SCHOOL OF MEDICINE
Department of Surgery
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Current Gastrinoma Therapy: The Futility of Surgery

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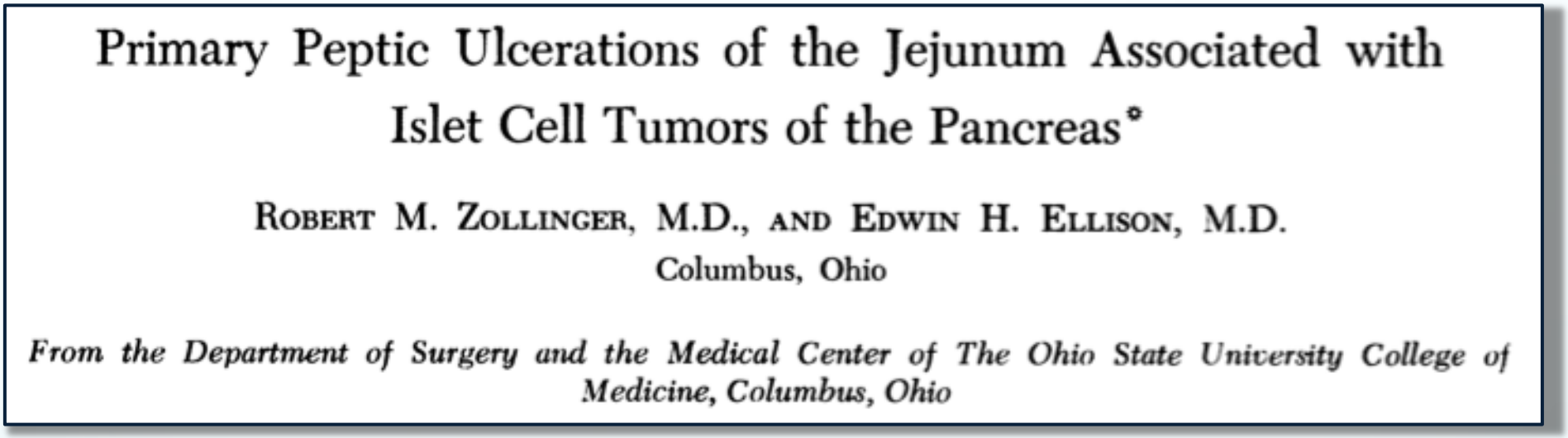
Definition of Gastrinoma

Gastrinoma



Primary Peptic Ulcerations of the Jejunum Associated with Islet Cell Tumors of the Pancreas*

ROBERT M. ZOLLINGER, M.D., AND EDWIN H. ELLISON, M.D.
Columbus, Ohio

From the Department of Surgery and the Medical Center of The Ohio State University College of Medicine, Columbus, Ohio

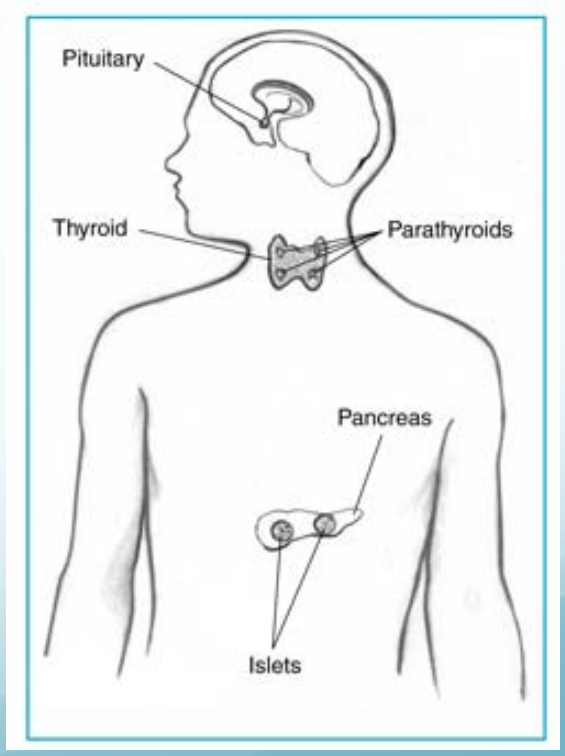
- First described in 1955 by Drs. Robert Zollinger and Edwin Ellison, surgeons at Ohio State University → **Zollinger-Ellison syndrome**

Gastrinoma

- Characterized by refractory peptic ulcer disease, diarrhea, and gastric acid hypersecretion due to a gastrin-secreting tumor
- Diagnosis suggested by increased gastrin levels, positive secretin test, increased basal acid output, in the setting of low stomach pH
- Historically, morbidity and mortality has been related to **sequelae of gastric acid hypersecretion**
- Now, due to excellent medical therapies available, mortality is related to **tumor burden**

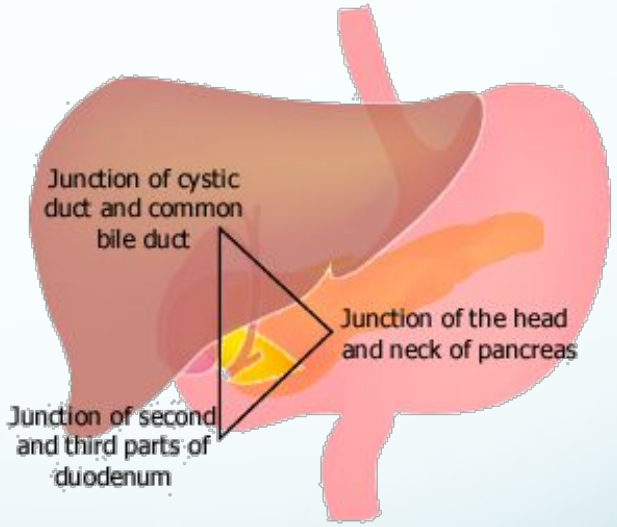
Gastrinoma

- Incidence: 0.1 – 3 patients/1 million in the US
  - Account for approximately 1% of peptic ulcer disease
  - 25% of ZES cases occur in association with MEN-1 syndrome
- Slight male predominance (60%)
- Malignancy determined by metastasis
- Majority of patients have a benign course (76%)
  - 96% survival at 10-yrs
  - Slow-growing tumor



