Radical Resection for Adenocarcinoma of the Pancreatic Head is USELESS

Arek Wiktor, MD
PGY-4
Outline

- How did we get to this point?
- Lymph Node Maps
- The Japanese Experience
- Prospective Randomized Trials
- Cancer Math 101
- Final Thoughts
History

- 1st successful resection: Halsted 1899
- 1st pancreaticoduodenectomy for adenocarcinoma: Dr. Alexander Brunschwig
- 1973- Dr. Joseph Fortner “regional resection” of the pancreas
- LN mapping by Cubilla and Kayahara
- Patterns of failure: recurrence most often are in peripancreatic region and within the liver
What is a “Radical” Operation?

- “Extended Pancreaticoduodenectomy”
- “Extended Radical Whipple”
- “Regional Pancreatectomy”
- “Extended Lymphadenectomy”
- “En bloc resection”
Lymph Node Stations

Kayahara et al. Cancer 85(3);583-90
Consensus Conference 1998: Castlefranco, Veneto, Italy

http://www.terninrete.it/headlines/articolo_view.asp?ARTICOLO_ID=111990
**Standard pancreatoduodenectomy:**
Regional lymphadenectomy around the duodenum and pancreas (stations 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, 17b and 8a)

**Radical pancreatoduodenectomy:**
Standard operation +
Skeletonization of hepatic arteries, SMA between aorta and inferior pancreaticoduodenal and celiac trunk, dissection of the anterolateral aspect of aorta and vena cava including Gerota’s fascia (standard + all station 8, 9, all 12, all 14, 16a2, 16b1)
“Standard Resection”
“Extended Resection”

Kayahara et al. Cancer 85(3);583-90
The Japanese Experience

5 yr Survival of 28 - 33.4%!!!

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<tr>
<th>References</th>
<th>No. patients (standard/Extended)</th>
<th>3-year survival (standard, %/extended, %)</th>
<th>5-year survival (standard, %/extended, %)</th>
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<tbody>
<tr>
<td>Ishikawa et al.⁴⁵†</td>
<td>59 (37/22)</td>
<td>13/22</td>
<td>13/18</td>
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<tr>
<td>Manabe et al.⁴⁶†</td>
<td>74 (42/32)</td>
<td>0/38</td>
<td>0/33</td>
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<td>Satake et al.⁴⁷†</td>
<td>151 (72/57)</td>
<td>34/39</td>
<td>27/28</td>
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<td>Imaizumi et al.⁸</td>
<td>316 (67/249)</td>
<td>10/13</td>
<td>8/9</td>
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<td>65 (11/54)</td>
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Samra et al. ANZ J Surgery, 2008; 78: 228-236
The Japanese Experience

5 yr Survival of 28 + 33.4%!!!

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Samra et al. ANZ J Surgery, 2008; 78: 228-236
## Comparison of 4 Randomized Trials

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<td>Institution</td>
<td>Multi</td>
<td>Single</td>
<td>Multi</td>
<td>Single</td>
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<tr>
<td>Adjuvant Tx</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>En bloc</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Only Adeno Carcinoma</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Similar LN stations</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
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Farnell et al. J Gastrointestinal Surgery 2008;12:651-656
The Italian Experience
Pedrazzoli et al. 1998

• 81 patients (40 standard vs 41 extended)
• 1991-1994
• Extended along aorta from diaphragm to IMA
• Pylorus preserved in maj, surgeon preference
• Mean LN harvest 13.3 vs 19.8 (p<0.03)
• Operative time 30 min longer
• 4 year survival no difference

Actuarial Survival

Actuarial Survival, LN Status

The Johns Hopkins Experience
Yeo et al. 2002

• 294 patients (146 standard vs 148 extended)
• 162 adenocarcinoma (80 standard vs 82 extended)
• Standard – Pylorus preserving
• Extended – Distal gastrectomy
• Mean LN harvest 17 vs 28.5 (p=.001)
• Operative time: 5.9 vs 6.4 (p=0.02)
“Extended Operation”

30-40% distal gastrectomy, LN station 3,4,5,6, 9, 16
Actuarial Survival
Standard vs Extended, Node Negative

