Gastric Cancer in a Young Postpartum Female

Kings County Hospital Center
SUNY Downstate
Case Conference
May 24, 2012
Case

- HPI:
  - 31 yo F, G5P3, 3 weeks s/p C-section, with gastric outlet obstruction.
  - Pt c/o refractory N/V of several months duration during pregnancy, which persisted after delivery.
  - Pt came to surgical attention after coffee ground emesis and melena.

- PMH: Hep B, asthma
- PSH: neg
- Meds: none
Case

• BMP:
  – 145/4/108/29/5/0.7<91

• CBC:
  – 3.6>13.3/41.9<171
Case

- Endoscopy demonstrated a large fungating, infiltrating mass involving the greater and lesser curvature of both the anterior and posterior body of the antrum and the body.
- Pathology was c/w an invasive adenocarcinoma – signet cell type.
Case

• Underwent uneventful subtotal gastrectomy with Roux en Y reconstruction.
• Tolerated regular diet on POD 5.
• Discharged to home on POD 7.
• Started chemoRT 5FU/LV.
• Functionally, doing well.
Surgical Pathology

- Adenocarcinoma, signet-ring cell type
- Grade G3 poorly differentiated
- Negative proximal margin
- Serosal invasion; positive distal margin
- Lymphovascular invasion
- 7/9 nodes positive for metastasis
- T4N3Mx
Questions

• Was Pt appropriately staged?
• Was lymphadenectomy adequate?
• What are the benefits of neoadjuvant and adjuvant therapies?
Epidemiology

• World-wide – 4th most common cancer
  – 990,000 new cases, 740,000 deaths per year

• US
  – 21,000 new cases, 10,500 deaths per year

• Survival poor in US due to late presentation
  – Overall 5-year survival – 27%
  – 2/3 present with Stage III or IV disease
  – 10% present with Stage I disease
Risk Factors

- **Nutritional**
  - High nitrate consumption
  - Salted meat or fish
  - Low fat or protein consumption
  - High complex carbohydrate diet

- **Social**
  - Low socioeconomic class

- **Environmental**
  - Smoking
  - Poor food preparation
  - Lack of refrigeration
  - Poor drinking water

- **Medical**
  - H. pylori infection
  - Gastric atrophy and gastritis
  - Adenomatous polyps
Pathology

- 90% adenocarcinoma
- Lymphatic metastasis common
- Increasing frequency of proximal lesions
# Lauren Classification

<table>
<thead>
<tr>
<th>Intestinal</th>
<th>Diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental</td>
<td>Familial</td>
</tr>
<tr>
<td>Gastric atrophy, intestinal metaplasia</td>
<td>Blood type A</td>
</tr>
<tr>
<td>Men &gt; women</td>
<td>Women &gt; men</td>
</tr>
<tr>
<td>Increasing incidence with age</td>
<td>Younger age group</td>
</tr>
<tr>
<td>Gland formation</td>
<td>Poorly differentiated, signet ring cells</td>
</tr>
<tr>
<td>Hematogenous spread</td>
<td>Transmural, lymphatic spread</td>
</tr>
<tr>
<td>Microsatellite instability</td>
<td>Decreased E-cadherin</td>
</tr>
<tr>
<td>APC gene mutations</td>
<td>P53, p16 inactivation</td>
</tr>
<tr>
<td>P53, p16 inactivation</td>
<td>P53, p16 inactivation</td>
</tr>
</tbody>
</table>
### Presenting Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>62</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>52</td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>26</td>
</tr>
<tr>
<td>Melena</td>
<td>20</td>
</tr>
<tr>
<td>Early satiety</td>
<td>18</td>
</tr>
<tr>
<td>Ulcer-type pain</td>
<td>17</td>
</tr>
</tbody>
</table>

STAGE
(CT, endoscopy with EUS)

- Consider palliative resection
- Refer to medical oncology
- No metastatic disease
Workup

- H&P
- Upper GI endoscopy and biopsy
- Chest and abdominal CT with PO & IV contrast
- Pelvic CT as indicated
- PET evaluation if no evidence of M1 disease
- Endoscopic US if no evidence of M1 disease
- Biopsy confirmation of metastatic disease
- HER2-neu testing if metastatic suspected
Endoscopy

- Single biopsy – 70% sensitivity
- Seven biopsies – 98% sensitivity
- 5% of malignant ulcers appear benign
- Linitis plastica difficult to detect

