Treatment Approaches in Pancreatic Cancer

George Van Buren, II, MD
Assistant Professor of Surgery
Elkins Pancreas Center
Baylor College of Medicine
March 10, 2016

Disclosure

• No conflict of interest
Objectives

• Understand the preoperative management of pancreatic cancer
• Discuss surgical options for cancer
• Recognize the role of recent surgical advances in pancreatic cancer
• Discuss future areas for improvement in pancreatic cancer

Surgical Anatomy

• Lies transversely in the retroperitoneum
• Duodenum on the right and inferiorly
• Spleen on the left
• Stomach anteriorly (lesser sac aka omental bursa)
• Transverse mesocolon anteroinferiorly
Pancreatic Adenocarcinoma: Statistics

- 4th Leading Cause of Cancer Death
- Lifetime risk of ~ 1/80
- Incidence 53,070
- Deaths 41,780
- Incidence increasing 1.5%/year

- 1-Year Survival (All Stages) 23%
- 5-Year Survival (All Stages) 8%
  - Stage I, Resected 23%

Cancer Facts and Figures 2016, American Cancer Society
### Trends in 5-Year US Survival Rates: 1975-2011

<table>
<thead>
<tr>
<th>ALL RACES</th>
<th>1975 TO 1977</th>
<th>1987 TO 1989</th>
<th>2005 TO 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>49</td>
<td>55</td>
<td>69†</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>22</td>
<td>29</td>
<td>35†</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>84</td>
<td>91†</td>
</tr>
<tr>
<td>Colorectum</td>
<td>50</td>
<td>60</td>
<td>66†</td>
</tr>
<tr>
<td>Esophagus</td>
<td>5</td>
<td>10</td>
<td>20†</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>72</td>
<td>79</td>
<td>88†</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>50</td>
<td>57</td>
<td>74†</td>
</tr>
<tr>
<td>Larynx</td>
<td>66</td>
<td>66</td>
<td>63†</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34</td>
<td>43</td>
<td>62†</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>3</td>
<td>5</td>
<td>18†</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>12</td>
<td>13</td>
<td>18†</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>82</td>
<td>88</td>
<td>93†</td>
</tr>
<tr>
<td>Myeloma</td>
<td>25</td>
<td>27</td>
<td>49†</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>47</td>
<td>51</td>
<td>72†</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>53</td>
<td>54</td>
<td>66†</td>
</tr>
<tr>
<td>Ovary</td>
<td>36</td>
<td>38</td>
<td>46†</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>4</td>
<td>8†</td>
</tr>
<tr>
<td>Prostate</td>
<td>68</td>
<td>83</td>
<td>99†</td>
</tr>
<tr>
<td>Stomach</td>
<td>15</td>
<td>20</td>
<td>30†</td>
</tr>
<tr>
<td>Testis</td>
<td>83</td>
<td>95</td>
<td>97†</td>
</tr>
<tr>
<td>Thyroid</td>
<td>92</td>
<td>94</td>
<td>98†</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>72</td>
<td>79</td>
<td>79†</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>69</td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>87</td>
<td>82</td>
<td>83†</td>
</tr>
</tbody>
</table>

#### Tumors of the Pancreas – Usually Exocrine

- **Head**: 60-70%
- **Neck/Body**: 5-10%
- **Tail**: 10-15%
- **Diffuse tumors involving entire gland**: 20%

- No histological difference between sites
- Carcinoma of the head
  - Obstructs bile duct
  - Ulcerates duodenal mucosa
- Carcinoma of the tail
  - Remains silent longer
  - Large & widely disseminated
Preoperative Management
Initial goals in the evaluation and treatment of patients with suspected pancreatic cancer are:

- Obtain a histologic diagnosis
- Safely establish biliary decompression
- Determine resectability
- Develop a stage-specific treatment strategy.

The most important initial step is to accurately classify patients into:

- Resectable (stages I and II),
- Unresectable (unresectable, stage III), and
- Metastatic (stage IV) groups based on radiographic imaging.

