Gastric Adenocarcinoma: Limited vs. Radical Lymphadenectomy

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Gastrectomy for Adenocarcinoma

- First Performed successfully by Billroth-1891
- Radical total gastrectomy-1940s
- Currently, subtotal gastrectomy for distal tumors
- Only tx that offers hope of cure
Gastric Adenocarcinoma

- **Two histologic subtypes:**
  - Intestinal (endemic areas, glandular formation)
  - Diffuse (low prevalence areas, poorly differentiated)

- **Geographic Variability**
  - Japan, China, Eastern Europe
  - 2nd leading cause of cancer death worldwide

- **More common in males**

- **Decline in incidence over last 70 years**
  - H. pylori, refrigeration, fruits/vegetables
  - No improvement in survival (15-25% in US)
DNR of Gastrectomy

- Japanese LN classification (JRSGC)
- Nodal basins 1-16
  - N1 (perigastric, 1-6)
  - N2 (1 arterial level beyond N1, 7-11)
  - N3 (HD ligament, root of mesentery, 12-14)
  - N4 (para-aortic, paracolic, 15 &16)
DNR of Gastrectomy

• “D” characterizes extent of lymphadenectomy
  • D1 = perigastric nodes
  • D2 = D1 + nodes from celiac branches
  • D3 = D2 + HD ligament, retropancreas, & root of mesentery
  • D4 = D3 + para-aortic & para colonic
DNR of Gastrectomy

- “R” refers to completeness of resection
  - R0 = histologically proven complete excision
  - R1 = residual microscopic tumor (pos. margins)
  - R2 = residual macroscopic tumor (tumor transection)
- R0 resection clearly impacts survival
  - German Gastric Cancer Study

<table>
<thead>
<tr>
<th></th>
<th>R0 resection (n=1182)</th>
<th>Entire Population (n=1654)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 yr. survival</td>
<td>36.1%</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

Japanese Experience

- Data collection started in 1950s
- LN mets/serosal invasion important to survival
- Complete (R0) resection important to survival
- **Hypothesis**: Greater LN dissection will result in improved 5-year survival.
## Japanese Experience

<table>
<thead>
<tr>
<th>Author</th>
<th>Date published</th>
<th># of Pts</th>
<th>5-yr survival</th>
<th>5-yr surv. w/ +LN</th>
<th>Additional info.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mine et al (Kyoto)</td>
<td>1970</td>
<td>277</td>
<td>27.5%</td>
<td>10.1-21.4%</td>
<td>Compared D2 to D3</td>
</tr>
<tr>
<td>Soga et al (Niigata)</td>
<td>1979</td>
<td>530</td>
<td>50.6%</td>
<td>29.9% (58.5% of tot)</td>
<td>---</td>
</tr>
<tr>
<td>Kodama et al (Fukuoka)</td>
<td>1981</td>
<td>708</td>
<td>58%</td>
<td>39% w/ D2</td>
<td>18% w/ D1</td>
</tr>
<tr>
<td>Nakajima et al (Tokyo)</td>
<td>1989</td>
<td>5862</td>
<td>37.4%</td>
<td>50% (N1) 24.4% (N2)</td>
<td>---</td>
</tr>
</tbody>
</table>

Soga, J. World J Surg. 1979  
Nakajima, T. Hepatogastroenterology. 1989
Western Response

- Randomized Controlled Trials
  - Dutch Gastric Cancer Group (Bonenkamp)
  - Medical Research Council (MRC) Gastric Cancer Surgical Trial (ST01) (Cuschieri)

- Prospective Cohort Studies
  - German Gastric Carcinoma Study Group (Siewert)
  - Italian perspective (Pacelli)
Dutch Study

996 pts randomized to D1 or D2 LN Dissection

711 with curable lesions

285 unresectable disease

380 pts D1

4%

25%

45%

331 pts D2

10%

43%

47%

Operative Mortality (p=0.004)

Post-op Complications (p<0.001)

5-year survival (p=NS)

Bonenkamp, J. Lancet, 1995

Bonenkamp, J. N E J M . 1999
MRC ST01

737 pts randomized to D1 or D2 LN Dissection

400 with curable lesions

337 unresectable disease

200 pts D1

6.5%

28%

35%

200 pts D2

13%

46%

33%

Post-op Mortality (p=0.04)

Post-op Complications (p<0.001)

5-year survival (p=NS)

Cuschieri, A. Lancet. 1996

Cuschieri, A. Br J Cancer. 1999
Quality Control?