Gastrinoma

- Poor prognostic factors: liver metastases, large primary tumor size, inadequate acid control, pancreatic primary site
  - 20-yr survival in patients without hepatic metastases = 95%
  - 10-yr survival in patients with hepatic metastases = 15%
- 90% located in “gastrinoma triangle”
- Duodenal gastrinomas 3-10x more common than pancreatic
  - Smaller (often <1.0 cm), multiple, LN > liver metastases



Current Surgical Therapies

Curative Resection in Zollinger–Ellison Syndrome

Results of a 10-Year Prospective Study

JEFFREY A. NORTON, M.D.,* JOHN L. DOPPMAN, M.D.,† and ROBERT T. JENSEN, M.D.‡

- Two groups, total n=73
  - Group 1 = prior to enhanced localization techniques
  - Group 2 = utilization of enhanced localization techniques
- Surgical technique:
  - Extensive laparotomy with exploration of liver, pelvis, small intestine, pancreas, stomach, duodenum, and lymph nodes
  - Enucleation of pancreatic tumors (vs. distal resection)
  - Excision of all discovered tumors to rim of normal bowel
  - Group 2: additional exploration via duodenotomy

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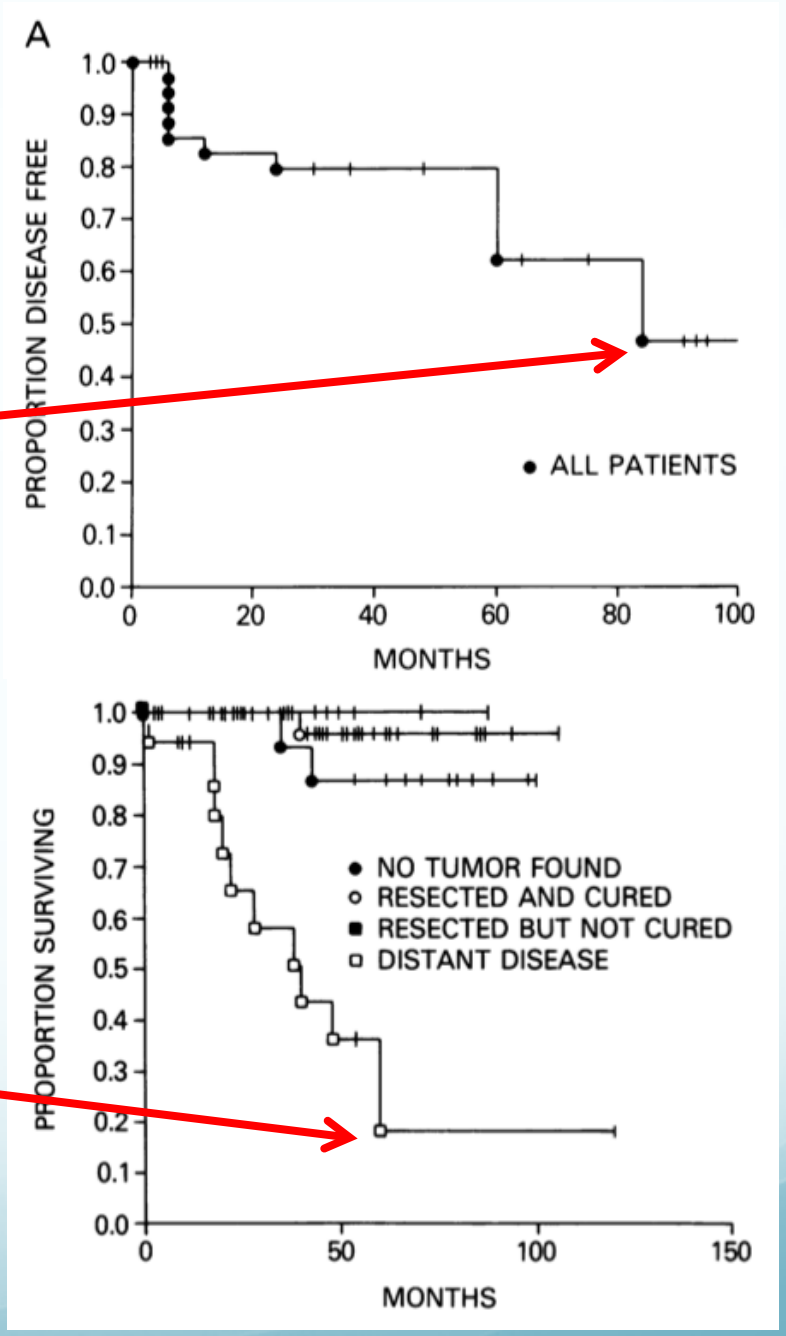
- Operative mortality = 0%, morbidity = 11%
- 92% of Group 2 patients had gastrinomas resected surgically (vs. 64%, $p < 0.01$)
- Overall 58% at 3- & 6-month followup were disease-free
  - Determined by negative gastrin level, secretin test, and imaging
  - Group 1 disease-free rate = 52% vs. group 2 = 62%, $p = 0.5$
- **Higher rate of gastrinomas found ≠ improved disease-free rate**

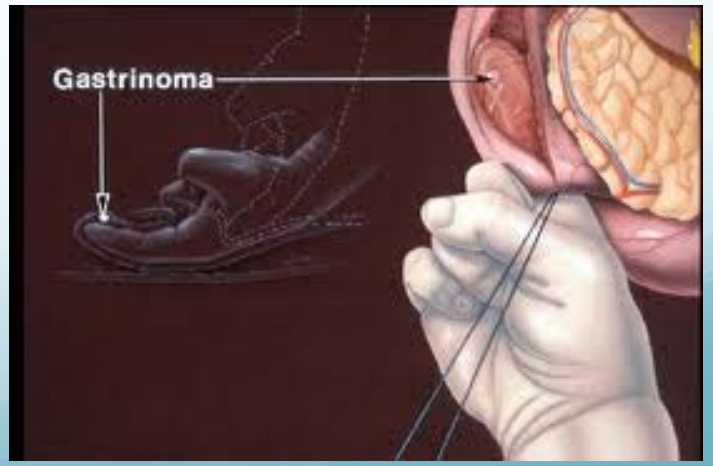
- Of the 58% with initial disease-free status, only about 50% remained at the end of long-term follow-up → **only 30% of pts remained disease-free**
- No statistically significant difference in survival among patients that underwent surgical exploration (90% at 5-yrs)
- Patients excluded for metastatic disease had significantly decreased survival of <20% at 5-yrs ($p < 0.001$)



Does the Use of Routine Duodenotomy (DUODX) Affect Rate of Cure, Development of Liver Metastases, or Survival in Patients With Zollinger-Ellison Syndrome?