"Trend towards improved survival"?
21% standard vs 5% extended had POSITIVE MARGINS
## Postoperative Complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard</th>
<th>Extended</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Complication</td>
<td>42 (29%)</td>
<td>64 (43%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Delayed Gastric Emptying</td>
<td>9 (6%)</td>
<td>24 (16%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Pancreatic Fistula</td>
<td>9 (6%)</td>
<td>19 (13%)</td>
<td>.05</td>
</tr>
<tr>
<td>Wound Infection</td>
<td>7 (5%)</td>
<td>16 (11%)</td>
<td>0.06</td>
</tr>
<tr>
<td>LOS</td>
<td>11.3</td>
<td>14.3</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Overall Morbidity 29 vs 43% (p<0.01)
6 REGIONAL VERSUS EXTENDED LYMPH NODE DISSECTION IN RADICAL PANCREATODUODENECTOMY FOR PANCREATIC CANCER: A MULTICENTER, RANDOMIZED CONTROLLED TRIAL

Yuji Nimura, Masato Nagino, Hiroyuki Kato, Shuichi Miyagawa, Akihiro Yamaguchi, Taira Kinoshita, Sonshin Takao, Tadahiro Takada, Koji Miyazaki, Shuichi Ishiyama, Hiroshi Shimada, Yoshifumi Kawarada, Hiroshi Takeda, Koro Sagota and Kenzo Yasui, Nagoya University Hospital, Nagoya, Japan, Nagoya University Hospital, Hokkaido University Hospital, Fujita Health University Hospital, Ogaki Municipal Hospital, National Cancer Center Hospital East, Kagoshima University Hospital, Teikyo University Hospital, Saga Medical University Hospital, National Sendai Hospital, Yokohama City University Hospital, Mie University Hospital, National Osaka Hospital, Kagoshima Medical Association Hospital and Aichi Cancer Center Hospital

PURPOSE: The purpose of this study was to evaluate, in a multicenter randomized controlled trial (RCT), whether an extended lymph node dissection in radical pancreatoduodenectomy prolongs the survival of patients with pancreatic cancer.

METHODS: From March 2000 to May 2003, 112 patients with carcinoma of the head of the pancreas were enrolled. After intraoperative investigation, patients were randomized to regional or extended (regional plus para-aortic) lymphadenectomy in radical pancreatoduodenectomy. None of the patients received any adjuvant therapy. All pathology specimens were reviewed and categorized, and morbidity, mortality, survival and quality of life were analysed. RESULTS: Of the 112 patients randomized, 11 were subsequently excluded because of the final pathology (7 chronic pancreatitis and 4 bile duct cancer), and the remaining 101 patients were analysed (51 regional vs 50 extended). There was no significant difference between the 2 groups with regard to age, gender and BMI. Although the mean operative time (426 minutes vs 547 minutes), intraoperative blood loss (1118 ml vs 1680 ml), number of retrieved lymph nodes (13 vs 40) and incidence of postoperative diarrhea (0 vs 24) differed in the 2 groups, there was no significant difference with respect to transfusion requirements, type of resection, overall morbidity excluding diarrhea, postoperative length of hospital stay (44 vs 42), mortality (0 vs 1), histological stage of the disease and QOL at 1 year after surgery. The 1-, 2- and 3-year survival rates for all 101 patients (78.7, 43.2, 32.4 vs 51.3, 39.9, 16.0%) and those with negative or positive node disease and disease-free survival (42.3, 17.8, 6.7 vs 48.8, 16.0, 12.0%) showed no significant difference between the 2 groups. CONCLUSIONS: In this multicenter RCT, radical pancreatoduodenectomy with extended lymph node dissection did not provide any survival benefit in the treatment of patients with resectable pancreatic cancer.