Graham DY. Gastroenterology 1982; 82:228.
Endoscopic U/S

- Sensitivity 77-93% for assessing T stage
- Sensitivity 65-90% for assessing N stage

Barium Study

- False negative rate as high as 50%
- Sensitivity as low as 14% in early cancer
- May help in the case of linitis plastica – “leather flask” appearance
CT Scan

- Best suited for evaluation of metastatic disease
  - Accuracy of T staging – 50-70%
  - Metastatic lesions <0.5cm frequently missed
  - 20-30% of patients with neg CT will have metastatic disease at laparoscopy or laparotomy

- Sensitivity and specificity of nodal evaluation
  - 65-97% and 77-93%

PET Scan

- More sensitive than CT for detection of distant metastasis
- Confirm malignant involvement of locoregional disease
- Sensitivity of detecting peritoneal carcinomatosis – 50%
- Most diffuse type gastric CA not FDG avid
Laparoscopy

- Allows direct visualization of liver, peritoneum, LN
- Allows cytologic evaluation
- When to perform?
  - NCCN – “Consider” for Pts with locoregional disease; i.e., lesion > T1 and not stage IV
  - When neoadjuvant therapy considered
Laparoscopic Cytologic Evaluation

• Positive cytology considered metastatic disease
• 33% of CT/PET neg Pts will be deemed to be unresectable
• R0 resection c neg laparoscopy and
  – neg cytology 98.5 month mean survival
  – pos cytology 14.8 month mean survival

Staging Intent

• Stratify Pts to 2 groups – resectable (Locoregional - Stage I-III) vs unresectable (Systemic - Stage IV)
  – presence of distant metastases and invasion of a major vascular structure, such as the aorta, or disease encasement or occlusion of the hepatic artery or celiac axis/proximal splenic artery

• Prognosis
<table>
<thead>
<tr>
<th>Primary Tumor</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 evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ; intraepithelial tumor without invasion of lamina propria</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria, muscularis mucosa, or submucosa</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor invades lamina propria or muscularis mucosa</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades serosa (visceral peritoneum) or adjacent structures</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades serosa (visceral peritoneum)</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades adjacent structures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph node(s) cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in 1-2 regional lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in 3-6 regional lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in 7 or more regional lymph nodes</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in 7-15 regional lymph nodes</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in 16 or more regional lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastasis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Anatomic Stage</th>
<th>Prognostic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
</tr>
<tr>
<td>IB</td>
<td>T2 T1</td>
</tr>
<tr>
<td>IIA</td>
<td>T3 T2 T1</td>
</tr>
<tr>
<td>IIB</td>
<td>T4a T3 T2 T1</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4a T3 T2</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4b T4b T4a T3</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4b T4b T4a</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
</tr>
</tbody>
</table>

TNM Staging Changes

• Tumors arising at the GE junction or in the cardia within 5 cm of the GE junction that extend into esophagus are staged using esophageal system

• T categories modified to correspond to T categories for esophageal and bowel CA

• N categories modified

• Positive cytology classified as M1 disease
Treatment

• Complete resection of tumor with wide margin of normal stomach is standard of care
  – Standard technique is via laparotomy
  – Laparoscopic and endoscopic techniques may be employed in early cancers
• Cancer of proximal stomach – total gastrectomy
• Cancer of distal stomach:
  – Subtotal gastrectomy
  – Proximal margin 4-6 cm
• Distal margin is prox duodenum
Questions

• Was Pt appropriately staged?
• Was lymphadenectomy adequate?
• What is the benefit of neoadjuvant therapy?
Lymphadenectomy

- D1 - limited dissection of only the perigastric lymph nodes (stations 1-6)
- D2 - removal of nodes along the hepatic, left gastric, celiac and splenic arteries as well as those in the splenic hilum (stations 1-11)
- D3 - D2 lymphadenectomy plus the removal of nodes within the porta hepatis and periaortic regions (stations 12-16)
Extended Lymphadenectomy

- LN behind or inferior to pancreas
- Aortocaval LN
- Mediastinal extension
- Portahepatis

- LN in these locations are evidence of non-resectability
Linitis Plastica

• Broad region of gastric wall or entire stomach infiltrated with cancer
• In one report, > 50% of Pts with linitis plastica had evidence of metastatic disease
• Survival rates poor
  – 50% 1 year; 8 % 7 year
• Some consider linitis plastica to be a contraindication to surgery