- D2 LAD not common in West
- Instruction w/ videotapes & booklets
- “Specially trained” surgeons assisted in Dutch trial
Learning Curve

- **Dutch Trial**
  - 4 yrs
  - 80 centers (? Surgeons)
  - 331 D2 resections
    - 4.1 resections/center
    - 1.03 resections/center/yr

- **MRC ST01**
  - ? yrs, say 5
  - 28 surgeons in Surgical Cooperative Group
  - 200 D2 resections
    - 7.1 resections/surgeon
    - 1.4 resections/surgeon/yr

Does this matter???
Learning Curve

• Parikh et al: 3-yr prospective study
  • 1 surgeon’s experience: D2 resection
    • 4 months training in Tokyo
    • Total 38 resections
  • Drastic drop off in M&M after 18 months
    • Conclusion: learning curve = 15-25 cases over 18-24 months

Pancreaticosplenectomy

- JRSG C standardized protocol for D1/ D2 resections
  - Spleen/ tail of pancreas
- Impact on morbidity?
Splenectomy

- Dutch Trial

<table>
<thead>
<tr>
<th>Spleen resection</th>
<th>Number of patients</th>
<th>% of subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1</td>
<td>D2</td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td>124</td>
</tr>
<tr>
<td>No</td>
<td>338</td>
<td>204</td>
</tr>
</tbody>
</table>

Most important risk factor for complications

(RR=2.13, CI=1.44-3.16)

Splenectomy

- MRC trial: morbidity & mortality

<table>
<thead>
<tr>
<th></th>
<th>No spleen removal</th>
<th>Splenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D\textsubscript{1}</td>
<td>D\textsubscript{2}</td>
</tr>
<tr>
<td>Morbidity</td>
<td>28 (20%)</td>
<td>15 (22%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>5 (4%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Total patients</td>
<td>138</td>
<td>69</td>
</tr>
</tbody>
</table>

p values relate to D\textsubscript{1} + D\textsubscript{2}.
Pancreatoco-splenectomy

- MRC trial: 5-year survival

<table>
<thead>
<tr>
<th>Spleen/pancreas resection</th>
<th>1.0</th>
<th>0.97–1.90</th>
<th>0.0716</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither resected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenectomy only</td>
<td>1.36</td>
<td>1.17–2.01</td>
<td>0.0020</td>
</tr>
<tr>
<td>Pancreatoco-splenectomy</td>
<td>1.53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inset graph showing survival rates over 7 years with different resection conditions.
Is splenectomy necessary?

- Griffith et al. 1995
  - Retrospective Review:
    - One surgery dept.
    - 207 pts.
      - 76 G +Sp, 119 G alone
    - Post-op morbidity
      - 41% vs. 14% (p<0.01)
    - Operative mortality
      - 12% vs. 2.5% (p<0.05)
    - Survival: significantly increased in all pts & stage III alone (p<0.01 & <0.05)

- Csendes et al. 2002
  - Prospective RCT:
    - One surgery dept.
    - 187 pts.
      - 90 TG +S, 97 TG alone
    - Post-op morbidity
      - Sig. increase in septic comp. only
    - Operative mortality
      - 4% vs. 3% (NS)
    - Survival: 42% vs. 36% (NS)

Griffith, J. Gut. 1995
Csendes, A. Surgery. 2002
Protocol Deviation

- Dutch trial:
- MRC trial: median # LN
  - $D_1 = 13$
  - $D_2 = 17$
- Japanese rules:
  - $D_2 > 25$ nodes

<table>
<thead>
<tr>
<th>TABLE 5. ADHERENCE TO THE PROTOCOL FOR LYMPH-NODE DISSECTION IN THE 711 PATIENTS WHO UNDERWENT RESECTION WITH CURATIVE INTENT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE OF PROTOCOL VIOLATION</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>Contamination (proof of lymph nodes from more than two lymph-node stations that were not supposed to be harvested)</td>
</tr>
<tr>
<td>Noncompliance (absence of lymph nodes from more than two lymph-node stations that were supposed to be harvested)</td>
</tr>
</tbody>
</table>
Summary of RCTs

- Well organized, well randomized, however...
  - Improvements in quality control
  - Effect of learning curve?
  - Effect of pacreatectomy/splenectomy?
  - Improvements in adherence to protocol
1654 pts underwent either D1 or D2 LN Dissection

558 pts D1
5.2%
29%
26.8%
25.3%

1096 pts D2
5%
30.6%
55.2%
38.4%

Operative Mortality (p=NS)
Post-op Complications (p=NS)
5-year survival stage II (p<0.001)
5-year survival stage IIIA (p=0.03)

Siewert J, Br J Surg. 1993
Italian Perspective

- Retrospective Cohort Study
  - One institution
  - Two surgical teams
  - 320 pts
    - 157 extensive
    - 163 limited
  - Improved 5-year survival
    - Stage III (48.7 vs. 29.8%, p=0.02)

Pacelli, G. Br J Surg. 1993
Conclusions

- Extensive (R2) LAD can be performed as safely as limited (R1)
- R2 LAD has a 5-year survival benefit in stage II and III tumors
- Further RCTs needed with better standardization of surgical procedure and limited splenectomy/pancreatectomy