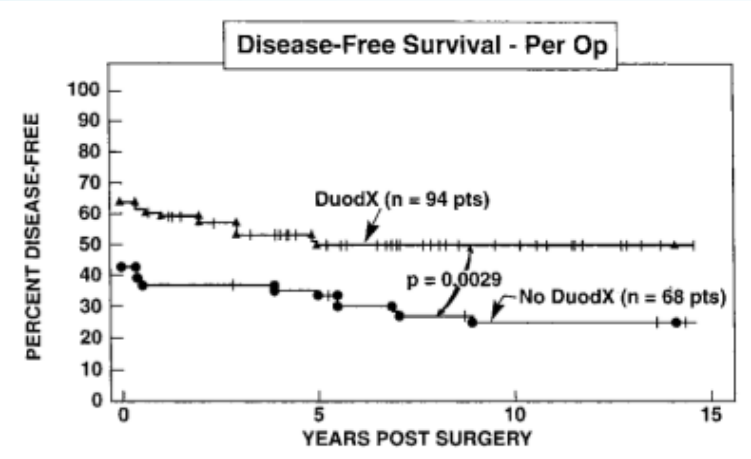
Jeffrey A. Norton, MD, H. Richard Alexander, MD,† Douglas L. Fraker, MD,‡ David J. Venzon, PhD,§ Fathia Gibril, MD,¶ and Robert T. Jensen, MD¶*

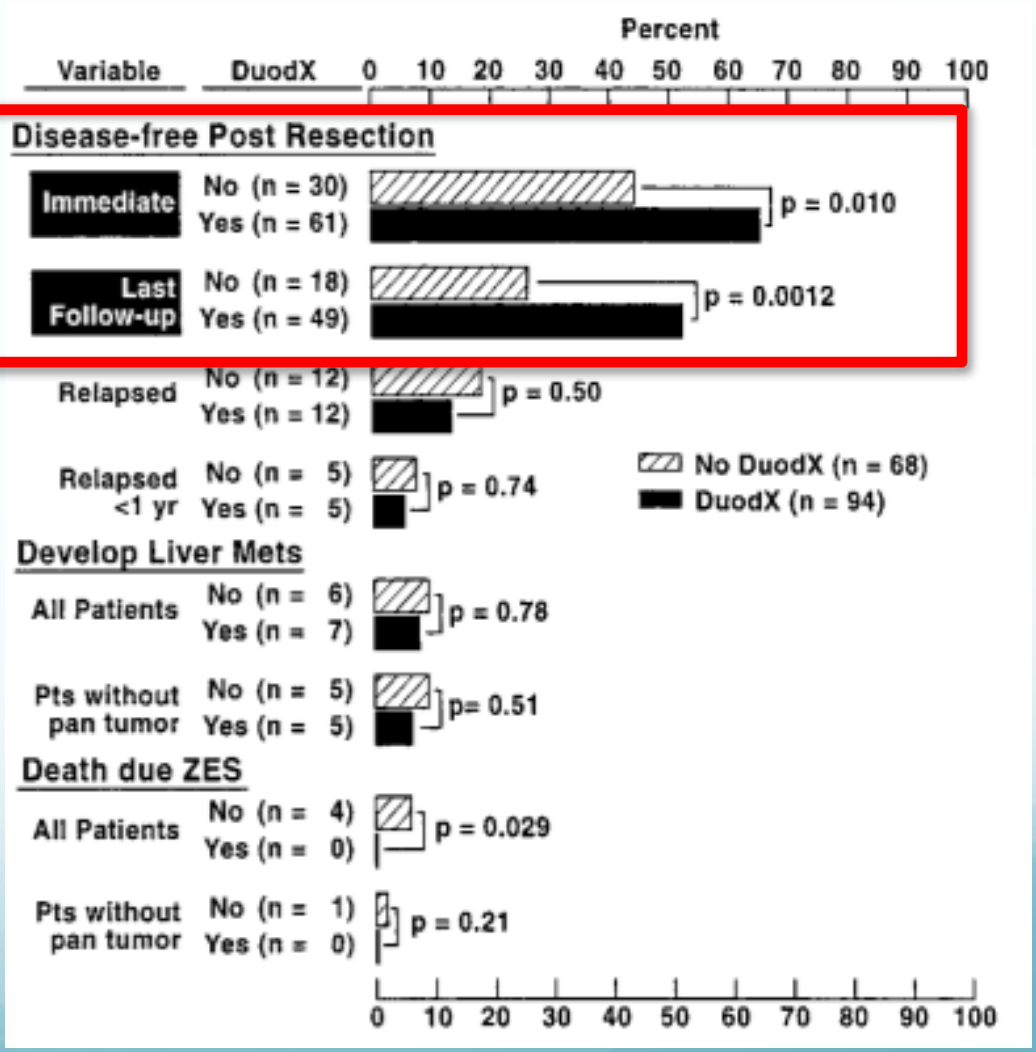
- N = 143 pts, prospective study
  - 89 pts underwent duodenotomy / 54 did not
- Duodenotomy consisted of 3cm longitudinal incision on anterolateral surface of 2nd portion of duodenum, palpation, ultrasound, and transillumination
- Duodenal gastrinomas more frequently found in patients receiving duodenotomy (98% vs. 76%, p=0.0001)



Does the Use of Routine Duodenotomy (DUODX) Affect Rate of Cure, Development of Liver Metastases, or Survival in Patients With Zollinger-Ellison Syndrome?