Multicenter randomized trail
Nimura et al. 2004

- 101 patients (51 standard vs 50 extended)
- LN harvest - standard 13 vs extended 40
- 1, 2, 3 – year survival the same in both groups

“extended lymph node dissection did not provide any survival benefit in the treatment of patients with resectable pancreatic cancer”
Actuarial Survival

Survival curve provided by Yuji Nimura, M.D., President, Aichi Cancer Center, Nagoya, Japan
The Mayo Clinic Experience
Farnell et al. 2005

- 79 patients (40 standard, 39 ELN)
- Non-pylorus preserving
- 75% patients received adjuvant chemotherapy

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<th>Variable</th>
<th>Standard</th>
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<tr>
<td>Operative Time</td>
<td>6.2 hrs</td>
<td>7.6 hrs</td>
<td>&lt; .001</td>
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<tr>
<td>Transfusion (1)</td>
<td>5%</td>
<td>23%</td>
<td>.01</td>
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<tr>
<td>Lymph Nodes</td>
<td>15</td>
<td>36</td>
<td>&lt; .001</td>
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Farnell et al. Surgery; 2005138:618-630
Overall Survival

Farnell et al. Surgery; 2005138:618-630
Positive Lymph Node Survival

Farnell et al. Surgery; 2005138:618-630
## Quality of Life at 4 months

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<th>Variable</th>
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<tr>
<td>Physical Well-being</td>
<td>0</td>
<td>-14.3</td>
<td>.37</td>
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<tr>
<td>Emotional Well-being</td>
<td>10</td>
<td>0</td>
<td>.30</td>
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<tr>
<td>Bowel Control</td>
<td>0</td>
<td>-25</td>
<td>.038</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>-50</td>
<td>.002</td>
</tr>
<tr>
<td>Appearance</td>
<td>0</td>
<td>-50</td>
<td>.005</td>
</tr>
<tr>
<td>Additional Concerns</td>
<td>5.6</td>
<td>-22.2</td>
<td>.002</td>
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53% of extended patients had “no control” or “little control” of bowels vs 9% in standard

Farnell et al. Surgery; 2005138:618-630
After interim analysis, the trial was terminated on July 31, 2003
The Mayo Clinic Experience

“Quality-of-life issues in our patients 4 months postoperatively, lack of improvement in survival, and the aforementioned published prospective randomized trials should put to rest the controversy that more radical operation confers improved survival.”

Farnell et al. Surgery; 2005138:618-630
Cancer Math 101
1998-2002
304 patients underwent pancreaticoduodenectomy for adenocarcinoma
158 patients with 2nd-echelon nodes
Median survival 26.5 mo vs 24.7 mo p=0.91

Pawlik et al. Archives of Surgery, 2005; 140:v584-591
Assumptions

1) Only patients who have pathologically involved second echelon lymph nodes can benefit from extended lymphadenectomy.

2) R0 resection is required for extended lymphadenectomy to confer a possible survival benefit.

3) Only patients who have involved second-echelon lymph nodes and are M0 may derive a potential survival benefit from the removal of additional pathologically positive lymph nodes.

Pawlik et al. Archives of Surgery, 2005; 140:v584-591
Fraction who may derive benefit

\[ = \text{FN2} \times \text{FNO} \times \text{FTMO} \]

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<th>Patients (%)</th>
<th>R0 Resection (%)</th>
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<td>Negative 1(^{st}) Negative 2nd</td>
<td>76 (48.1)</td>
<td>89.5%</td>
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<tr>
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<td>65 (41.1)</td>
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4/17 (23.5%) Alive

1/17 (5.9 %) ALIVE without recurrent disease
Fraction who may derive benefit

\[ = FN2 \times FN0 \times FTM0 \]

\[ = 10.8\% \times 47.1\% \times 5.9\% \]

\[ = 0.3\% \]

Pawlik et al. Archives of Surgery, 2005; 140:v584-591
Feasibility of Randomized Trial

• 3/1000
• 5yr survival standard: 27.3%
• 5 yr survival extended: 27.52%
• 202,000 patients in each arm
• 1010 year accrual period

Pawlik et al. Archives of Surgery, 2005; 140:v584-591
400 patients
4 Randomized Trials
What Have We Learned?

Pawlik et al. Archives of Surgery, 2005; 140:v584-591
What Have We Learned?

- Extended lymphadenectomy adds 1 hour to operative time
- Significantly more LN are taken
- Less bowel control and more diarrhea

Does NOT increase survival
Final Thoughts

- Systemic disease
- Local therapy yields minimal improvement
- Less radical surgery as in breast and gastric cancer
- Early detection and ? chemoprevention
- Gene expression and protein biochip technology
- Better adjuvant / neo-adjuvant therapies
- Immunotherapy
Final Thoughts

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Thank You