Pancreaticoduodenectomy: The Whipple Procedure. Contributions from Yale

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Smilow Cancer Center

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Pancreaticoduodenectomy: The Whipple Procedure.
Contributions from Yale

No Disclosures

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A Case Report...

- **HPI:**
  - 60y.o. female with epigastric ‘fullness’ for seven years, history of duodenal diverticulum by radiograph
  - Ten weeks’ progressive jaundice, dark urine, anorexia, ten pounds of weight lost

- **Objective Findings:**
  - Deeply jaundiced female with palpable mass beneath right costal margin
  - Serum bilirubin - 6.8 mg/100 mL, Amylase – 13.4 mg/100mL

- **To the OR:**
  - Choledochoduodenostomy, cholecystostomy
  - Jaundice resolved, cholecystostomy spontaneously closed three weeks’ postop

- **Pathology indicates adenocarcinoma of the ampulla of Vater**

- **Return to the OR seven weeks later**
  - Resection of the head of the pancreas, ampulla, and medial aspect of duodenum
  - Pancreaticoenterostomy created from the remnant duodenal wall

- **The patient rapidly decompensated postoperatively and died approximately 30 hours after closure**
A Case Report...

What went wrong?

• Autopsy revealed complete dehiscence of the pancreatico-enterostomy

• Concern that the amylase rich fluid would preclude an anastomosis to the pancreas

• Two stage operation considered routine

• Pancreatic remnant oversewn
Early Pancreatic Resections at Yale

THE SURGERY OF CARCINOMA OF THE PANCREAS AND AMPULLARY REGION*

REPORT OF SIX ADDITIONAL CASES

SAMUEL C. HARVEY, M.D.,
AND
ASHLEY W. OUGHTERSON, M.D.
NEW HAVEN, CONN.

FROM THE DEPARTMENT OF SURGERY, YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN, CONN.

- First two-stage resection at Yale in May, 1941; patient survived three months
- First one-stage resection at Yale in July, 1941; alive for at least nine months after surgery
- Strong consideration was being made for a one-stage procedure with pancreatic re-anastomosis
- Pancreaticoduodenectomy in its current recognized form accepted by the late 1940’s
A procedure in evolution

- Operative Mortality 1970’s
  15-20%

- Length of Stay 25-35d

- Morbidity?
  - >50%
  - Serious ~30%
A routine procedure?

- Biliary Drain
- Pancreatic Drain
- Nasogastric Tube
- Gastrostomy/Jejunostomy
- Operative Drain(s)
A procedure in evolution

Optimal results obtained in high volume centers and high volume surgeons

• Operative Mortality
  - 1970’s: 15-20%  
  - 2000’s: <3%  
  - YNHH 2006-2016, n=403: 1.9%

• Length of Stay
  - 1970’s: 25-35d  
  - 2000’s: 8-11d  
  - YNHH 2006-2016, n=403: 7.7d

• Morbidity?
  - >50%  
  - Serious ~ 30%
Difficult Challenges Remain

• Improve our understanding of the etiology of morbidity

• Identify subgroups of patients:
  – High risk
  – Eligible for fast track discharge

• Modify management
  – Timely intervention
  – Simplify care
  – Early discharge

• ISGPS definitions of Complications
Difficult Challenges Remain

• **Delayed Gastric Emptying (DGE)**
  – Most common Whipple-specific complication
  – Incidence 13-44%; associated with increased lengths of stay
  – Definition? – international consensus, 2007
    • Postoperative nasogastric suction > 4 days
    • Reinitiation of nasogastric suction > POD#3
    • Inability to tolerate solid diet > POD#7

• **Postoperative Pancreatic Fistula (POPF)**
  – Most common cause of procedural re-intervention
  – Incidence 6-25%; course can be benign or severe
  – Definition? – international consensus, 2005
    • Any measurable drain output on or after POD#3 with an amylase content > 3x serum amylase
Comprehensive Analysis of Variables Affecting Delayed Gastric Emptying Following Pancreaticoduodenectomy

John W. Kunstman · Annabelle L. Fonseca · Maria M. Ciarleglio · Xiangyu Cong · Abby Hochberg · Ronald R. Salem