Pancreatic Cancer Staging

Exocrine and Endocrine Pancreas Staging - AJCC 7th Edition

ANATOMIC STAGE/PROGNOSTIC GROUPS

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Primary Tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
- T2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
- T3: Tumors extends beyond the pancreas but without involvement of the celiac axis or superior mesenteric artery
- T4: Tumor involves the celiac axis or superior mesenteric artery (unresectable primary tumor)

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

Distant Metastasis (M)

- M0: No distant metastasis
- M1: Distant metastasis

Pancreatic Protocol CT Scan

- CT scan of the abdomen, and pelvis is required for all patients.
- Triphasic thin (#5 mm), multislice CT scan
  - Arterial, venous, and delayed phase
    - in conjunction with sagittal and coronal views.
- Water is used to opacify the stomach.
- Purpose of the scan is to:
  - detect any metastatic disease
  - assess the relationship of the tumor to the surrounding vasculature.
- Particular attention is paid to the relationship of the tumor to:
  - portal vein (PV), superior mesenteric vein (SMV), superior mesenteric artery (SMA), hepatic artery, and celiac axis.
- Will aid in identification of aberrant anatomy of the hepatic artery
  - present in 20% of cases and must be noted prior to surgery.

EUS

EUS Imaging of Pancreas Mass
Endoscopic Ultrasound (EUS)

- Performed to obtain a tissue diagnosis of a solid mass
- Biopsy can give information if high grade or low grade tumor
- May be used as an adjunct to the CT scan
- Further evaluate venous involvement
- Sensitive test for portal vein > SMA involvement
- Can detect small pancreatic masses missed by CT
- Fine needle aspiration for tissue Dx if neoadjuvant

Endoscopic retrograde cholangiopancreatography (ERCP)

- Specialized technique used to study the bile ducts, pancreatic duct and gallbladder.
- ERCP may be used to:
  - Open the entry of the ducts into the bowel (sphincterotomy)
  - Stretch out narrow segments (bile duct strictures)
  - Remove or crush gallstones
  - Diagnose conditions such as biliary cirrhosis or sclerosing cholangitis
  - Take tissue samples to diagnose a tumor of the pancreas, bile ducts, or gallbladder
  - Drain blocked areas
  - Place stent
Staging Laparoscopy
A Selective Approach

- Large primary tumor (>4 cm)
- Tumor in the body or tail of the pancreas
- Equivocal findings of metastasis on CT
- Presence of ascites
- Severe weight loss (>20 pounds)
- Hypoalbuminemia
- Markedly elevated CA 19-9
- Locally advanced disease (if clinical trial planned)


Classifying Resectability

- Resectable
  - 17 to 23 month median survival
- Borderline resectable
  - Up to 20 month median survival
- Locally advanced/unresectable
  - 8-14 month median survival
- Metastatic
  - 4-6 month median survival
How do we define resectable vs borderline vs unresectable?

Resectability

• Relationship of tumor to vasculature
Resectable

- No distant metastases
- Clear fat plane around celiac, hepatic and superior mesenteric arteries
- No abutment of superior mesenteric vein or portal vein

80% accurate

Borderline Resectable

- No distant metastases
- SMV/PV
  - Tumor abutment with impingement and narrowing of the lumen
  - Encasement or thrombus with proximal and distal vein segment that allows for reconstruction
- Hepatic artery
  - Short segment encasement or abutment
- SMA
  - Abutment only

AHPSA/SSOS/SSAT Consensus Conference on Resectable and Borderline Resectable Pancreatic Cancer: Rationale and Overview of the Conference

1. Tumors considered localized and resectable should demonstrate the following:
   a. No distant metastases.
   b. No radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement.
   c. Clear fat planes around the celiac axis, hepatic artery, and SMA.

2. Tumors considered borderline resectable include the following:
   a. No distant metastases.
   b. Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with usable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
   c. Gastric/duodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
   d. Tumor abutment of the SMA not to exceed >180° of the circumference of the vessel wall.
• Katz 2008 reported 160 patients with borderline resectable disease (using the Varadhachary definition)

• Introduced three types of borderline resectable disease, now often referred to as Katz type A, B, and C.

• Type A (Anatomic):
  – borderline resectable tumor anatomy as defined in the Varadhachary manuscript.

• Type B (Oncologic/Biologic):
  – borderline resectable because of a concern for possible extrapancreatic metastatic disease and included those with CT findings suspicious for, but not diagnostic of, metastatic disease as well as those with known local-regional lymph node metastases.

