Conventional Gastrectomy for Gastric Cancer

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Grand Rounds
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Overview

- Gastric Adenocarcinoma
- Conventional vs Radical Lymphadenectomy
- Non-randomized studies
- RCTs
- Recent studies
- Survival Differences
- Conclusion
Gastric Carcinoma

- Second leading cause of cancer deaths in men world-wide (2007 ACS)\(^1\)
- 13th cause of male death in US
- 2:1 M:F
- Fresh fruit/vegetables
- Smoked/salted/pickled foods, H. Pylori, atrophic gastritis
Gastric Carcinoma

- Not homogenous disease
- Intestinal vs diffuse type
- Proximal vs distal location
- Dramatic differences between nations
<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>52.6</td>
</tr>
<tr>
<td>U.S.</td>
<td>6.3</td>
</tr>
<tr>
<td>UK/Germany</td>
<td>16-20</td>
</tr>
</tbody>
</table>

**Figure 9a. International Variation in Age-Standardized Stomach Cancer Incidence Rates Among Males**

Source: Globocan 2002.
Gastric Carcinoma

• Subtotal vs Total gastrectomy - based on location of tumor

• Survival
  • U.S. - 24%
  • Europe - 20-25%
  • Japan - 60-70%
Figure 1  Lymph node groups 1–6 (N1)

Figure 2  Lymph node groups 7–11 (N2)
Lympadenectomy

- Japanese - D2 lymphadenectomies
  - 1960’s
  - “Radical”
  - D3 considered “Radical” in Japan
- Western - D1 lymphadenectomies
Stage Migration

- More extensive lymphadenectomy = more accurate staging
- “Upstaging”
- Improves stage-specific survival in D2 or D3 resections
  - D2 - 20%
  - D3 - 43%
• Siewert (Germany) 1998 - Annals of Surgery

• n=1654

• Prospective, non-randomized

• Defined extent of lymphadenectomy by # of LNs in specimen

• Planned for all D2, retrospectively called inadequate resections D1
Non-Randomized Studies

Figure 4. Cumulative survival in patients with R0 resection: effect of D1 and D2 lymph node dissection.

Figure 5. Cumulative survival in patients with resected stage II gastric cancer: effect of D1 and D2 lymph node dissection.
Non-Randomized Studies

- Roukos (German) 1998 - Surgery
  - n=125
  - D2 patients only
  - Prospective
  - Showed 31 patients with N2 nodes resected with intent to cure
  - 17% 5-yr survival
RCTs - British

• Cuschieri: 1996/1999 - Lancet/Br J Cancer$^6,7$

• n=400

• Intra-operatively randomized

• Median F/U 6.5 years

• 90% followed to death or 5 years
Disease-Specific Survival - No benefit
Increased post-operative complications and death in D2 group (p < 0.05)

<table>
<thead>
<tr>
<th>Treatment allocated</th>
<th>Post-op course/complications</th>
<th>Total morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Minor*</td>
</tr>
<tr>
<td>$D_1$</td>
<td>145 (72.5%)</td>
<td>30 (15%)</td>
</tr>
<tr>
<td>$D_2$</td>
<td>108 (54%)</td>
<td>45 (22.5%)</td>
</tr>
</tbody>
</table>

*Minor complications included wound infections without wound dehiscence, minor chest infections/pulmonary collapse, deep vein thrombosis without pulmonary embolism or leg oedema.

Table 3: Categorisation of postoperative morbidity in first 371 randomised patients
RCTs - Dutch

- Bonenkamp: 1995/1999 - Lancet / NEJM\textsuperscript{8,9}
  - n=711
  - Pre-operatively randomized
  - Median F/U 6 years
Overall Survival - No benefit
<table>
<thead>
<tr>
<th></th>
<th>D1 (n=380)</th>
<th>D2 (n=331)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-op Death</td>
<td>15 (4%)</td>
<td>32 (10%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Complications</td>
<td>94 (25%)</td>
<td>142 (43%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Increased post-operative complications and death in D2 group (p < 0.05)
No stage-specific survival seen in either study

Despite 30% D2 stage migration in Dutch study
RCTs - Flaws

- Distal pancreatectomy/splenectomy
  - British - 56% vs 4% (both)
  - Dutch - 30% vs 3% (distal pancreatectomy)
  - Distal pancreatectomy did not alter M&M
- Protocol non-compliance / contamination (Dutch)
  - 6% of D1 dissections showed extra LNs
  - 51% of D2 dissections showed missing LNs
RCTs - Flaws

- Surgeon training
- Video & pamphlet (British)
- 6 month training by Japanese surgeon & 11 regional supervisors thereafter (Dutch)
- 25-50 case learning curve for D2
- Dutch trial showed surgeon experience not an independent predictor of outcome
Recent Studies

• Sasagawa (Costa Rica): 2008, Am J Surg\textsuperscript{11}
  • n=199 (CR), n=497 (Japanese Cohort)
  • All received D2 resection
  • F/U not specified
  • Japanese surgeon assisted with all operations
Recent Studies

- Overall 5 yr survival
  - 72.5% Costa Rica
  - 69.7% Japan

- Morbidity / Mortality
  - 39% / 5% - Costa Rica (p < 0.05)
  - 27% / 0.8% - Japan (p < 0.05)
Recent Studies

• Japanese radiologists, endoscopists, pathologists, surgeons, and nurses came to Costa Rica to train Costa Ricans

• Improvement in survival may be multi-factorial

• No proof of D2 effect on survival

• Different population, unable to directly compare to European RCTs
Why are Japanese survival rates higher?

• Surgical Technique? **NO!**
• Different Disease?
• Technical Differences?
Different Disease

- Tumor biology
  - Incidence of intestinal type higher in high prevalence areas - better prognosis
- Different tumor markers
  - Japanese - higher nm23
  - British - higher c-erbB-2 and PCNA\textsuperscript{12}
  - Japanese-American’s survival\textsuperscript{13}
• Understaging of Western tumors
• D2 stage migration effect
• More early (low stage) tumors
• Better screening
• Chemotherapy
Technical Differences

• Pathologic staging different

• Japanese pathologists look at nuclear and structural atypia over invasion

• Cases called high or even low grade dysplasia by Western pathologists were called carcinoma by Japanese pathologists\textsuperscript{14}
Technical Differences

- Japanese surgeons dissect LNs themselves on the fresh specimen
- Significantly higher LN yield\textsuperscript{15}
- Patient population
  - Less obesity
  - Younger age (8 yrs compared to Dutch)
- Less cardiovascular disease\textsuperscript{15}
Conclusion

• Improved Japanese survival likely multi-factorial, unrelated to extent of LN dissection

• Even if D2 resection can be safely performed in Western patients, there is still no solid evidence that it should be done

• Lessons from Halstead’s radical mastectomy