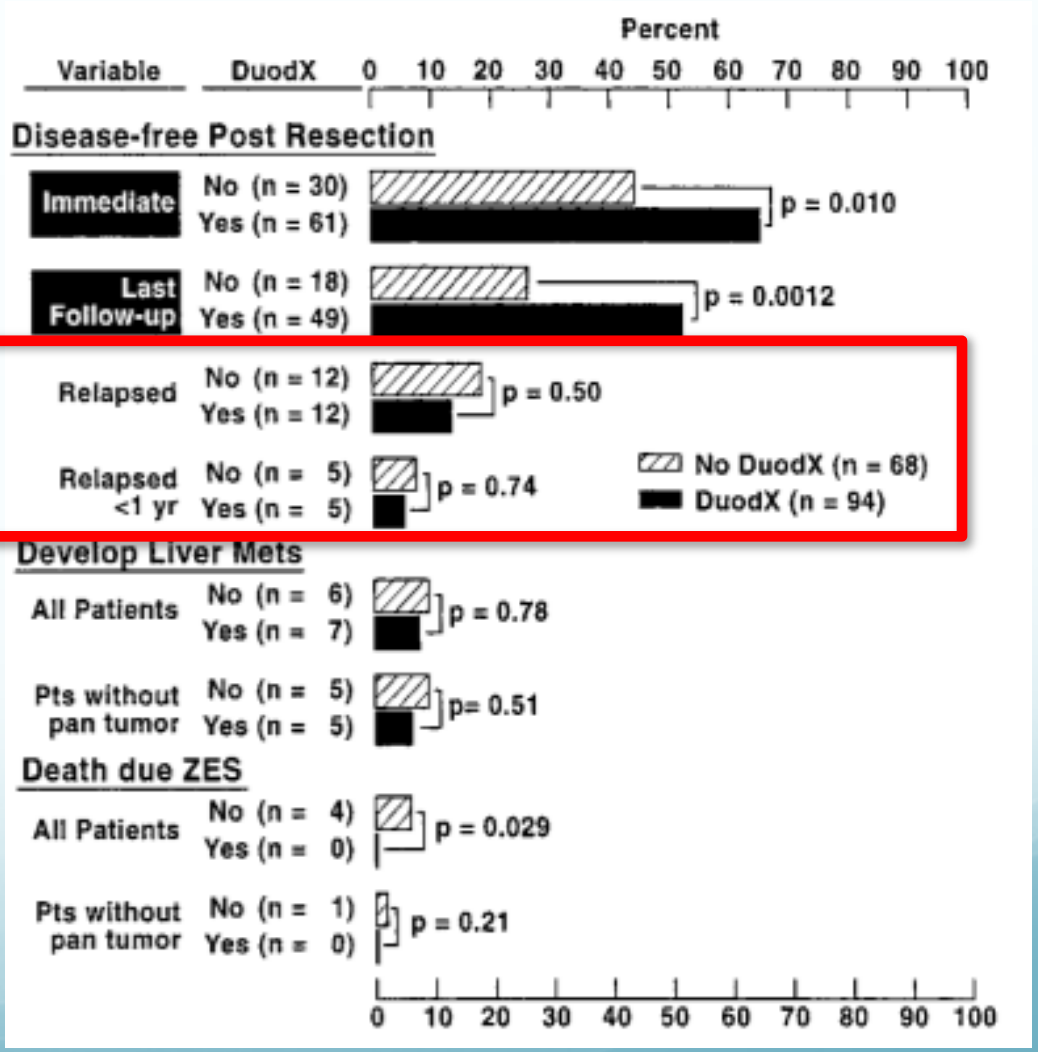
- Improved immediate disease-free rate and long-term cure rate in duodenotomy group
  - Disease-free: 65% vs. 44%, P<0.01
  - Cure-rate at 10 yrs: 50% vs. 25%, P<0.0029





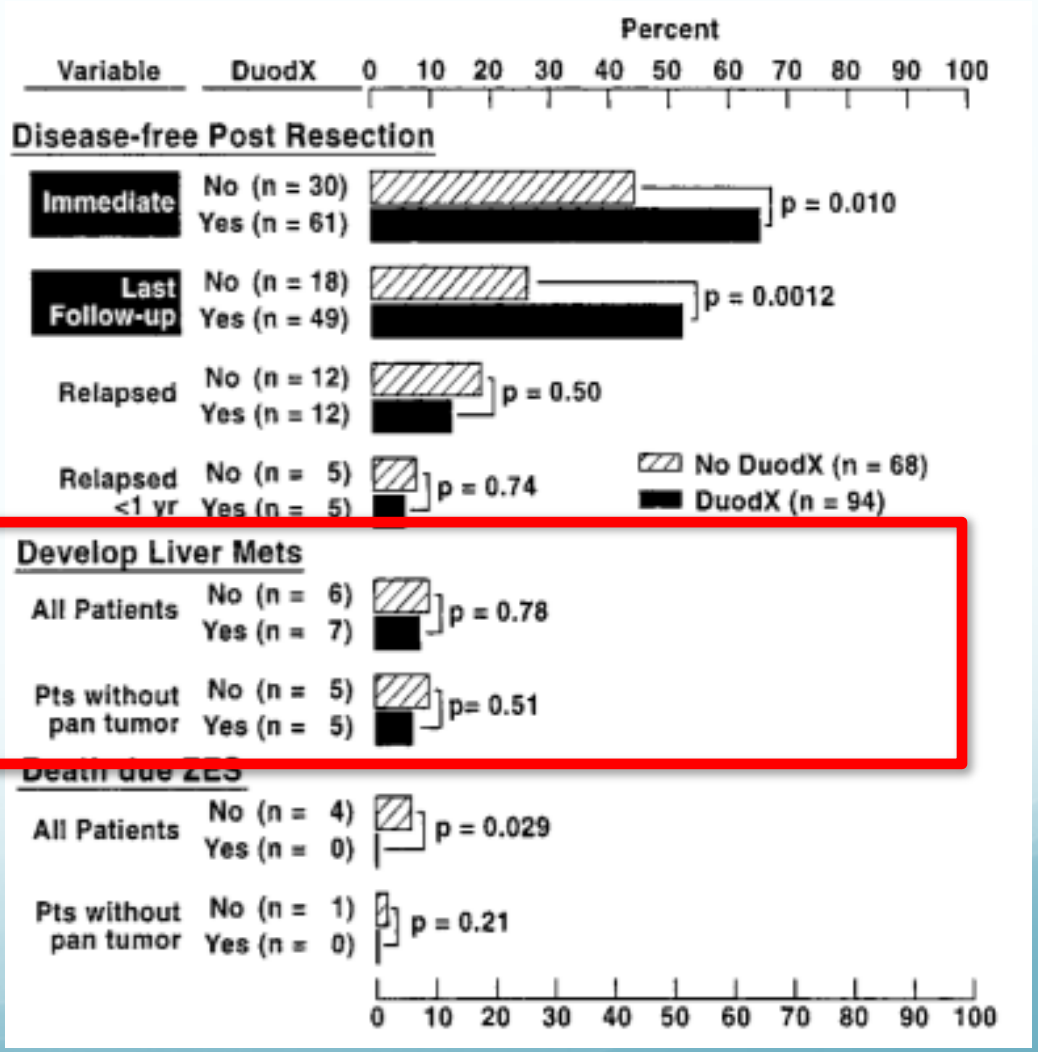
Does the Use of Routine Duodenotomy (DUODX) Affect Rate of Cure, Development of Liver Metastases, or Survival in Patients With Zollinger-Ellison Syndrome?

