The Whipple Operation for Pancreatic Cancer: Optimism vs. Reality

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Grand Rounds
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Overview

- Pancreatic ductal adenocarcinoma
- Pancreaticoduodenectomy (Whipple procedure)
- Morbidity / mortality
- Survival / "Cure"
- Palliation
- Conclusion
Pancreatic Ductal Adenocarcinoma

- Incidence of 10 per 100,000
- US Incidence: 33,730 - 2006 estimate
- US Deaths: 32,300 - 2006 estimate\(^1\)
- Traditional death : incidence ratio of 0.99\(^2\)
- Fourth leading cause of cancer mortality\(^1\)

Pancreatic AdenoCA

- Presenting symptoms - Jaundice, wt loss/fatigue, epigastric pain

Distribution¹ -

- Head - 78%
- Body - 11%
- Tail - 11%

Ratio of Stage I : Stage IV -

- Head - 0.70
- Body - 0.24
- Tail - 0.10

Pancreaticoduodenectomy
“Whipple”

- Halstead - 1st transduodenal excision of tumor of ampulla of Vater in 1899
- Kausch - 1st two stage pancreaticoduodenectomy (PD) in Germany in 1909 for ampullary tumor
- Brunschwig - 1st pancreaticoduodenectomy for pancreatic cancer in 1937
- Whipple - 3 patients with pancreaticoduodenectomy in 1935, total of 37 operations, shifted to one stage operation by the 1940s.
Whipple
Whipple - Indication

- Performed for variety of reasons
  - Periampullary adenocarcinoma
    - Pancreatic, ampullary, duodenal, biliary
  - Pancreatitits
  - Cystic neoplasms
  - Islet cell neoplasms
  - Other - trauma, metastasis, adenoma, abscess
9,044 / 100,313 (9%) patients with pancreatic adenocarcinoma underwent resection\(^1\)

**Adjusted Pancreatic Cancer Survival from 1995-2001** \(^2\)

- Overall 1 year survival 24%
- Overall 5 year survival 4.6%

Whipple - Controversies

- Morbidity / Mortality
- Survival / Cure
- Palliation
- Operative, Pre/Post-op Management
  - Biliary drainage, pylorus preservation, vein/artery resection, extended lymphadenectomy, chemotherapy/radiation therapy, adjuvant/neoadjuvant, laparoscopic exploration, octreotide use
Morbidity / Mortality

- Historically (until the 1960s-1970s) morbidity > 50% and mortality >20%

- In ideal settings, morbidity now ~40% and mortality rates often < 5%

- Limited applicability of “ideal” morbidity/mortality numbers
## Morbidity / Mortality

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td><strong>Morbidity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>1.4</td>
</tr>
<tr>
<td>No</td>
<td>641</td>
<td>98.6</td>
</tr>
<tr>
<td><strong>Reoperation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>624</td>
<td>96</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>384</td>
<td>59</td>
</tr>
<tr>
<td>Yes</td>
<td>266</td>
<td>41</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>124</td>
<td>19</td>
</tr>
<tr>
<td>Pancreatic fistula</td>
<td>92</td>
<td>14</td>
</tr>
<tr>
<td>Wound infection</td>
<td>66</td>
<td>10</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Bile leak</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Marginal ulcer</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><strong>Postoperative length of stay (days)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>16.5 ± 10.4</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>6–88</td>
<td></td>
</tr>
</tbody>
</table>

516 PDs / 202 pancr CA

- Morbidity: 223/516 (43%)
- Mortality: 3.9% overall
- 4.7% in pancr CA pts

# Morbidity / Mortality

NY study - 1972 patients with PD from 1984 to 1991

<table>
<thead>
<tr>
<th># of hospitals</th>
<th>% total pts</th>
<th>% mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min (&lt;10)</td>
<td>124</td>
<td>24</td>
</tr>
<tr>
<td>Low (10-50)</td>
<td>57</td>
<td>54</td>
</tr>
<tr>
<td>Medium (51-80)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>High (&gt;81)</td>
<td>2</td>
<td>19</td>
</tr>
</tbody>
</table>

Figure 2. Scattergram of crude in-hospital mortality rates according to hospital volume.

