Importance of Surveillance in Multiple Endocrine Neoplasia – 1 and Surgery in Sporadic Zollinger-Ellison Syndrome

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Background

Zollinger-Ellison syndrome (ZES) is a rare disorder characterized by gastric acid hypersecretion (GAH) from gastrin-secreting tumors of the GI tract. One-quarter to one-half of these patients have multiple endocrine neoplasia type 1 (MEN-1), while the remainder have sporadic tumors.

Several large prospective studies from the National Institute of Health (NIH) support a role for routine surgical exploration in sporadic patients with localized disease; while, the role for surgery in MEN-1 patients remains contentious as these patients are rarely, if ever, cured of ZES.

Most of the current surgical recommendations reflect extensive research from the NIH; and therefore may not be directly applicable to tertiary care centers managing these patients according to different protocols.

This study represents one of the largest studies of operative versus non-operative management of ZES patients at a tertiary care hospital. Our findings support surgery to improve survival in sporadic cases of ZES and provide recommendations on how to proceed in MEN-1. We have also identified a novel indicator associated with lack of postoperative cure and liver metastasis - lymph node involvement at surgery.

Materials & Methods

• Retrospective chart review of 49 ZES patients seen at the Hospital of the University of Pennsylvania (HUP) between 8/1994 and 1/2012. Two patients excluded due to lack of records.

• Patients underwent H&P, measurement of basal acid output (BAO), fasting serum gastrin, and secretin provocative testing. Extent of gastrinoma assessed using CT, MRI, EGD, and somatostatin-receptor scintigraphy.

• Operations were based on standardized surgical exploration for cure or for resection of observed mass. Disease status post-resection determined with fasting serum gastrin, secretin provocation testing, and gastric analyses. Patients evaluated at 3-6 months and then yearly with biochemical studies and imaging.

• Disease-related death defined as death due to metastatic tumor (n=6) or failure to control GAH leading to death (n=1).

• Log-rank test used to determine significance between groups for survival data. Cox proportional hazards modeling was used for comparisons between similar groups based on MEN-1 and surgical status. Unpaired t-test and Fisher's Exact Test for subgroup analysis as appropriate.

Tables

Table 1. Clinical and demographic data of 49 patients with ZES.

Characteristic	All Patients	Surgical Status			MEN-1 Status		
		Surgery	No Surgery	*P*	MEN-1	Sporadic	*P*
No. of patients	49	34	15		16	33	
Gender – Male (N [%])	22(45%)	15(44%)	6(40%)	*0.55*	8(50%)	13(39%)	*1.00*
Ethnicity							
White	85%	88%	83%	*0.71*	88%	83%	*1.00*
Black	13%	9%	17%	*0.38*	6%	17%	*0.38*
Asian	2%	3%	0%	*1.00*	6%	0%	*0.39*
Other	0%	0%	0%	*1.00*	0%	0%	*1.00*
MEN-1 present (N [%])	16 (33%)	9 (26%)	7 (46%)	*0.20*	100%	0%	*N/A*
Mean duration (yrs)							
Onset to diagnosis	4.4	4.2	4.9	*0.84*	3.5	4.1	*0.85*
Diagnosis to surgery	0.8	0.7	N/A	*N/A*	0.6	0.9	*0.70*
Prior gastric surgery	10%	12%	8%	*1.00*	6%	12%	*1.00*
Preop. Imaging (N [%])							
Liver involvement	11 (24%)	5 (16%)	6 (46%)	*0.13*	3 (23%)	8 (25%)	*1.00*
Primary w liver mets	6 (13%)	2 (7%)	4 (31%)	*0.12*	2 (15%)	4 (13%)	*1.00*

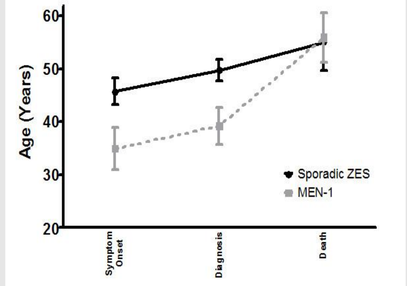
Table 2. Primary tumor type and extent of disease at surgery.

Tumor Characteristic	All Patients N (%)	MEN-1 N (%)	Sporadic N (%)	*P*
Primary location				
Duodenum	16 (50)	4 (44)	12 (52)	*1.00*
Pancreas	7 (22)	4 (44)	3 (13)	*0.08*
Lymph Node	2 (9)	0	2 (9)	*1.00*
Liver	2 (9)	0	2 (9)	*1.00*
Indeterminate	5 (9)	1 (11)	4 (17)	*1.00*
Other	0	0	0	*N/A*
Extent				
Primary	9 (29)	2 (22)	7 (30)	*1.00*
Primary and Lymph Node(s)	15 (47)	5 (56)	10 (43)	*0.70*
Primary with Liver metastases	3 (10)	1 (11)	2 (9)	*1.00*
Lymph Node Metastases only	1 (3)	1 (11)	0	*0.28*
Liver Metastases only	1 (3)	0	1 (4)	*1.00*
No tumor found	3 (10)	0	3 (13)	*0.54*

Table 3. Clinical characteristics and association with postoperative cure or liver metastasis in surgical ZES patients.