- **No difference in relapse rate with duodenotomy**



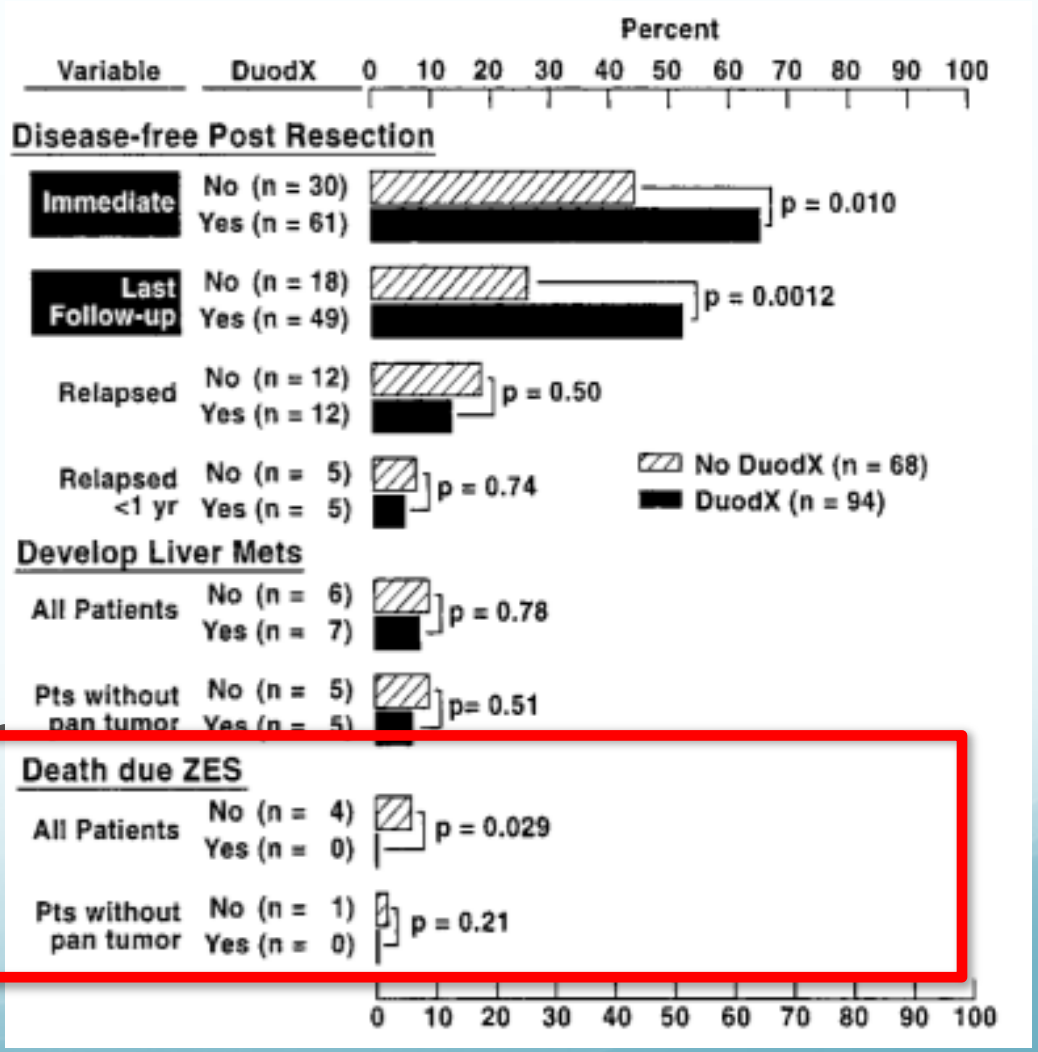
Does the Use of Routine Duodenotomy (DUODX) Affect Rate of Cure, Development of Liver Metastases, or Survival in Patients With Zollinger-Ellison Syndrome?

- No difference in relapse rate with duodenotomy
- No difference in occurrence of liver metastases with duodenotomy



Does the Use of Routine Duodenotomy (DUODX) Affect Rate of Cure, Development of Liver Metastases, or Survival in Patients With Zollinger-Ellison Syndrome?

- No difference in relapse rate with duodenotomy
- No difference in occurrence of liver metastases with duodenotomy
- No difference in disease-related death in duodenal-only disease



Comparison of Surgical Results in Patients With Advanced and Limited Disease With Multiple Endocrine Neoplasia Type 1 and Zollinger-Ellison Syndrome

Jeffrey A. Norton, MD,* H. Richard Alexander, MD,† Douglas L. Fraker, MD,‡ David J. Venzon, PhD,§ Fathia Gibril, MD, and ‖ Robert T. Jensen, MD‖

- N = 81, 4 groups based on extent of disease
  - Operations performed on pts w/ either single lesion 2.5-6cm in size, 2+ lesions >2.5cm, or 1 lesion >6cm
- 1/3 of patients had an immediate surgical complication

Table 5. TYPES OF OPERATIONS PERFORMED

Surgical Procedure	Group 2A (n = 17)	Group 2B (n = 31)	Total (n = 48)
Enucleation	2 (12%)†	12 (39%)	14 (29%)
Resection			
Duodenal tumor resection	9 (53%)	21 (68%)	30 (62%)
Removal of lymph node metastases	9 (53%)	21 (68%)	30 (62%)
Distal pancreatectomy	4 (24%)‡	18 (58%)	22 (46%)
Pancreaticoduodenotomy	0 (0%)	2 (6%)	2 (4%)
Liver resection	0 (0%)	4 (13%)	4 (8%)
Other abdominal operations*	2 (12%)	5 (16%)	7 (14%)