• Type C (Physiologic):
  – borderline resectable due to marginal performance status or significant pre-existing medical comorbidity thought to require protracted evaluation that precluded immediate surgery.
Locally Advanced Unresectable

Once we have defined resectability, we need to decide how to treat the patient
Surgery is Most Effective Treatment for Pancreatic Cancer

![Graph showing survival rates for early stage pancreatic cancer patients after surgery, no treatment, and radiation therapy.](image)

**Table 4**

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of patients (%)</th>
<th>1-y</th>
<th>2-y</th>
<th>3-y</th>
<th>4-y</th>
<th>5-y</th>
<th>Median survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>5298 (4.4%)</td>
<td>44.6%</td>
<td>24.6%</td>
<td>18.5%</td>
<td>15.3%</td>
<td>13.6%</td>
<td>10.0</td>
</tr>
<tr>
<td>IB</td>
<td>6992 (5.4%)</td>
<td>40.6%</td>
<td>22.0%</td>
<td>16.1%</td>
<td>15.9%</td>
<td>11.7%</td>
<td>9.1</td>
</tr>
<tr>
<td>II A</td>
<td>12,222 (10.1%)</td>
<td>38.1%</td>
<td>16.2%</td>
<td>10.2%</td>
<td>7.7%</td>
<td>6.5%</td>
<td>6.1</td>
</tr>
<tr>
<td>II B</td>
<td>14,398 (11.8%)</td>
<td>65.9%</td>
<td>16.5%</td>
<td>9.8%</td>
<td>6.7%</td>
<td>5.1%</td>
<td>9.7</td>
</tr>
<tr>
<td>III</td>
<td>15,481 (13.0%)</td>
<td>30.2%</td>
<td>9.5%</td>
<td>4.8%</td>
<td>3.5%</td>
<td>2.7%</td>
<td>7.7</td>
</tr>
<tr>
<td>IV F</td>
<td>65,162 (55.2%)</td>
<td>8.8%</td>
<td>2.5%</td>
<td>1.6%</td>
<td>0.9%</td>
<td>0.7%</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Total** | 131,713 | 10.0 | 9.1 | 6.5 | 6.1 | 9.7 | 7.7 |

**Validation of the 6th Edition AJCC Pancreatic Cancer Staging System**

Report from the National Cancer Database

Bilimoria. Cancer. 2007
Whipple

• First published report of a successful pancreaticoduodenectomy (PD) was published by Allen O. Whipple in 1935.

• Whipple reported 3 patients who underwent a 2-stage procedure with pancreatic duct ligation:
  – one patient died in the perioperative period
  – another died 8 months later from cholangitis
  – the last from metastases after 28 months.

Zeh et al. Advances in Surgery. 2011

Whipple

• Initial report was followed by a series describing a single-stage procedure, the fundamentals of which we recognize today as the Whipple procedure.

• These fundamentals included
  – resection and reconstruction in one stage
  – avoidance of cholecystoenterostomy by implantation of the bile duct into the jejunum,
  – implantation of the pancreatic duct into the jejunum.

Zeh et al. Advances in Surgery. 2011
Whipple
Mortality rates of 30% were common for several decades.

In 1968 John Howard reported a series of 41 consecutive PDs without a mortality.

Attention to surgical detail combined with advances in critical care and anesthesia have led to steady and dramatic improvements in postoperative outcomes following pancreaticoduodenectomy.

Recent reports demonstrate a morbidity rate of 30% to 40% with 1% to 5% mortality.

Zeh et al. Advances in Surgery. 2011

Whipple Procedure Becoming Safer

Patients were categorized into subgroups according to the decade in which they underwent an operation (the 1980s, 1990s, or 2000s) and trends in short-, intermediate-, and long-term outcomes were examined.

Multimodality Therapy

- The limited efficacy of surgery for pancreas cancer has led to the development of multimodality protocols combining surgery with chemotherapy and radiation in an effort to improve survival.

- Surgical resection with subsequent adjuvant chemotherapy has demonstrated increase survival as compared to surgery alone, however, the overall survival for both groups remains dismal.

Neoptolemos (FU) NEJM 2004; oettle (gem)JAMA 2007
Adjuvant Treatment-CONKO-001

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Gemcitabine</th>
<th>Surgery Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>179</td>
<td>175</td>
</tr>
<tr>
<td>PD</td>
<td>140 (81%)</td>
<td>146 (85%)</td>
</tr>
<tr>
<td>N</td>
<td>34 (19%)</td>
<td>27 (15%)</td>
</tr>
<tr>
<td>N*</td>
<td>52 (29%)</td>
<td>48 (27%)</td>
</tr>
<tr>
<td>N*</td>
<td>127 (70%)</td>
<td>127 (71%)</td>
</tr>
</tbody>
</table>

Adjuvant Treatment-Summary

- Gemcitabine x 6 months **doubles** overall survival at 5 years
- Role of adjuvant radiation is yet undefined after almost 30 years of study
- 5FU CRT better than observation
- Gemcitabine CRT appears superior to 5FU CRT (RTOG 9704)
- NCCN guidelines allow for both chemotherapy alone or chemoradiation as adjuvant therapy