Pro’s / Con’s of Extended Lymphadenectomy

• **Advantages:**
  – Don’t leave residual disease behind
  – Accurate staging

• **Disadvantages:**
  – Increased morbidity and mortality
  – No survival benefit
Japanese Experience
Extended Lymphadenectomy
Medical Research Council Trial

• 400 Pts with resectable disease randomized to D1 or D2 lymphadenectomy

<table>
<thead>
<tr>
<th>Extent</th>
<th>D2</th>
<th>D1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postop Morbidity</td>
<td>46%</td>
<td>28%</td>
</tr>
<tr>
<td>Operative Mortality</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>5-year Survival</td>
<td>33%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Extended Lymphadenectomy
Dutch Gastric Group Trial

• 711 Pts treated with curative intent randomized to D1 or D2 lymphadenectomy

<table>
<thead>
<tr>
<th></th>
<th>D2</th>
<th>D1</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postop Morbidity</td>
<td>43%</td>
<td>25%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Operative Mortality</td>
<td>10%</td>
<td>4%</td>
<td>0.004</td>
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</tbody>
</table>

Dutch Gastric Group Trial
Long Term Follow-up

- All cause mortality not statistically different
- Gastric cancer deaths significantly higher in D1 group

<table>
<thead>
<tr>
<th></th>
<th>D2</th>
<th>D1</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-year Survival</td>
<td>28%</td>
<td>22%</td>
</tr>
<tr>
<td>Gastric CA-related</td>
<td>37%</td>
<td>48%</td>
</tr>
<tr>
<td>deaths</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Suggest that D2 resection should be done when low operative mortality

Impact of Lymph Node Dissection on 5-Year Survival

<table>
<thead>
<tr>
<th># of nodes</th>
<th>T1/2 N0</th>
<th>T1/2 N1</th>
<th>T3 N0</th>
<th>T3 N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-9</td>
<td>61 (57-66) n=560</td>
<td>33 (25-40) n=184</td>
<td>33 (29-37) n=528</td>
<td>14 (12-17) n=871</td>
</tr>
<tr>
<td>10-19</td>
<td>67 (61-74) n=269</td>
<td>51 (41-61) n=124</td>
<td>50 (43-57) n=261</td>
<td>25 (20-29) n=499</td>
</tr>
<tr>
<td>20-29</td>
<td>71 (60-83) n=49</td>
<td>65 (50-80) n=31</td>
<td>56 (43-68) n=47</td>
<td>33 (24-42) n=88</td>
</tr>
<tr>
<td>30-39</td>
<td>87 (74-100) n=61</td>
<td>25 (0-67) n=4</td>
<td>58 (37-79) n=58</td>
<td>42 (26-57) n=92</td>
</tr>
<tr>
<td>40+</td>
<td>93 (79-100) n=14</td>
<td>70 (41-99) n=11</td>
<td>83 (62-100) n=14</td>
<td>50 (30-70) n=28</td>
</tr>
</tbody>
</table>
Lymphadenectomy and Surgical Practice

• In practice, only 50% of patients end up with an R0 resection

• Intergroup 0116 experience
  • D2 – 10%
  • D1 – 36%
  • D0 – 54%

Neoadjuvant Therapy

- Increase resectability rate
- Reduce rate of local and distant recurrence
- Improve survival
Trials

• MAGIC Trial
  – 503 Pts with resectable disease randomized to periop chemoTx vs surgery alone
  – HR 0.75; 5 year improvement 36 vs 23%

• French FNLCC/FFCD Trial
  – 224 Pts with resectable disease

• EORTC Trial
  – No demonstrable benefit
  – Stopped early due to poor accrual
Adjuvant Therapy

- 80% of patients who die from gastric cancer experience local recurrence
Intergroup 0116

- 556 Pts s/p surgery for gastric adenoCA randomized to surgery alone vs surgery + postop chemoRT
- Fluorouracil and leucovorin + XRT
- Median survival 36 mo vs 27 mo
- HR for death 1.35

I0116 Long-term Survival

Take Aways

• Laparoscopy (with peritoneal cytology) should be performed in Pts with > T1 disease without overt metastasis.

• When performed at high-volume centers, D2 lymphadenectomy may increase disease free survival.

• Neoadjuvant Tx and adjuvant ChemoRT likely benefit Pts with non-metastatic gastric CA.