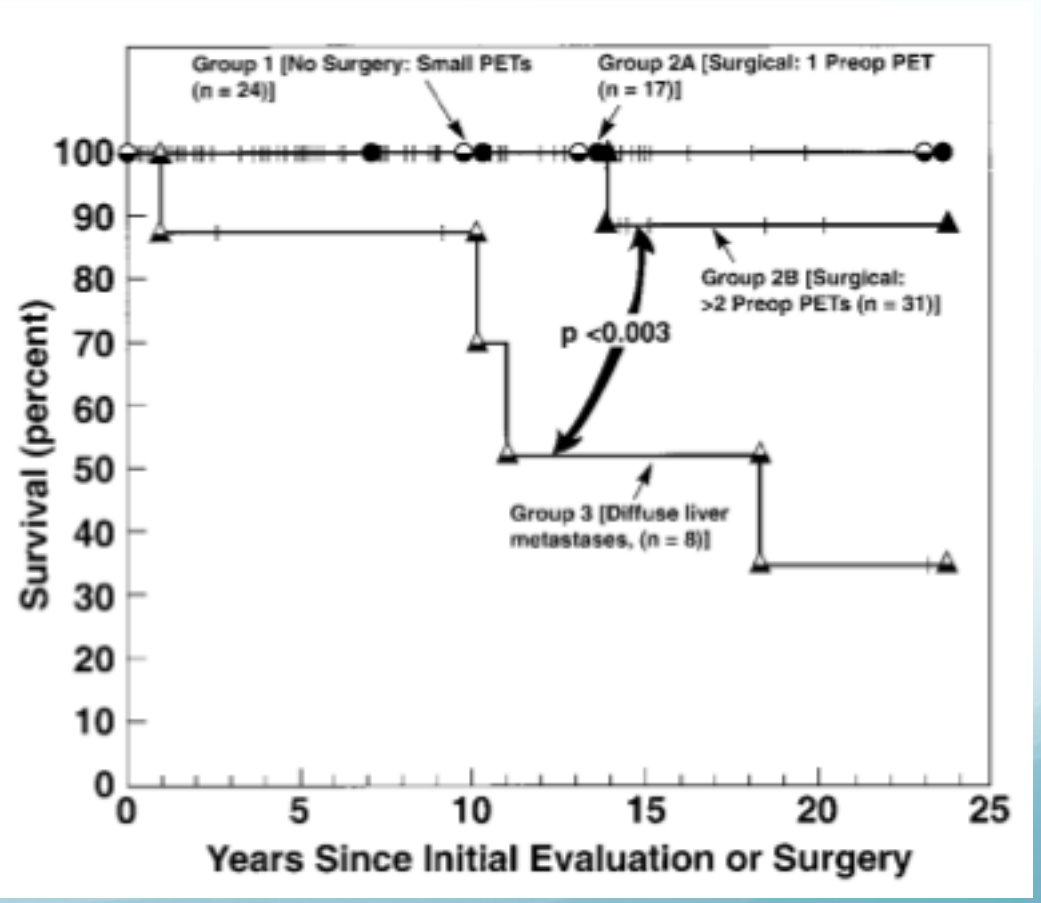
Table 6. LONG-TERM FOLLOW-UP AND SURGICAL OUTCOME

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%)

- **Although initially there is a disease-free state reported in some pts, this is not sustained at 5-yr follow-up**

Comparison of Surgical Results in Patients With Advanced and Limited Disease With Multiple Endocrine Neoplasia Type 1 and Zollinger-Ellison Syndrome

- No difference in survival among all groups except pt with liver metastases (Grou 3)
- Significantly higher disease related death rate in Group 3



Surgery Increases Survival in Patients With Gastrinoma

Jeffrey A. Norton, MD, Douglas L. Fraker, MD, H. R. Alexander, MD, Fathia Gibril, MD, David J. Liewehr, MS, David J. Venzon, PhD, and Robert T. Jensen, MD

- Prospective study comparing resected and unresected disease
- N=160 patients with “resectable disease”
  - 35 pts elected to not undergo resection
- Demonstrates lower rate of hepatic metastases and improved survival in surgical group over 20 years
- **First study** to demonstrate correlation between surgical cure and improved survival

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- Not a randomized trial
- Possible selection bias based on patients that chose not to undergo surgery
  - Listed reasons include inability to give informed consent, pt refusal based on PCP, co-morbidities, lesion <2.5cm in MEN-1 pts
- Surgical group included patients where no tumor was found → therapeutic negative ex-lap?
  - N = 10 patients (6%)

Resolved and Unresolved Controversies in the Surgical Management of Patients With Zollinger-Ellison Syndrome

Jeffrey A. Norton, MD, and Robert T. Jensen, MD†*

- Role of gastrectomy
  - Previously used for control of acid hypersecretion, now unnecessary with PPIs
  - Hypergastrinemia → increased risk of gastric carcinoid, but rare and most (90%) are not invasive
- Role of parietal cell vagotomy
  - Produces 75% decrease in basal acid output
  - Only 9% of patients were able to stop all antisecretory drugs post-operatively
  - PPIs currently preferred to PCV by current experts

Resolved and Unresolved Controversies in the Surgical Management of Patients With Zollinger-Ellison Syndrome

Jeffrey A. Norton, MD, and Robert T. Jensen, MD†*

- Role of Whipple pancreaticoduodenectomy
  - Currently not recommended by most experienced centers
  - Limits treatment of liver metastases, reoperation
- Surgical re-exploration for recurrent disease
  - Significantly lower disease-free rate found at follow-up (47% after initial vs. 23% after reoperation, $p = 0.022$)
- Role of surgery in advanced disease
  - Defined primarily by liver metastases, of which only 5-15% are resectable
  - Although currently recommended, there are no controlled studies to demonstrate survival benefit

Current Medical Therapies

Proton Pump Inhibitors

- Available since the 1980s; remains first line therapy for ZES (previously H2 receptor antagonists)
- Irreversibly inhibits the H+/K+ ATPase
- Treatment failure (sequelae of acid hypersecretion) observed in only 1.2% of patients
- Now available in generic form = improved affordability for chronic therapy

Consequences of Long-Term Proton Pump Blockade: Insights from Studies of Patients with Gastrinomas