Survival

- 5 year survival s/p Whipple for pancreatic ductal adenocarcinoma: < 10% vs 20-25% ?

- Does 5 year survival = cure ?

- Actual survival vs actuarial (Kaplan-Meier) survival
Survival

“Long-Term Survival After Resection for Ductal Adenocarcinoma of the Pancreas: Is It Really Improving”, 1995

n=186 from 1981-1991 with pancreatic ductal adenoCA undergoing pancreatic resection

Overall actuarial 5 year survival: 6.8%

Operative mortality 3%, morbidity 32%

Survival

- All survivors > 3 yrs (31/186) underwent histopathologic specimen re-review

- 12/31 (39%) had a change in diagnosis:
  - Islet cell tumor (3), ampullary CA (4), cystadenoCA (3), cholangioCA (1), intraductal mucinous hypersecretory tumor (1)

- Mean survival 53 months vs 17.5 months

- Validates previous study of 23 3-yr survivors showing 29% reversal of pancreatic ductal adenoCA diagnosis

1. Ibid
Survival

146/175 pts with pancreatic adenoCA had complete resections

5 yr survival 12% vs 6.8% for all PDs

Possible causes for higher reported survival rates:

- Tumor biology changes
- Patient selection
- Operative technique
- Adjuvant/neoadjuvant therapy
- Exclusion of incomplete resections
- Inclusion of less lethal lesions
“Cure”

- 5 year survival following resection for pancreatic ductal adenocarcinoma:\n  - 12/118 (10.2%)
  - 5/12 (died of metastatic or recurrent pancreatic cancer: 60, 61, 62, 64, 64 months)
- Mentioned 13 additional 5-year survivors after pancreaticoduodenectomy with other tumors who were excluded
- Noted would have produced 19% survival

Palliation

Given poor true cure rate, is there role for palliation / tumor debulking?

- Retrospective review 1996, PD n=64, bypass n=62

- Bypass patients had major visceral or extensive peripancreatic soft-tissue involvement

- PD patients had macro/microscopic positive margin

- Post op chemo/rad therapy improved survival but was not given equally between two groups

Palliation

Figure 1. The actuarial survival curves (Kaplan-Meier) for patients undergoing palliative pancreaticoduodenectomy (N = 64) and palliative bypass (N = 62).

1. Ibid
Figure 2. The actuarial survival curves for patients undergoing palliative pancreaticoduodenectomy (PD) with (W/, N = 50) and without (N = 14) postoperative chemotherapy and radiation therapy and palliative bypass with (W/, N = 30) and without (N = 32) therapy.

1. Ibid
Palliation

Dr. George Crile, Jr. argued in 1970 for bypass procedures over PD for all patients given continue poor survival rates

Compared 28 pts with apparently localized pancreatic adenoCA on whom he operated from 1953 to 1966 to 28 patients operated upon by surgical colleagues from 1938 to 1966

Palpable tumors only (prior to radiographic imaging of pancreas)

Fig. 1. Survival of patients who underwent operations for adenocarcinoma of the head of the pancreas.
Palliation

Conclusion

From the 1970’s to the early 1980’s significant controversy arose regarding the role of PD for pancreatic ductal adenocarcinoma

Concurrent with rise of CT scans, potential for earlier intervention, renewed enthusiasm for aggressive therapy

Mortality has improved in specialized centers, however many patients still suffer significant mortality in less experienced centers
Conclusion

- Survival benefits have been more difficult to prove with significant studies demonstrating 5 year survival for all patients undergoing PD of around 10%

- True cure prognosis more dismal still

- No clear role for palliation with PD especially given endoscopic palliation

- Hope for improvements with immunotherapy, gene therapy, chemotherapy, radiation therapy
Conclusion

Lord Smith of Marlow: “Although the average long-term results of pancreaticoduodenectomy for cancer are poor, no man is an average and resection does provide the only chance of cure”¹

Dr. George Crile, Jr: “The question in carcinoma of the pancreas is whether we are going to select treatment on the basis of our hopes for cure of the patient or on the basis of the certainties about the duration of his survival as a member of a group”²
