

The slide features a dark blue background. On the left side, there are several vertical stripes of varying shades of blue and white. Overlaid on these stripes are several circles of different sizes, also in shades of blue, arranged in a vertical line.

AN ARGUMENT FOR SURGERY FOR GASTRINOMA

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WHAT IS A GASTRINOMA?

- Gastrin secreting cells derived from multipotential stem cells of endodermal origin or “enteroendocrine cells”
- Location
 - Pancreas
 - Small intestine
 - Approximately 70% are found in the duodenum
 - Lymph nodes adjacent to pancreas
 - Heart, liver, bile ducts, ovary, kidney, mesentery



AKA ZOLLINGER-ELLISON SYNDROME

- First described by Zollinger and Ellison in 1955



- Ulceration of upper jejunum
- Hypersecretion of gastric acid
- Non-beta islet tumors of pancreas



CLINICAL FEATURES

- Peptic Ulcers (>90% of patients with ZES)
- Diarrhea
 - Volume
 - Maldigestion and malabsorption
 - Secretory
- Metastatic disease
 - Liver



EPIDEMIOLOGY

- 20 and 50 years old at time of diagnosis
- More common in males
- Sporadic (~80%)
- Associated with Multiple Endocrine Neoplasia type 1 (MEN1)
 - Parathyroid tumors
 - Pituitary tumors
 - Pancreatic tumors



DIAGNOSIS

- Fasting serum gastrin concentration
 - Higher levels more common in pancreatic tumors, larger tumor size, metastatic disease
- Secretin stimulation test
 - Perform if fasting serum gastrin is nondiagnostic
 - Secretin stimulates release of gastrin from gastrinoma cells but inhibits gastrin release from normal G cells
- Gastric acid secretion studies



TREATMENT. A DUAL APPROACH.

- Hypersecretion of gastric acid
 - Vagotomy
 - H₂-receptor antagonists
 - Proton Pump Inhibitors (PPIs)
- Gastrinoma
 - Role of surgical resection for long-term survival



WHY THE DEBATE?

- Most patients had died of complications related to acid hypersecretion
- Gastrinomas are uncommon
- Follow-up has been short



NIH-LED PROSPECTIVE STUDY OF RESULTS OF SURGICAL RESECTION OF TUMORS

- Annals of Surgery 1992
 - Primarily assessed rates of cure and disease-free survival for sporadic gastrinomas only
- NEJM 1999
 - Addressed rates of cure for patients with sporadic gastrinomas as compared to patients with MEN1-related gastrinomas
- Annals of Surgery 2001
 - Examined long-term survival in patients with gastrinomas and MEN1



SPORADIC GASTRINOMAS – RATES OF SURGICAL CURE AND DISEASE-FREE SURVIVAL

Norton JA, Doppman JL, Jensen RT. *Curative resection in Zollinger-Ellison syndrome. Results of a 10-year prospective study.* Ann Surg. 1992 Jan; 215(1):8-18.



NIH-LEAD PROSPECTIVE STUDY OF RESULTS OF SURGICAL RESECTION OF TUMORS

- Allowed for incorporation of advances in preoperative or operative localization of tumors
- Long-term follow up

- Exclusion criteria
 - Evidence of liver metastases on imaging
 - MEN1
 - Severe comorbidities precluding surgical exploration

PREOPERATIVE PREPARATION

- Medical suppression of gastric acid secretion

Cimetidine		Rantidine		Famotidine		Omeprazole	
n	Mean Dose (mg/day) (range)	n	Mean Dose (mg/day) (range)	n	Mean Dose (mg/day) (range)	n	Mean Dose (mg/day) (range)
11 (15%)	6050 (2400-12000)	39 (53%)	2260 (300-5400)	9 (12%)	308 (80-800)	14 (19%)	84 (60-120)

- Localization of tumor
 - 52% of patients had tumor localized on preoperative imaging studies

SURGICAL REMOVAL OF GASTRINOMA

- Initial study population of 73 patients with sporadic gastrinomas who underwent standard extensive laparotomy
 - After 1987 patients routinely underwent EGD with transillumination of the duodenum and duodenotomy
- Overall 57/73 (78%) had resection of tumor with improved resection rates with addition of intraoperative localization techniques
 - Improved identification of duodenal wall tumors

DEFINITION OF CURE

- Normal fasting serum gastrin concentration
- Negative secretin tests
- Negative imaging studies (US, CT, MRI)



3-6 MONTH FOLLOW-UP

- Initial surgical cure – there was no statistical difference in surgical cure overall, or for any location of primary tumor