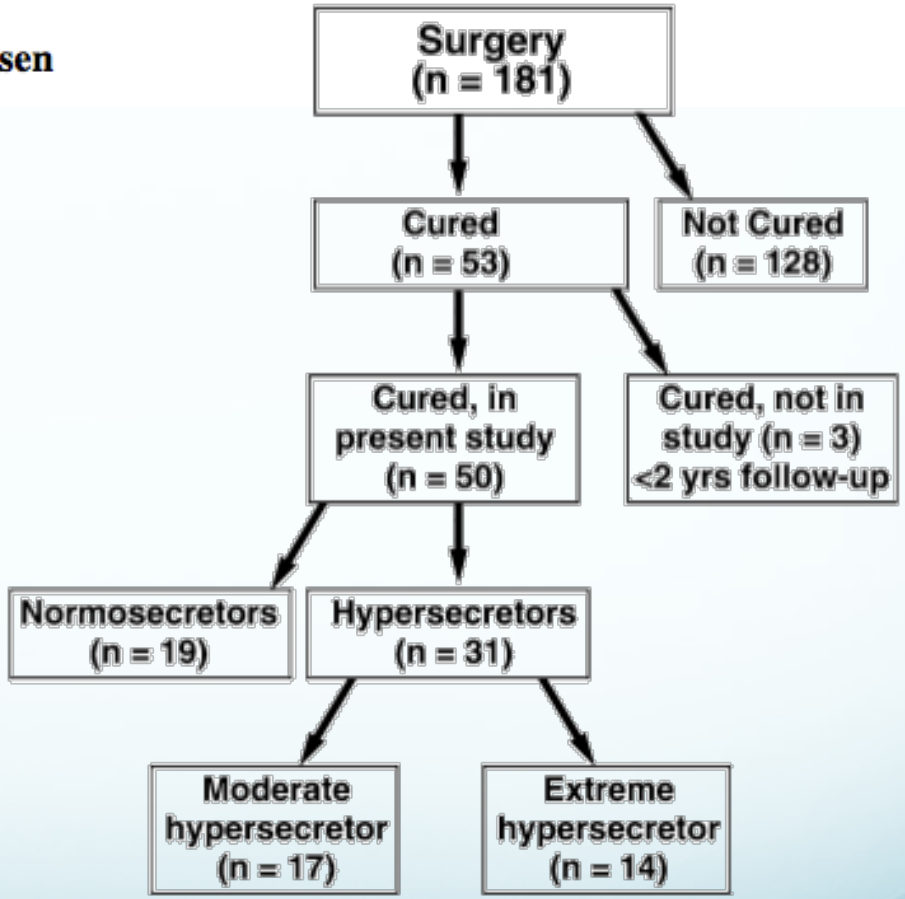
Robert T. Jensen

- Minimal side effects
  - Malabsorption
    - Due to hypo/achlorhydria – theoretic effect on Fe, B12, Ca
    - Only shown clinically to be significant in B12 absorption
    - Current recommendations w/ chronic therapy – check yearly level
  - Promotion of gastric carcinoids
    - Early concern due to mice models
    - Observed in <1% of human patients with sporadic ZES
    - Higher in association with ZES/MEN-1
- Tolerance?
  - Unlike H2RAs, tolerance over time not observed with chronic usage of PPIs
  - In fact, many ZES patients are able to decrease their dosage after initiation of therapy

Mechanism of Acid Hypersecretion Post Curative Gastrinoma Resection

Jeremiah V. Ojeaburu · Tetsuhide Ito · Pellegrino Crafa · Cesare Bordi · Robert T. Jensen

- Fifty patients s/p curative resection evaluated for persistent acid secretion
- 62% remained acid hypersecretors (n = 31)
- 82% required continued long-term use of an antisecretory drug (n = 41)
- Proposed mechanism is trophic effect of gastrin on parietal cells and ECL cells, which is not reversible



