmol/L) *(1)*	1.52 ± 0.02
PTH (mid) (fold normal) *(2)*	1.88 ± 0.33-fold
PTH (IRMA) (fold normal) *(2)*	2.43 ± 0.28
Urinary calcium (mmol/24 hr) *(3)*	8.63 ± 1.0
Fasting gastrin (fold increase) (median) *(4)*	7.9
BAO (mEq/hr)	38.2 ± 4.3
Bone density, any Z score decreased ≥ 2SD *(5)*	46%

Abbreviations: See Table 1 legend.

(1) Normal serum total and ionized calcium levels are 2−2.5 mmol/L and 1.17−1.31 mmol/L, respectively. Data immediately before 1st PTX are from 69 patients.

(2) Normal plasma PTH mid molecule and PTH IRMA values are 50−340 pg/mL and 10−65 before 9/94 and after 9/99. From 9/94−9/99 normal values were 9.4−49 pg/mL. Values are means from 52 patients taken immediately before the 1st PTX. PTH mid molecule levels are expressed as fold increase over the upper limit of normal to allow comparison of values from other labs.

(3) Fasting serum gastrin levels are from 53 patients who were assessed immediately before and after PTX and expressed as fold increase over the upper limit of normal (i.e. 100 pg/mL) to allow comparison from different labs as described previously {24,25}.

(4) Normal values of urinary calcium are 1.25−62.5 mmol/24 hours. To convert to mg/24 hours multiple by 40.

(5) Bone density studies were performed in 56 patients and the result expressed as the percentage of patients showing any area evaluated with a Z score decreased at less 2SD for age matched controls.

Table 3

Parathyroidectomy characteristics and results in 84 patients with MEN1/ZES.

Characteristic	Number (% of patients)
1st PTX. # glands removed	
<3	35 (42%)
3−3.5	40 (47%)
4	9 (11%)
mean number	2.8 ± 0.1
Parathyroid graft	
No. patients receiving immediate graft	9 (11%)
Yrs F/U	
<5	33 (39%)
5−9.9	30 (37%)
10−19.9	15 (18%)
≥20	6 (7%)
mean number	7.2 ± 0.7
Parathyroid status last F/U	
Normocalcemic	34 (40%)
Hypercalcemic	33 (39%)
Hypocalcemic	17 (20%)
Taking Vitamin D/Calcium	13 (15%)
Mean Last Lab values *(1),(2)*	
Total calcium (mmol/L)	2.29 ± 0.03
Ionized calcium (mmol/L)	1.28 ± 0.02
PTH (mid) (fold increased)	0.80 ± 0.28-fold
PTH (IRMA)	93 ± 19
Urinary calcium (mmol/24 hr)	3.91 ± 0.4
Fasting gastrin (fold increased) (median)	4.97-fold
BAO (mEq/hr)	13.5 ± 3.2

*(1)*Normal values present in Table 2 legend.

*(2)*Total and ionized calcium levels from 80 patients were averaged, PTH levels from 70 patients, urinary calcium from 47 patients, fasting gastrin levels from 72 patients and BAO measurements from 27 patients.

Table 4

Results of Parathyroidectomy in 84 MEN1/ZES patients.

No. glands removed	# pts	Age 1st PTX (yrs)	Yrs F/U post 1st PTX	Persistent HPT (%)	Recurrent HPT (%)	Hypopara (%)	Normocalcemia No Ca/VitD (%)	Time to recurrence (yrs)
<3	35	33 ± 1.6	20.7 ± 1.9	15 (43%)	16(46%)	1 (3%)	2 (6%)	12.0 ± 2.0
3−3.5	40	38.0 ± 1.7	14.5 ± 1.5	5 (12%)	18 (45%)	4 (10%)	14 (35%)	10.4 ± 1.6
≥4	9	36.7 ± 4.4	9.9 ± 1.5	0 (0%)	5 (55%)(1)	2 (22%)	2 (22%)	6.0 ± 0.8
Total	84	36.0 ± 1.2	16.5 ± 1.2	20 (24%)	39 (46%)	7 (7%)	18 (21%)	10.7 ± 1.2

Abbreviations. See Table 1 legend. pts, patients; F/u, follow-up; hypopara, hypoparathyroidism; Ca./VitD, taking calcium and/or vitamin D

(1)Four of the 5 recurrences were in the graft.

