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

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- 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)
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
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- No difference in relapse rate with duodenotomy
- No difference in occurrence of liver metastases with duodenotomy
- No difference in disease-related deaths in duodenal-only disease
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
Although initially there is a disease-free state reported in some pts, this is not sustained at 5-yr follow-up.
No difference in survival among all groups except patients with liver metastases (Group 3)

Significantly higher disease-related death rate in Group 3
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
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%)
Role of gastrectomy

- Previously used for control of acid hypersecretion, now unnecessary with PPIs
- Hypergastrinemia $\Rightarrow$ 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
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
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

15 Patients

Octreotide

3 Month Evaluation (13 Patients)

2 Patients Severe Side-Effects (Stopped <3 mos)

Nonresponders (n = 7) (47%)

Responders (n = 8) (53%)

Stable Disease (n = 7) (47%)

Decrease in Tumor Size (n = 1) (6%)
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  (n = 1) (6%)
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.
References