Approaches to Surgical Treatment of Gastric Cancer

Byrne Lee, MD FACS
Chief, Mixed Tumor Surgery Service
Disclosures

• I do not have anything to disclose
Outline

• Background
• Diagnosis
• Histology
• Staging
• Surgery
Background

- **Worldwide**
  - 4\textsuperscript{th} most common cancer in men, 5\textsuperscript{th} most in women
  - 3\textsuperscript{rd} most common cause of cancer deaths in men, 5\textsuperscript{th} in women
- **United States**
  - Doesn’t breach the top 10
  - 24,590 new cases in 2015
  - 10,720 deaths
- **Incidence generally 2x in men**
North America: 5.8

Eastern Asia: 42.4
Risk Factors

• H. pylori
  – Approximately 36 and 47 percent of all gastric cancers in developed and developing countries are solely attributable to *H. pylori* infection. This accounts for almost 350,000 gastric cancers annually worldwide.

• Salt and salt cured foods
• Cured meat
• Nitroso compounds (nitrates, nitrites)
• EBV (5-10%)
• Smoking (1.53x)
• Socioeconomic Class (distal in low, proximal in high)
• Blood Group A (20% excess of gastric cancer)
• History of gastric ulcers (25% have a history)
Diagnosis

• **Early Stage Gastric Cancer**
  • Asymptomatic (80%) / Nonspecific (15%)
  • Anemia, weight loss and dysphagia (<5%)

• **Advanced Stage Gastric Cancer**
  • Weight loss (60%)
  • Pain in the abdomen (50%)
  • Anorexia (30%), Nausea/Vomiting (30%)
  • Dysphagia (25%)/ Persistent reflux sx (20%)
  • Melena /Anemia (20%), Early satiety (20%), Abdominal fullness (5%)

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 3 month</td>
<td>40%</td>
</tr>
<tr>
<td>3-12 months</td>
<td>40%</td>
</tr>
<tr>
<td>Longer than 12 month</td>
<td>20%</td>
</tr>
</tbody>
</table>
Diagnosis - Endoscopy
Histology
Histology

- WHO Classification
  - Carcinoma
  - Intestinal
  - Tubular
  - Papillary
  - Mucinous
  - Diffuse
  - Signet Ring
  - Adenosquamous
  - Small cell
  - Undifferentiated
Table 1
American Joint Committee on
TNM Staging Classification for
(7th ed., 2010)

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>Code</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 lamina propria</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor invades lamina propria</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor penetrates subserosa; invasion of visceral peritoneum</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades serosa (visceral peritoneum)</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades serosa (visceral peritoneum)</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades adjacent structures <strong>,</strong> <strong>,</strong></td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>Code</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 metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in 1 - 2 regional nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in 3 - 6 regional nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in 7 or more regional nodes</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in 7 - 15 regional nodes</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in 16 or more regional nodes</td>
</tr>
</tbody>
</table>

Note: T1a and T1b are considered to be the same stage in the 7th edition of the AJCC staging system. T4b is a separate stage in the 8th edition, reflecting the penetration of adjacent structures.
Staging

- T1a
- T1b
- T2
- T3
- T4a
- T4b

Tumor in stomach wall

Adjacent organ
Staging: EUS
Accurately Diagnosis & Staging

EGD

Tumor Markers

Endoscope

Light

Stomach

EUS (cT~65-92%, cN ~30-90%)

CT Scan (cN 51-84%, cM)

Exact Location, Distance from EGJ, Histology, H. pylori, HER2 testing
Accurate cT Stage So Important?

<table>
<thead>
<tr>
<th>T stage</th>
<th>% LN spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>~ 5%</td>
</tr>
<tr>
<td>T1b</td>
<td>~ 24%</td>
</tr>
<tr>
<td>T2</td>
<td>~ 52%</td>
</tr>
<tr>
<td>T3</td>
<td>~ 67%</td>
</tr>
<tr>
<td>T4a</td>
<td>~ 74%</td>
</tr>
<tr>
<td>T4b</td>
<td>~ 82%</td>
</tr>
</tbody>
</table>

- Least likely to have LN involvement if <2cm, well differentiated, non-ulcerated (1.7%)
- More likely in
  - larger tumors >4cm
  - poorly differentiated
  - proximal location
  - presence of lymphovascular invasion

To predict the incidence and distribution of LN metastasis in detail before operation for AGC, can use Maruyama *Index - Nippon Geka Gakkai Zasshi* 1989, 90, 1318-1321.
Surgery

• Which kind of resection do I do?
  – Upper 1/3: Total Gastrectomy
  – Lower 2/3: Distal/Subtotal gastrectomy
  – Large mid lesions, infiltrative lesions (linitis): Total

• Proximal Gastrectomy
  – Meta-analysis PG v TG
    • 5yr OS: 60.9% v 64.4%
    • Recurrence: 38.7% v 24.4%
    • Anastomotic Stenosis: 27.4% v 7.4%
    • PG associated with increased reflux