Table 5

Effect of gastrin levels on HPT parameters/treatment

	Fasting gastrin level (median) (pg/mL)		
Parameter	**Parameter absent**	**Parameter present**	**P value**
ZES onset prior HPT	680	1300	0.17
Family History MEN1	648	1055	0.80
Age PTX >35	1050	998	0.81
HPT recur after PTX	1060	600	0.24
HPT persist after PTX	784	1094	0.19
> 4 glands removed	909	1030	0.68
HPT present last F/U	1131	600	0.32
Graft hyperfunctioning	1060	398	0.25

Abbreviations. See Table 1-4 legends.

Table 6

Prognostic factors for correction of HPT

	At last F/U:		
Chararacteristic	**Hypercalcemia (n=33)**	**No hypercalcemia (n=51)**	**P value** *(3)*
I. ZES features			
ZES 1st MEN1 symptom	9%	43%	0.0006
Liver metastases present	24%	24%	0.39
Yrs ZES onset last F/U>18	45%	51%	0.57
II. MEN1 features			
Age onset MEN1 >27.5 yrs old	27%	45%	0.078
Positive family history MEN1	85%	78%	0.33
Germline MEN1 mutation present *(1)*	100%	79%	0.0069
III. HPT Feature			
Age HPT detected >28.5 yrs	39%	61%	0.045
Yrs onset HPT last F/U >19.5	45%	51%	0.39
IV. PTX Feature			
Age PTX>35 yrs	42%	53%	0.24
Yrs last F/u to PTX>15	61%	43%	0.090
PTX ≥3−3.5 glds	33%%	59%	0.31
PTX result			
Persistent HPT	36%	16%	0.029
Recurrent HPT	64%	35%	0.010
Yrs to recur after PTX>10	38%	67%	0.072
V. Lab value prior PTX *(2)*			
Ca total increased >110%	78%	28%	0.0020
PTH increased > 160%	80	36%	0.102

(1) The presence of germline mutations was assessed in 70 patients including 28/31 (85%) of the HPT present group and 42/51 (84%) of the HPT absent group.

(2) Preoperative calcium values and PTH values prior to the first PTX were available from 46 and 27 patients.

[3]P values were calculated using the Fishers Exact test with median values for continuous variables.

Table 7

Persistent and recurrent disease in current series and literature of MEN1 patients with HPT treated with subtotal parathyroidectomy (3−3.5 glds)

Author (ref)	yr	No of pts	Postop persistent disease (%)	Postop recurrent disease (%)	# RECURR.	Years follow-up (mean/median)
Current study	2007	41	12	44*	18	7.9
Previous series						
Prinz [11]	1981	9	11	12	1	9.5
Rizzoli [56]	1985	20	15	15	3	5.5
Malmeus [5]	1986	6	0	33	2	5
Samaan [51]	1989	8	12	14	1	5.5
Kraimps [10]	1992	14	14	36	5	8
Hellman [72]	1992	34	0	9	3	9
Obara [17]	1992	9	0	11	1	5.4
O'Riordan [16]	1993	54	0	16	9	10
Thompson [73]	1995	34	6	9	3	5.4
Burgess [74]	1998	37	8	19	7	8
Hellman [53]	1998	9	22	44	4	6
Dotzenrath [40]	2001	25	nd	12	3	5.2
Kaczirek [52]	2002	4	25	0	0	5.8
Hubbard [7]	2006	21	0	5	1	5.2
Lee [6]	2006	6	0	17	1	7.2
Previous series						
Mean		19.33	8.20	16.80		6.71
sd		14.75	8.39	11.98		1.71
SUM		290.00			44	

*P<0.00001 compared to recurrence rate for all literature cases (44/290=15%).

Table 8

Summary of findings showing MEN1/ZES patients have a more severe form of HPT than MEN1 patients alone and predictive factors for severity.

I.	**Increased severity of HPT**
	a. Higher frequency of nephrolithiases at presentation[62% vs 40 ±6%,(7 series,literature), p<0.05][(1)]
	b. Higher serum PTH levels at presentation[2.4-fold normal vs 1.67 ± 0.38,(8 series,literature), p<0.05][(1)]
	c. Higher relapse rate post subtotal PTX[44 % vs 17%, P<0.00001, (15 series literature)][(2)]
II.	**Predictive factors for increcreased recuurence post subtotal PTX**[(3)]
	a. ZES initial clinical manifestation of MEN1 (p=0.0006)
	b. Presence of MEN1 germline mutation (P=0.0069)
	c. HPT diagnosed <28.5 yrs of age (p=0.045)
	d. Serum calcium levels at presentation >110% normal (P=0.0020)

(1) References for literature series in text

(2) References in Table 7

(3) Data from analysis in Table 6