	Post-operative cure N (%)	Liver Metastases N (%)
Presenting Symptoms		
Diarrhea	4 (24)	4 (27)
Peptic symptoms	4 (29)	2 (13)
Nausea/Vomiting	1 (20)	1 (20)
Abdominal Pain	3 (33)	3 (38)
Weight Loss	1 (17)	1 (17)
Primary		
Duodenum	2 (17)	3 (60)
Pancreas	1 (20)	2 (40)
Lymph Node	1	0
Indeterminate	0	0
Liver	2	-
Extent at Surgery		
Primary Only	5 (71)	0
Primary and Lymph Nodes	1 (9)	5 (33)
Primary with Liver metastases	0	-
No tumor found	0	0

Figures



Characteristic	All Patients	MEN-1	Sporadic	*P*
No. of patients	49	16	33	
Age (mean years ± SEM)				
Onset of GAH	42.9 ± 2.2	34.9 ± 4	45.7 ± 2.5	0.03
Diagnosis of ZES	46.7 ± 1.9	39.3 ± 3.5	49.7 ± 2.1	0.01
Age at death	55.4 ± 3.9	55.9 ± 4.9	55.1 ± 5.4	0.91
Age at last follow-up	54.1 ± 1.9	50.6 ± 3	55.7 ± 2.3	0.2

Figure 1: Clinical Course of MEN-1 versus sporadic ZES patients. Data points composed of mean years ± SEM.

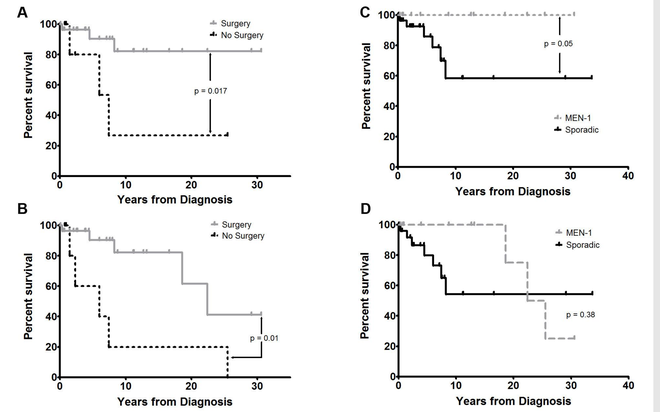


Figure 2: Comparison of survival from disease diagnosis to death. (A) Disease-related and (B) all-cause death for all patients treated with (n=29) and without (n=8) surgery. (C) Disease-related and (D) all-cause death for all patients with ZES (n=49) with (n=16) or without (n=33) MEN-1.

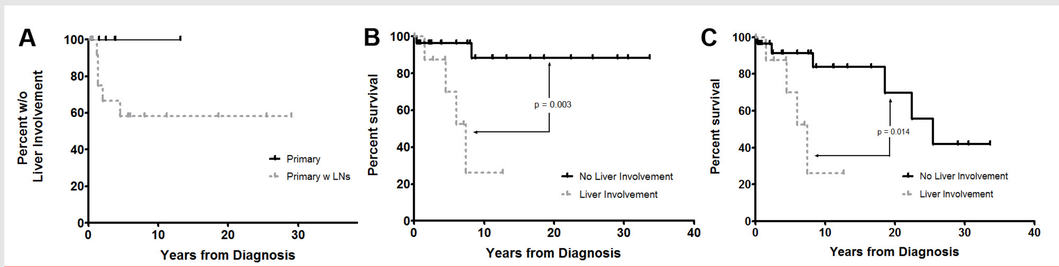


Figure 3: Association between extent of disease with liver metastasis and mortality. (A) Comparison is made of those with disease limited to primary tumor at diagnosis (n=7) and those with primary and lymph node involvement (n=14). (B) Disease-related and (C) all-cause mortality based on liver involvement (n=10) versus no liver involvement (n=28) at time of diagnosis.

Conclusions

• The presence of MEN-1 predicts earlier onset and diagnosis of ZES but a more benign clinical course rarely characterized by disease-related death.

• Sporadic ZES is associated with disease-related mortality that is reduced by early surgical intervention. Interestingly, surgery prolonged survival without delaying liver metastasis.

• Survival benefit from surgery was limited to sporadic cases of ZES. Given the lack of survival benefit in our MEN-1 group, we support a conservative approach to disease management in these patients instead focusing on symptom control with pharmacologic agents.

• Liver involvement at diagnosis was the most important determinant of survival.

• Lymph node involvement at surgery likely increases risk of liver metastasis and decreases likelihood of postoperative cure.

• Liver metastasis almost always occurred within 2 years of diagnosis supporting theory of rapidly progressive, malignant form of gastrinoma that defies prediction and advocates for swift surgical intervention in sporadic patients.

Limitations:
Retrospective, post-hoc study.
Trend towards liver involvement in unoperated group.
Trend towards less follow-up for unoperated patients