Also known as...

When to put your knife down
Gastrinoma

- Definition and History
- Diagnosis
- Historic Management
- Sporadic vs MEN-1
- Defining surgical candidates
- Nonsurgical therapies
Zollinger-Ellison Syndrome

First described in 1955 in *Ulcerations of the jejunum associated with islet cell tumors of the pancreas*

Patients present with abdominal pain, diarrhea, or symptoms of peptic ulcers (nausea, vomiting, bleeding, perforation)

Robert Milton Zollinger 1903-1992
Diagnosis

Fasting gastrin levels
- <100 pg/ml = normal
- >1000 pg/ml = ZES

Secretin provocative test
- Measure fasting gastrin level
- Give IV secretin
- Measure gastrin at 2, 5, 10, and 20 minutes
- Increase in gastrin of more than 200 pg/ml is found in 87% of ZES patients
- No false-positives
- False-negative possible due to *H. pylori*

Evaluate for MEN 1
Tumor Localization

- 70-90% located in gastrinoma triangle
  - Superiorly – Confluence of the cystic duct and common bile duct
  - Inferiorly – Junction of the second and third portions of the duodenum
  - Medially – Junction of the neck and body of the pancreas
- CT
- Somatostatin receptor scintigraphy
  - Does NOT increase surgical cure rate
Historical Management

When first described, morbidity/mortality of ZES was due to effects of acid hypersecretion

Total gastrectomy

Better understanding of acid secretion and advent of PPIs has changed the disease course.

Mortality now related to metastatic disease.
## Sporadic vs MEN 1

<table>
<thead>
<tr>
<th></th>
<th>Sporadic ZES</th>
<th>MEN1 ZES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>65-75%</td>
<td>25-35%</td>
</tr>
<tr>
<td><strong>Genetic Locus</strong></td>
<td>Unknown</td>
<td>11q13</td>
</tr>
<tr>
<td><strong>Tumor Location</strong></td>
<td>Pancreas &gt; Duodenum</td>
<td>Duodenum ≥ Pancreas</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>Solitary</td>
<td>Multifocal</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Large (&gt;2 cm)</td>
<td>Small (&lt;2 cm)</td>
</tr>
<tr>
<td><strong>Metastatic potential</strong></td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td><strong>20-Year Survival</strong></td>
<td>&lt;70%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td><strong>Surgical Cure</strong></td>
<td>Possible</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
Management of MEN1 ZES

Originally, resection was recommended only for sporadic gastrinomas.

Controversy of surgical intervention for MEN 1 patients
1. No group has followed sufficient numbers of these patients for a long enough time in a controlled study.
2. Lower metastatic potential.
3. These patients, even with metastatic disease, have a 15-year survival of 52%.
4. Even in patients dying of metastatic neuroendocrine tumors, it is unknown whether it is due to metastatic gastrinoma, another PET, development of a thymic carcinoid, or a gastric carcinoid.
Management of MEN1 ZES

Overall 10-year survival rate 94%
34% of patients with sporadic gastrinomas were free of disease at 10 years
None of the ZES/MEN1 patients were free of disease
Management of MEN1 ZES

MEN1 tumors now more easily identified by routine use of somatostatin receptor scintigraphy and duodenotomy

While both techniques have been shown to identify more tumors, NEITHER technique has been shown to increase rate of surgical cure

In a study by Norton et al, while duodenotomy increased short-term and long-term disease-free rates, it did not effect the rate of liver metastases.
Changing views on surgical intervention

Most important prognostic factor = presence of liver metastases

Primary tumor size is highly predictive of liver metastases

Presence of lymph node metastases does not affect survival
## Elements for Staging Gastrinoma

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No primary tumor at operation or imaging</td>
</tr>
<tr>
<td>T1</td>
<td>Primary tumor $\leq 1$ cm</td>
</tr>
<tr>
<td>T2</td>
<td>Primary tumor 1.1-2 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Primary tumor 2.1-2.9 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Primary tumor $\geq 3$ cm</td>
</tr>
<tr>
<td>Nx</td>
<td>Lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Lymph node metastases</td>
</tr>
<tr>
<td>Mx</td>
<td>Distant metastases cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
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</table>
# Staging Gastrinomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Lymph Node</th>
<th>Distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>T0</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
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<tr>
<td>II</td>
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<td>M0</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>III</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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</table>

Resection of gastrinoma

**RO** = Complete removal of tumor with negative margins and normal postoperative fasting gastrin

**R1** = Resection with microscopic margins or elevated postoperative fasting gastrin

**R2** = Resection with gross residual disease
Resection of gastrinoma

Survival was similar for R2 resection and no resection
Stage I – 18% R2
Stage II – 41% R2
Stage III – 81% R2
Selecting candidates for resection

Stage 0
  Observation

Stage I/II
  Surgical resection

Stage III
  Should NOT undergo routine surgical exploration
Nonsurgical therapy

Chemotherapy
Interferon
Hormonal therapy – somatostatin analogs
Chemoembolization
Chemotherapy

No proven benefit in most GI endocrine tumors
Beneficial in selected patients with aggressive poorly differentiated tumors
   Streptozotocin + 5-FU or Doxorubicin
       Up to 67% response in undifferentiated islet cell tumors
   Etoposide and cisplatin
       Up to 41% response rate in fast-growing neuroendocrine carcinomas
Rarely used, only in select patients
   Short duration of response
       Poor prognosis
   Significant side effects
   Better options
Somatostatin analogs

Tumors express somatostatin type-2 receptors (SST2)

Somatostatin analogs used to inhibit growth

Viable therapy for metastatic gastrinoma
Somatostatin analogs

15 patients with liver metastases
7 Nonresponders
8 Responders
  7 Stable disease
  1 Decrease in tumor size

Duration of response
  $\geq 1$ year = 33.3%
  $\geq 2$ years = 26.7%
  $>4$ years = 6.7%
Somatostatin analogs

Five-year survival for gastrinoma patients with liver metastases is 20-40% (compared to 100% without metastases)

Five-year survival is 100% in patients with liver metastases that either did not increase in size or increased only slowly (Sutliff et al)
Somatostatin + Interferon

Better response than either monotherapy
European studies with combination of octreotide and alpha interferon showed objective tumor response

14 patients (Creutfeld et al)
- One had tumor regression
- Five had stable disease for up to 34 months

22 patients, CT scans at 3-month intervals (Nold et al)
- 12 had stable disease
- 1 had $\geq 25\%$ reduction
Embolization

Selectively embolize hepatic arterial blood supply to tumors
Goal: Alleviate symptoms and delay need for systemic chemotherapy
Embolization – inject vaso-occlusive material (gelfoam)
Chemoembolization – concurrent administration of hepatic intra-arterial cytotoxic chemotherapies
No proven survival benefit
Need randomized controlled studies
Further direction of research

Markers to predict aggressiveness of tumors and their response to therapy.
Goal: To design therapy to specific tumor.
Conclusions

Surgical therapy not indicated for all gastrinomas MEN1 patients gain minimal benefit with surgical intervention.

Patients with metastatic disease benefit from palliative medical therapy.

Repeat resection for recurrent disease is not indicated as there has been no proven survival benefit. These patients may benefit from medical therapy.
References


Current Surgical Therapy. Cameron JL, 8th ed.


Herder WW et al.: Considerations concerning a tailored, individualized therapeutic management of patients with (neuro)endocrine tumours of the gastrointestinal tract and pancreas. Endocrine-Related Cancer, 2004.