Surgery

A
Gallbladder
Liver
Esophagus
Stomach
Duodenum
Pancreas
Jejunum

B
Esophago-jejunal anastomosis
Roux loop of jejunum (45 cm)
Duodenal stump

C
Enter-enterostomy

Bilroth I
Bilroth II

D
Roux-en-Y
Surgery - Lymphadenectomy
Surgery - Lymphadenectomy

- Proper staging and treatment may not be provided

- Less than 50% of the patients received adequate LND by 2008

  - Esophageal 16.4%
  - Gastric 37.4%
  - Small Bowel 31.4%
  - Colon 72.9%
  - Rectum 58.2%

- 15 LN retrieved
  - Community 26.2%
  - Comprehensive 30.2%
  - Teaching 39.6%

- Multimodality?
  - Surgery Alone 55-58%

- Recurrence is high
  - Locoregional recurrence – up to 38%

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Surgery - Lymphadenectomy

- **Total Gastrectomy**
  - D1: 1-7
  - D1+: 1-7, 8a, 9, 11p
  - D2: 1-7, 8a, 9, 11p, 11d, 12a

- **Distal Gastrectomy**
  - D1: 1, 3, 4sb, 4d, 5, 6, 7
  - D1+: D1, 8a, 9
  - D2: D1, 8a, 9, 11p, 12a
Surgery - Lymphadenectomy

- Distal Gastrectomy
  - D1: 1, 3, 4sb, 4d, 5, 6, 7
  - D1+: D1, 8a, 9
  - D2: D1, 8a, 9, 11p, 12a
Surgery - Lymphadenectomy

- Independent Prognostic Survival Predictors:
  - Total LN count (or number of negative LNs examined; p < 0.0001)
  - Number of positive LNs p < 0.0001
  - Age p < 0.0001
  - Primary site; p = 0.0002
  - T category p = 0.0271
  - Race p = 0.0301
  - Gender p = 0.0261

Surgery - Lymphadenectomy
Dutch Trial

• Problems:
  – Adherence: 36% in D1 and 51% in D2 had LN stations with no nodes found
  – No adjuvant therapy
  – Learning curve, supervision

• Long Term Results D1 v D2
  – 5yr OS: 45 v 47%
  – Cumulative risk of relapse lower with D2
    • 41% v 29% p=0.02, HR 0.84 (0.65-1.09)
  – R0 resection, no postop mortality, risk of 5 yr relapse
    • 43% v 47%, p=0.22

• Conclusions:
  – Routine use of D2 lymphadenectomy not indicated
    • Higher complications, in hospital mortality, LOS
    • No difference in overall survival
    • No significant difference in risk of 5 yr relapse (if R0 resection and no in hospital mortality)

Surgery Lymph Nodes: Cochrane Analysis

• D1 vs D2
  – Overall survival
    • OS (n = 5; HR 0.91, 95% CI 0.71 to 1.17)
    • DFS (n=3; HR 0.95, 95% CI 0.84 to 1.07)
    • DSS (HR 0.81, 95% CI 0.71 to 0.92),
  – D2 lymphadenectomy was also associated with a higher postoperative mortality rate
    • RR 2.02, 95% CI 1.34 to 3.04

D2 LND Can Be Morbid but Beneficial

- **Dutch D1D2**
  Bonenkamp et al. NEJM, 1998

- **MRC ST01**
  Cuschieri et al. BJC, 1998

- **Wu et al.**
  Lancet Oncol., 2006

- **IGCCSG-R01**
  Degiuli et al. Br JSurg 2010

- **15 year Dutch trial**
  Songun et al. Lancet Oncol 2010
D2 or not to D2?

- Most expert surgeons at high volume centers around the world including US adhere to the concept of radical gastrectomy with extensive lymphadenectomy (D2) for AGC.

- Japanese Research Society for Gastric Cancer
- Korean Gastric Cancer Association
- Italian Gastric Cancer Study Group
- German Gastric Carcinoma Study Group
- Brazilian Gastric Cancer Association
- National Comprehensive Cancer Network (> 15 LN, D1+ or modified D2 only by experienced surgeons at high volume centers)

Japanese Gastric Cancer Association 2002
Options for Surgical Approach

• After a century of open surgery (Theodor Billroth, 1881), the first laparoscopic surgery for gastric cancer was performed by Seigo Kitano in 1991

• A total of 34,645 lap cases has been performed for gastric cancer since 1991 in Japan

• Initial indications
  – Early gastric cancer
    • cT1N0M0 (Stage IA); cT1N1M0 (Stage IB)
    • cT2N0M0 (Stage IB)
  – Still considered experimental in Japan

• Expanding application around the world
  – Advanced gastric cancer
Goals of Any Surgical Approach the Same

- R0 resection for maximum oncologic control
- Minimize trauma to the patient / protect patients’ QOL
Understand the Benefits Of MIS