- Age
- Gender
- Indication – Malignant/Benign
- Surgery – Pylorus-preserving/Classic
- Gastric continuity – Retrocolic/Antecolic
- Operative blood loss
- Operative crystalloid infusion
- Operative colloid infusion
- Operative transfusion
- Operative urine output
- Routine nasogastric tube placement
- Routine operative drain placement
- Diabetes mellitus
- Hypertension
- Pre-operative pancreatitis
- Pulmonary disease
- Coronary artery disease
- Renal function (creatinine)
- Aggregate comorbidity score
- Intra-abdominal abscess
- Pancreatic fistula formation
- Biliary/gastric anastomotic leak
- Wound infection
Comprehensive Analysis of Variables Affecting Delayed Gastric Emptying Following Pancreaticoduodenectomy

- \( N = 235 \)
- \( \text{DGE} = 42 \) (17.9%)

<table>
<thead>
<tr>
<th>Variables significantly correlated with increased DGE incidence</th>
<th>( P ) value, univariate</th>
<th>( P ) value, multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic fistula formation</td>
<td>0.0003</td>
<td>0.0024</td>
</tr>
<tr>
<td>Comorbid pulmonary disease</td>
<td>0.0032</td>
<td>0.0045</td>
</tr>
<tr>
<td>Operative Period</td>
<td>0.0072</td>
<td>NS</td>
</tr>
<tr>
<td>Intra-operative blood loss</td>
<td>0.0168</td>
<td>0.0422</td>
</tr>
<tr>
<td>Intra-operative crystalloid infusion</td>
<td>0.0177</td>
<td>NS</td>
</tr>
<tr>
<td>NGT placement</td>
<td>0.0207</td>
<td>NS</td>
</tr>
<tr>
<td>Intra-abdominal abscess formation</td>
<td>0.0208</td>
<td>0.0139</td>
</tr>
<tr>
<td>Intra-peritoneal drain placement</td>
<td>0.0287</td>
<td>NS</td>
</tr>
<tr>
<td>Aggregate comorbidity</td>
<td>0.0288</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Conclusion: Perturbation of the operative bed by a secondary complication is dominant risk factor for DGE incidence.

**Hypothesis:** The majority of patients undergoing a Whipple procedure can forgo routine NG tube placement

<table>
<thead>
<tr>
<th>Routine NGT</th>
<th>Selective NGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>125</td>
</tr>
<tr>
<td>125 (100%)</td>
<td>9 (7.2%)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1.70 median</td>
<td>1.67 mean</td>
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</table>
### Nasogastric Drainage May Be Unnecessary after Pancreaticoduodenectomy: A Comparison of Routine vs Selective Decompression

<table>
<thead>
<tr>
<th></th>
<th>Routine NGT</th>
<th>Selective NGT</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-insertion/insertion of NGT</td>
<td>15 (12.0%)</td>
<td>10 (8.0%)</td>
<td>0.292</td>
</tr>
<tr>
<td>Time to Diet Tolerance, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>9.15 (1.60)</td>
<td>4.9 (0.40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>3 – 163</td>
<td>3 – 33</td>
<td></td>
</tr>
<tr>
<td>Length of Stay, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>10.47 (1.01)</td>
<td>6.82 (0.36)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>5 – 86</td>
<td>4 – 35</td>
<td></td>
</tr>
</tbody>
</table>

- In the selective group, 84.8% of patients spared NGT completely, with no increase in NGT replacement, LOS, dietary tolerance, or operative morbidity

- **Conclusion:** As in other forms of abdominal surgery, selective NGT placement appears an acceptable treatment strategy

Operative Drains and Pancreatic Fistulae

- Placement of operative drains following pancreaticoduodenectomy is practiced by most surgeons
  - Detection and possibly mitigation of pancreatic fistulas
  - Early drainage of biliary or enteric anastomotic leakage

- The need for mandatory drainage was challenged since at least 2001, but remains very controversial.

Prospective Randomized Clinical Trial of the Value of Intraperitoneal Drainage After Pancreatic Resection

Kevin C. Conlon, MD, MBA,* Daniel Labow, MD,* Dennis Leung, PhD,† Alex Smith, MA,† William Jarnagin, MD,*
Daniel G. Coit, MD,* Nipum Merchant, MD,* and Murray F. Brennan, MD*

Based on these results, closed suction drainage should not be considered mandatory or standard after pancreatic resection.