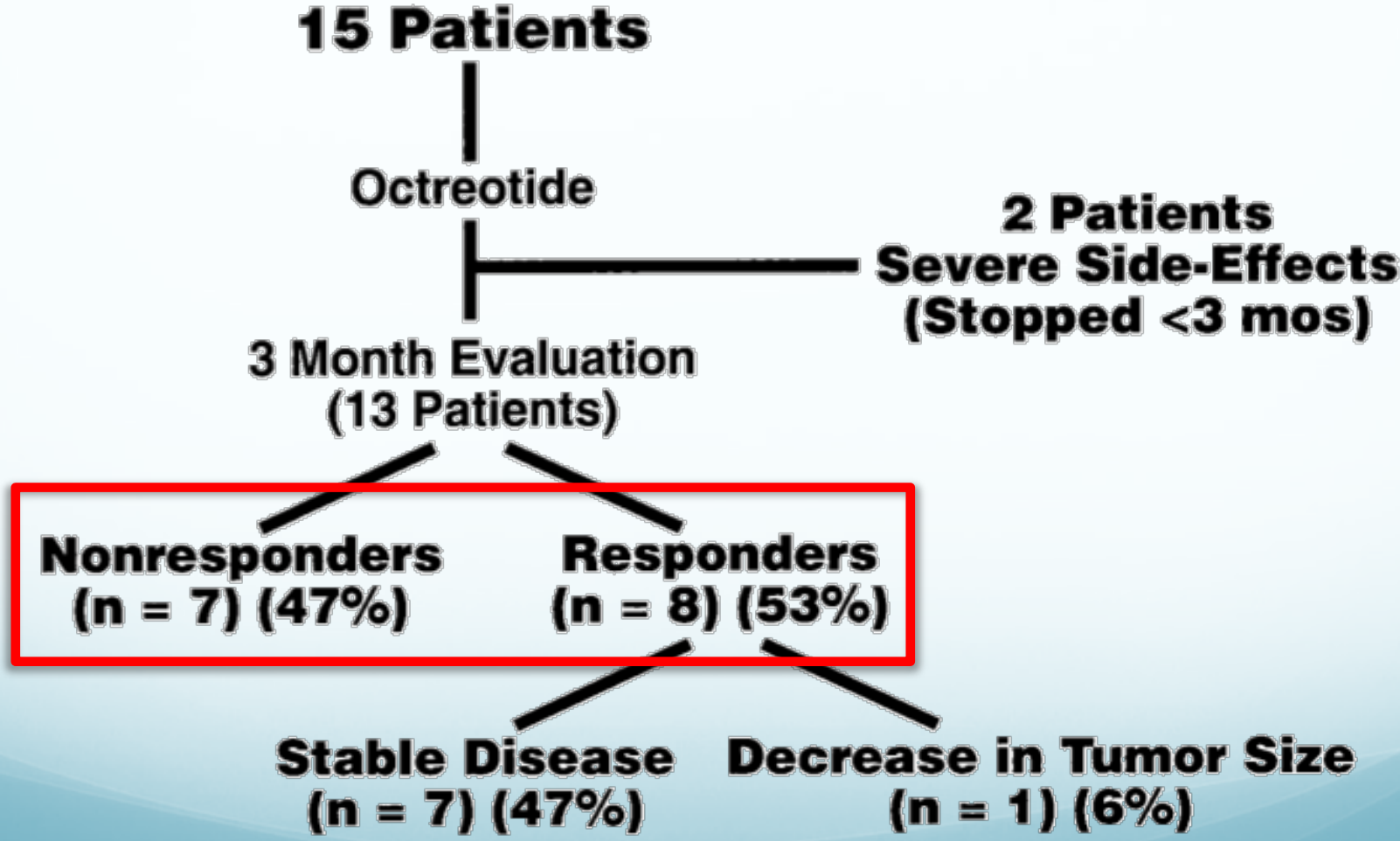
Somatostatin Analogues

- Antiproliferative and pro-apoptotic effect on neuroendocrine cells
- Found to suppress and/or normalize gastric acid secretion in 50-100% of gastrinoma pts
- Currently most commonly indicated in metastatic disease
  - Stabilizes progression of disease in 30-70% of patients
  - Symptomatic improvement and reduction in gastrin levels seen in 60-80% of patients

Prospective Study of the Antitumor Efficacy of Long-Term Octreotide Treatment in Patients with Progressive Metastatic Gastrinoma

- N = 15 pts with malignant gastrinoma, hepatic metastases
- 73% of patients had undergone prior gastrinoma resection
- Major side effects: nausea, vomiting, abdominal pain, diarrhea, gallstones
  - Only 2 pts had side effects significant enough to halt therapy

Prospective Study of the Antitumor Efficacy of Long-Term Octreotide Treatment in Patients with Progressive Metastatic Gastrinoma



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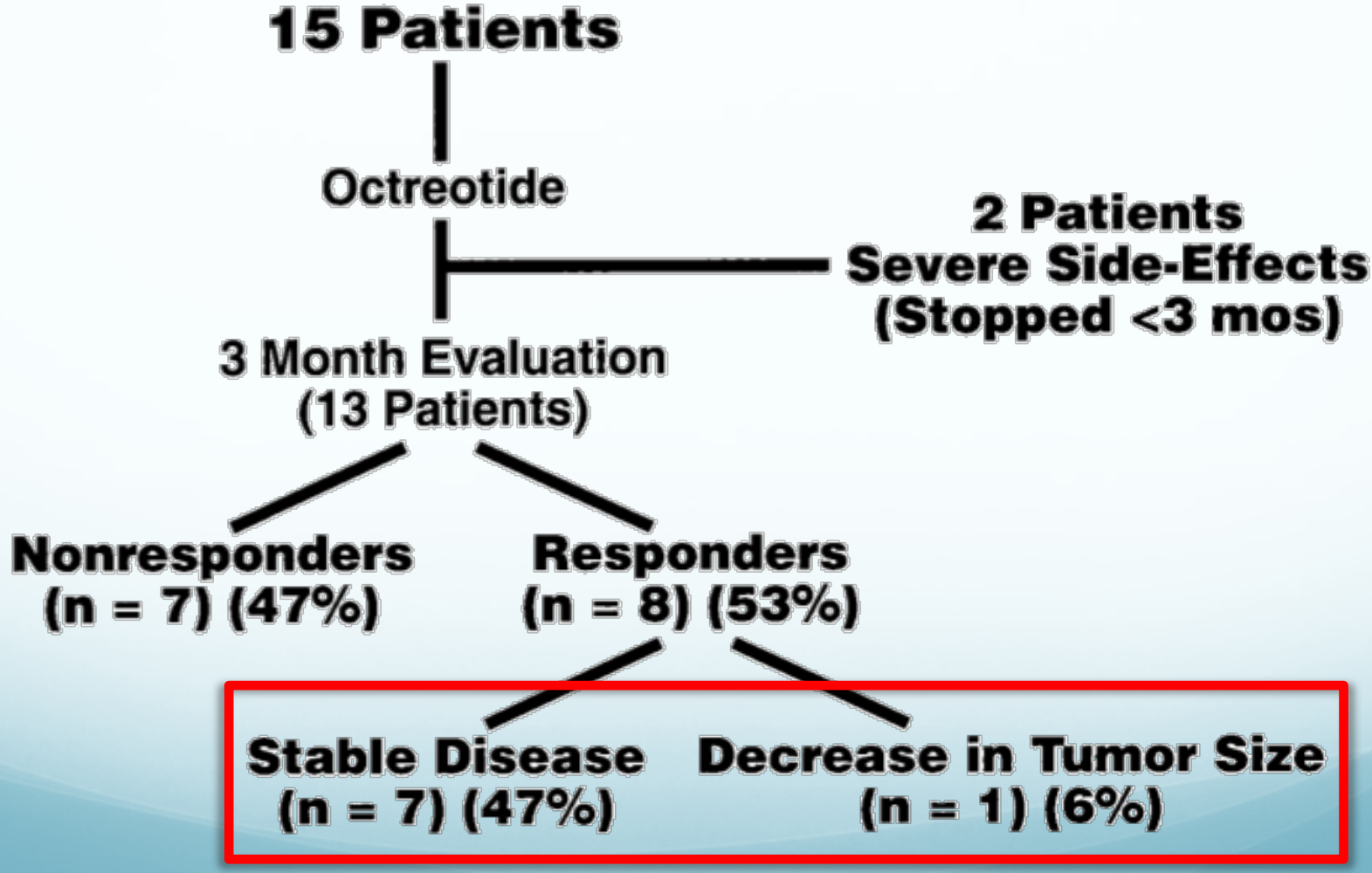

Conclusions

- Zollinger-Ellison syndrome caused by gastrinoma has a **generally benign course** with adequate control of gastric acid hypersecretion

Conclusions

- Standard surgical therapy for resection of sporadic ZES may provide **occasional cures**, but this **has not consistently translated into improved prognosis** – even with modern improvements

Conclusions

- For ZES and MEN-1, surgery is currently **not widely recommended** due to extensive disease at presentation.
- Regardless, there is **no demonstrated cure rate** nor **impact on survival** and the more invasive surgery needed may **limit future reoperation.**

Conclusions

- Current first-line medical management is **well-tolerated** in patients with minimal side effects and **excellent control of symptomatic disease**.
- Even in inoperable metastatic disease, medical therapies have shown benefit and remain a promising area of future study.

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