• 38 studies 2000-2009
• 6 RCT
  – Kitano S 2002
  – Lee JH 2005
  – Huscher C 2005
  – Hayashi H 2005
  – Kim YW 2008
  – Kim HH 2010
• 32 NRCT
• 3055 patients total
• 54% LDG/46% ODG

- Shorter hospital stay
- Less blood loss
- Less pain medicine
- Decrease systemic complications
- No increase in operative complications

- Longer operative times
- Less lymph node retrieval
- Mostly in EGC patients
- Technically difficult D2
- Studies on-going for AGC

Meta-Analysis of RCT and NRCT by MSKCC
## Await Long-Term Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Design/Phase</th>
<th>Eligibility</th>
<th>Primary Endpoint</th>
<th>Estimated Enrollment</th>
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<tbody>
<tr>
<td>JCOG0912</td>
<td>III LADG vs Open</td>
<td>Stage I</td>
<td>Overall Survival</td>
<td>920</td>
</tr>
<tr>
<td>KLASS I</td>
<td>III LADG vs Open</td>
<td>Stage I</td>
<td>Overall Survival</td>
<td>1400</td>
</tr>
<tr>
<td>JLSSG0901</td>
<td>Randomize II/III LADG vs Open</td>
<td>T2, T3, T4a N0-2 M0</td>
<td>Morbidity rate Relapse free Survival</td>
<td>500</td>
</tr>
<tr>
<td>KLASS II</td>
<td>III LADG vs Open</td>
<td>ACG</td>
<td>Three yr DFS</td>
<td>1000</td>
</tr>
</tbody>
</table>

High powered retrospective studies support equivalent outcome but prospective studies are pending.
## Survival

**Presented by:** Bryan Goldner, D.O.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean</th>
<th>Median</th>
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<tbody>
<tr>
<td>IA</td>
<td>97.4</td>
<td>NR</td>
</tr>
<tr>
<td>IB</td>
<td>82.9</td>
<td>101</td>
</tr>
<tr>
<td>IIA</td>
<td>70.0</td>
<td>59</td>
</tr>
<tr>
<td>IIB</td>
<td>63.9</td>
<td>45</td>
</tr>
<tr>
<td>IIIA</td>
<td>49.1</td>
<td>25</td>
</tr>
<tr>
<td>IIIB</td>
<td>40.8</td>
<td>19</td>
</tr>
<tr>
<td>IIIC</td>
<td>28.4</td>
<td>14</td>
</tr>
<tr>
<td>IV</td>
<td>21.4</td>
<td>10</td>
</tr>
</tbody>
</table>

### Survival (Months)

<table>
<thead>
<tr>
<th>Survival (Months)</th>
<th>Cumulative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>12.0</td>
<td>0.02</td>
</tr>
<tr>
<td>24.0</td>
<td>0.04</td>
</tr>
<tr>
<td>36.0</td>
<td>0.06</td>
</tr>
<tr>
<td>48.0</td>
<td>0.08</td>
</tr>
<tr>
<td>60.0</td>
<td>0.10</td>
</tr>
</tbody>
</table>

- **IA:** 1 91 87 83 78 75
- **IB:** 2 87 78 72 68 63
- **IIA:** 3 86 72 60 56 49
- **IIB:** 4 81 66 55 44 44
- **IIIA:** 5 72 51 41 35 31
- **IIIB:** 6 65 42 32 27 24
- **IIIC:** 7 55 30 20 15 13
- **IV:** 8 43 20 12 10 8
Conclusions

• Patient Condition – Age, comorbidities, prior surgeries, wishes = goals of therapy
• Tumor Factors – accurate preoperative staging a must
  • Confirm histology with biopsy, H. pylori, HER2 status
  • Location & tumor depth - guides extent of stomach resection
  • cT & cN staging – guides extent of lymphadenectomy
• Timing of Surgery
  • Would patient benefit from neoadj chemotherapy/ radiation?
  • Would patient benefit from surgery upfront?
• Surgical Approach
  • Open vs Laparoscopic vs Robotic
Patient with gastric cancer
- EGD bx proven
- Worked up with CTAP
- +/- EUS
- +/- PET

Base Treatment Strategy on Evidence

M0

M1

Chemotherapy
Radiotherapy
Palliative Surgery
Palliative Care

M1: Chemotherapy

M0: cT1ab → cN0
- cT1a (M)
  - Differentiated ≤ 2cm, UL (-)
  - Endoscopic resection
- cT1b (SM)
  - Differentiated ≤ 1.5, UL (-)
  - Gastrectomy D1+ LND
- Standard Gastrectomy D2 NLD
- Gastrectomy, Combined resection D2 LND

M0: cT2/3/4a/4b → cN+
- +/- Neoadjuvant chemotherapy/radiation
- +/- Adjuvant chemotherapy/radiation
Thank You