TABLE 4. Ability to Initially Surgically Cure Patients With Zollinger-Ellison Syndrome as a Function of Primary Tumor Location

Group*	Location of Resected Primary Gastrinoma											
	Duodenum			Pancreas			Lymph Nodes			Total		
	No. With Tumor Found	No. Cured†	% Cured‡	No. With Tumor Found	No. Cured	% Cured	No. With Tumor Found	No. Cured	% Cured	No. With Tumor Found	No. Cured	% Cured
I	4	2	50	12	11	92	6	5	83	22§	18§	82
II	16	10	62	11	8	73	7	5	71	34	23	67
Both	20	12	60	23	19	83	13	10	77	56§	41§	37

- Malignant potential – liver or lymph node

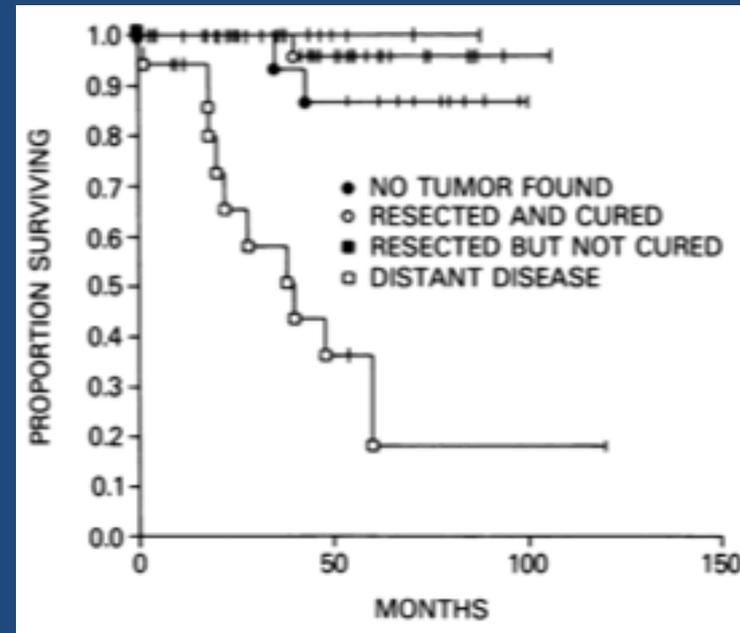
TABLE 5. Presence of Metastatic Disease* With Duodenal and Pancreatic Primary Lesions

Location of Primary Gastrinoma	n	No. With Metastases (%)
Pancreas	23	5 (22)
Duodenum	20	11 (55)†

* Metastatic disease was defined as the percentage of tumor in an adjacent lymph node (n = 12) or the liver (n = 4) in patients with a primary gastrinoma at the indicated site in group 1 and group 2.

LONG TERM FOLLOW-UP

- Recurrence
 - 10/42 patients
- 5-year disease-free rates
 - Duodenal 40%
 - Pancreatic 70%
 - Lymph node 60%
- Anti-secretory medications in patients who are disease-free after surgery
- Overall survival
 - Surgical groups 90%
 - Metastatic disease <20%



COMPARISON OF RATES OF CURE FOR SPORADIC AND MEN1-RELATED GASTRINOMAS

Norton, JA, et al. *Surgery to cure the Zollinger-Ellison syndrome*. N Engl J Med. 1999 Aug 26;341(9):635-44.

- Included the original group of 73 patients with sporadic gastrinomas plus, an additional 50 patients with sporadic tumors
- Also assessed 28 patients with MEN1-related tumors



NIH STUDY EXTENDED

- Sporadic tumors
 - 51% of patients were disease free immediately after surgery
 - Disease-free survival 40% at 5 years, 34% at 10 years
- MEN1 related tumors
 - 16% of patients were disease free immediately after surgery
 - Disease-free survival 4% at 5 years, 0% at 10 years

SURGICAL RESECTION OF GASTRINOMAS IN PATIENTS WITH MEN1

Norton JA, et al. *Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome.* Ann Surg. 2001 Oct;234(4):495-505-6.