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What does the Yale Data demonstrate?

• Two consecutive cohorts, 50 patients each
  – Group 1 - Selective drainage (30%)
  – Group 2 - No drainage

  – Group 1 - POPF 22.6%
  – Group 2 - POPF 7.5%

• No increased morbidity
• No increased need for procedural intervention
What does the Yale Data demonstrate?

• **Highly selective drainage:** Validation cohort
  
  – Operative drains in 7 patients (3%)
  – Drains placed for concern for anastomotic fidelity or in obvious contaminated field
  – Series of 237 patients analyzed with 3 deaths (1.3%)

• **Conclusion:** *In properly selected patients:*

  Pancreaticoduodenectomy Can Be Performed Safely With Rare Employment of Surgical Drains

*Kunstman J, Starker L, Healy J and Salem RR: Am Surg 2017*
How to select low-risk patients?

- Identified four key risk factors for fistula formation:
  - Pancreatic texture (firmer = better)
  - Indication for surgery (pancreatic cancer = better)
  - Size of pancreatic duct (larger = better)
  - Operative blood loss (less EBL = better)
How to select low-risk patients?

A Prospectively Validated Clinical Risk Score Accurately Predicts Pancreatic Fistula after Pancreatoduodenectomy

Mark P Callery, MD, FACS, Wande B Pratt, MD, MPH, Tara S Kent, MD, FACS, Elliot L Chaikof, MD, PhD, FACS, Charles M Vollmer Jr, MD, FACS
Evaluation of a recently described risk classification scheme for pancreatic fistulae development after pancreaticoduodenectomy without routine post-operative drainage

John W. Kunstman MD, Eric Kuo MD, Annabelle L. Fonseca MD, Ronald R Salem MB, ChB

- Regarding the FRS metric:
  - Patients at YNHH tend to have a lower-risk FRS
  - The negative predictive value of the FRS is strong
  - The positive predictive value of the FRS is modest

![Graph showing Fistula risk score (points) vs Total patients and Total fistulae]
Does the FRS work in patients without drains?

- Patients without drains that developed fistulas:
  - Present later
  - Often present on readmission
  - Diagnosis and treatment are the same as patients with drains
  - Outcomes do not seem to be adversely affected

- Can alternate objective data substitute for lack of a drain?
Type of Anastomosis: Pancreaticogastrostomy vs. Pancreaticojejunostomy?

- Does anastomosing the pancreas to the stomach create a more durable anastomosis that is less likely to leak than anastomosing it to the jejunum in the routine fashion?

- Several manuscripts favored PG vs. PJ creating increased interest in this anastomosis particularly in Europe
  - Most recommended with soft pancreas and narrow PD

- Conflicting Data in US

- Problems with available studies:
  - Insufficiently powered
  - Not stratified to account for risk score
Type of Anastomosis: Pancreaticogastrostomy vs. Pancreaticojejunostomy?

Pancreatogastrostomy vs. Pancreatojejunostomy: A Risk-Stratified Analysis of 5,316 Pancreatoduodenectomies

Brett L. Ecker, MD1, Matthew T. McMillan, BA1, Laura Maggino, MD1,2, Valentina Allegrini, MD2, Horacio J. Asbun, MD3, Chad G. Ball, MD, MSc4, Claudio Bassi, MD2, Joal D. Beane, MD5, Stephen W. Behrman, MD6, Adam C. Berger, MD7, Mark Bloomston, MD8, Mark P. Callery, MD9, John D. Christein, MD10, Euan Dickson, MD11, Elijah Dixon, MD, MSc4, Jeffrey A. Drebin, MD, PhD1, Carlos Fernandez-Del Castillo, MD12, William E. Fisher, MD13, Zhi Ven Fong, MD12, Ericka Haverick, BSN8, Robert H. Hollis, MD10, Michael G. House, MD5, Steven J. Hughes, MD14, Nigel B. Jamieson, MD11, Tara S. Kent, MD9, Stacy J. Kowalsky, MD15, John W. Kunstman, MD16, Giuseppe Malleo, MD2, Ronald R. Salem, MD16, Kevin C. Soares, MD17, Vicente Valero III, MD17, Ammara A. Watkins, MD9, Christopher L. Wolfgang, MD, PhD17, Amer H. Zureikat, MD15, and Charles M. Vollmer Jr., MD1
Pancreatogastrostomy vs. Pancreatojejunostomy: A Risk-Stratified Analysis of 5,316 Pancreatoduodenectomies

- PG not associated with improved fistula rates within any risk zone
C-reactive protein – A new marker for morbidity?

- C-reactive protein (CRP) is an acute-phase reactant that binds surface receptors of dying cells

- Correlates with anastomotic leaks in the GI tract; most notably in colorectal anastomoses

**Hypothesis:** CRP correlates with pancreatic fistula formation following a Whipple
  - CRP measured daily in patients postoperatively (N = 140)
C-reactive protein – A new marker for morbidity?

• **Preliminary Findings:**
  – On POD#2, mean CRP was increased from 196±66 to 271±46 in patients who were ultimately found to harbor a fistula or abscess ($p<0.001$)

  - Mathematical modelling revealed two best fit scenarios:
    - On POD#2-4 maximum CRP > 275mg/L 96% sensitivity in predicting POPF or abscess
    - If POD#2-4 mean CRP > 275mg/L 86% specific in predicting POPF or abscess
    - Using both measurements provides excellent accuracy minimizing false positives or negatives

    - CRP < 200mg/L on POD#3 negative predictive value of 98.7% for POPF or abscess (applied to 47% of patients)

  – CRP has better predictive value for abscess and fistula than fever, WBC or platelet count
  – Addition of CRP to Fistula Risk Score improved prediction POPF compared to FRS alone
**Whipple Procedure:**

**Recent outcome data:**

**Most Recent 160 patients:**

- NG 3 1.8%
  - Subsequent 15 9.4%
- Drains 12 7.5%
- ICU stay 1 day
- DGE 26 16%
- POPF 19 11%
- Blood Tx 7 4.4%
- LOS (median) 5 days
- Mortality 1 0.6%
Whipple Procedure:
Borderline and Locally Advanced Pancreas Cancer

Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer

Stacey M Stein¹,⁷, Edward S James¹,⁷, Yanhong Deng², Xiangyu Cong², Jeremy S Kortmansky¹, Jia Li¹,³, Carol Staugaard¹, Doddamane Indukala⁴, Ann Marie Boustani⁴, Vatsal Patel⁴, Charles H Cha⁵, Ronald R Salem⁵, Bryan Chang⁶, Howard S Hochster¹ and Jill Lacy*¹
Whipple Procedure:  
Phase II.  
mFOLFIRINOX

- 31 Patients, Locally Advanced Pancreas Cancer
- 44 Patients, Metastatic Pancreas Cancer

- All treated with modified FOLFIRINOX
  - 20 unresectable, 11 borderline resectable
  - No disease progression on therapy
  - 13 proceeded to surgical resection
  - All patients who underwent surgery had R0 resection
Whipple Procedure:  
Phase II.  
*mFOLFIRINOX*

LAPC cohort who underwent resection (13)

- All underwent R0 resection
- 6 patients received radiation therapy post FOLFIRINOX
- At median follow up of 24 months

  - Median Overall Survival not reached
  - 10 patients alive
  - 6 patients free of disease
Phase II.  \textit{mFOLFIRINOX}

- Conclusions relevant to surgical resection:
  - Progression of disease on therapy is unlikely
  - RO resection is possible in properly selected patients
  - No significant increase in morbidity should be expected
BRCA2 mFOLFIRINOX
mFOLFIRINOX
mFOLFIRINOX  RT
Summary

• Pancreaticoduodenectomy is an ever-evolving procedure
  – Can be performed safely, especially in a high-volume environment
  – Current surgical efforts focus on minimizing morbidity

• Future postoperative management will be patient-specific, rather than dogmatic
  – Many patients do not require routine nasogastric decompression
  – Many patients may forgo operative drain placement

• Adjuncts, such as the fistula risk score and CRP measurement, will assist in selecting patients for fast-track discharge or earlier intervention

• Improvements in systemic therapy may allow R0 resection in patients presenting with Locally Advanced and Borderline Resectable tumors