SURGICAL EXPLORATION IN PATIENTS WITH ZES AND MEN1

- 81 patients with MEN1 and ZES
 - Group 1 – tumors <2.5cm – no surgery
 - Group 2A – Single PET 2.5-6cm – surgery
 - Group 2B – 2 or more lesions 2.5cm in diameter or larger OR one tumor >6cm - surgery
 - Group 3 – diffuse liver metastases – no surgery

LONG-TERM FOLLOW-UP

Table 6. LONG-TERM FOLLOW-UP AND SURGICAL OUTCOME

Parameter	Group 1 (n = 25)	Group 2A (n = 17)	Group 2B (n = 31)	Group 3 (n = 8)	Total (n = 81)
Duration of follow-up (yr)					
From onset of ZES	14.3 ± 2.1	13.3 ± 1.7	16.3 ± 1.7	17.5 ± 4.2	15.2 ± 1.1
From first NIH admission	8.5 ± 1.4	7.9 ± 1.5	9.0 ± 1.3	12.4 ± 3.1	9.1 ± 0.8
From surgery	—	7.6 ± 1.5	6.5 ± 1.0	—	6.9 ± 0.8
Percent disease-free					
Immediate*	—	6 (35%)	3 (10%)	—	9 (19%)
Disease-free ≥5 yr	—	0 (0%)	0 (0%)	—	0 (0%)
Liver metastases developed	0	1 (6%)	2 (6%)	—	3 (6%)
Survival					
Disease-related death during follow-up	0	0 (0%)	1 (3%)	4 (50%)	5 (10%)§
Survival-10 yr	100%	100%	100%	88%	
Survival-15 yr	100%	100%	89%	52%	
Reoperation related to PET†	NA	1 (6%)	2 (6%)	—	3 (6%)
Surgical complications‡					
Early (<30 days)	—	6 (35%)	8 (26%)	—	14 (29%)
Late (>30 days)	—	2 (12%)	3 (10%)	—	5 (10%)

NIH, National Institutes of Health; PET, pancreatic endocrine tumor; ZES, Zollinger-Ellison syndrome.

Negative secretin test and imaging studies as well as normal fasting gastrin within 2 weeks of surgery, as defined previously.²⁵

† Three patients had repeat abdominal explorations for recurrent PETs.

‡ Early complications included postoperative pancreatitis (n = 2), deep vein thrombophlebitis (n = 1), abscess (n = 4), bleeding (n = 1), fistula drainage (n = 2), infection (n = 1), prolonged ileus (n = 1). Late complications included small bowel obstruction (n = 3), biliary stricture (n = 1), and development of an abscess (n = 2).

§ Different from survival in other three groups (P < .003).

|| For parameters assessed for surgical groups, the denomination was 48 patients (groups 2A and 2B).

Norton JA, et al. *Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome.* Ann Surg. 2001 Oct;234(4):495-505-6.

CONCLUSIONS ON SURGICAL RESECTION

- Exploratory laparotomy and resection of the primary tumor should be performed
 - Patients without diffuse metastatic disease
 - Sporadic tumors
 - Patients with MEN1 and ZES with tumors >2.5cm and no evidence of metastatic disease
 - Anti-secretory medications can usually be stopped or significantly decreased in patients who are disease-free after surgery
 - Cure is rare, survival is excellent. Thus, many patients will still require long-term anti-secretory therapy
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COMPLICATIONS OF LONG-TERM USE OF PROTON PUMP INHIBITORS

- Expensive (\$3276/year) – can affect long-term compliance
- Achlorhydria leading to B12, iron, calcium malabsorption
- Increased risk of osteoporosis and hip and spine fractures with use longer than 5 years
- Increased risk community acquired pneumonia
- Drug-drug interactions
 - Clopidogrel! Increased risk (up to 40%) of coronary stent occlusions



GASTRIC SURGERY

- Total or partial gastrectomy should be considered in select patients
 - Hypergastrinemic states associated with increased risk of gastric carcinoids
 - In sporadic ZES risk of carcinoids is <2%
 - In MEN1 gastric carcinoids are found in 13-37% of patients of which 10-20% will be aggressive and require resection via total or partial gastrectomy
- Parietal cell vagotomy
 - Decrease basal acid secretion to allow for use of cheaper and less potent H2-Blockers



PARIETAL CELL VAGOTOMY

- 86% have had long-term inhibition of acid secretion
- 36% patients discontinued regular use of acid-inhibiting medications.
- Parietal cell vagotomy increased the sensitivity of H₂-receptor antagonists
- Allowed more than 1/3 of patients to stop PPIs and switch to H₂-receptor antagonists which are cheaper and less potent

CONCLUSIONS

- Exploratory laparotomy and resection of the primary tumor should be performed in most patients without metastatic disease on presentation
 - Due to low rates of biochemical cure, but long-term survival, many patients with ZES will require high-dose, long-term use of PPIs. Physicians and patients need to be aware of the risks of these medications.
 - Parietal cell vagotomy should be considered in patients at the time of laparotomy to reduce basal acid secretion and increase sensitivity to H₂-receptor antagonists.
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THANK YOU!