**TABLE 2** Prospective and randomized trials evaluating adjuvant therapy vs. surgery alone for pancreatic cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample size</th>
<th>Treatment arm</th>
<th>Median survival (vs. surgery alone)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>1985</td>
<td>43</td>
<td>XRT + 5 FU</td>
<td>20 (vs. 11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Takada et al.</td>
<td>2002</td>
<td>158</td>
<td>MMC + 5 FU</td>
<td>13.5 (vs. 15.5)</td>
<td>NS</td>
</tr>
<tr>
<td>ESPAC 1</td>
<td>2004</td>
<td>289</td>
<td>XRT + 5 FU or XRT + 5 FU*</td>
<td>20.1 months (vs. 15.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Konige et al.</td>
<td>2006</td>
<td>89</td>
<td>5 FU + Cisplatin</td>
<td>12.9 (vs. 15.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>CONKO 001</td>
<td>2007</td>
<td>568</td>
<td>Gemcitabine</td>
<td>22.1 (vs. 20.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>EORTC 2204</td>
<td>2007</td>
<td>123</td>
<td>XRT + 5 FU</td>
<td>15.6 (vs. 12.0)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

XRT radiotherapy, 5 FU 5-flourouracil, MMC mitomycin C

* The nonchemotherapy arm included patients receiving surgery plus XRT and surgery alone
* The primary end point of this study included patients with periampullary cancers, but data from the subgroup with pancreatic head cancers are also included here
What is the role of neoadjuvant therapy?

“Advantages” Neoadjuvant Therapy

- All patients get intended therapy unlike adjuvant trials
  - 25-30% of patients untreated in CONKO-001
  - Delays caused by postop recovery and complications
- Potential for improving rate of surgical resection and R0 resection rate
- Improved efficacy relative to adjuvant Rx due to intact tumor vasculature
  - Avoidance of hypoxia-induced resistance factors
  - More effective chemotherapy delivery with an intact blood supply,
- Immediate treatment of undetected systemic disease without delay
- Optimal patient selection for surgery through exclusion of patients with rapidly progressive metastatic disease
  - Spares patients with rapid progression from unnecessary surgery

-Crane et al. Best Practice & Research Clinical Gastroenterology Vol. 20, No. 2, pp. 365-382, 2006
-Evans et al. Preoperative Gemcitabine based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. JCO 2008
Resected 36 mo vs Not Resected 7 mo

### Table 3. Published Experience With Preoperative Gemcitabine-Based Chemoradiation and Surgery for Localized Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>28</td>
<td>20</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td>Gemcitabine dose, mg/m²²</td>
<td>300-500 weekly</td>
<td>50 2×/week</td>
<td>1,000 weekly</td>
<td>1,000 weekly</td>
<td>400 weekly</td>
</tr>
<tr>
<td>Radiation dose, Gy</td>
<td>50.4</td>
<td>50.4</td>
<td>36</td>
<td>None</td>
<td>30</td>
</tr>
<tr>
<td>Median survival of all patients, months</td>
<td>NA</td>
<td>25</td>
<td>NA</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>Median survival of resected patients, months</td>
<td>NA</td>
<td>17</td>
<td>27</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Median survival of patients not resected, months</td>
<td>NA</td>
<td>26</td>
<td>28</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable
*Radiation therapy was not administered, and 26 of the 50 patients also received cisplatin 25 mg/m²².
In patients with metastatic pancreatic adenocarcinoma, nab-paclitaxel plus gemcitabine significantly improved overall survival, progression-free survival, and response rate, but rates of peripheral neuropathy and myelosuppression were increased.

Demonstrated a significant improvement in OS compared to patients receiving gemcitabine alone [(median of 8.5 vs. 6.7 months) (HR 0.72, P=0.000015)].
Technical Advances

Laparoscopic/Robotic Pancreatic Surgery
Perception Trumps Reality

Clinical, pretreatment Stage I  
(N = 9,559)

Surgery  
2,736 (28.6%)

Pancreatectomy  
2,630 (27.5%)

Unresectable  
106 (1.1%)

No Surgery  
6,823 (71.4%)

Not Offered Surgery  
3,644 (38.2%)

Patient Refused  
403 (4.2%)

Advanced Age  
869 (9.1%)

Unknown  
1,291 (13.5%)

Comorbidities  
616 (6.4%)

Bilimoria K, National Failure to Operate on Early Stage Pancreatic Cancer, Ann Surg 2007 Aug

Goals of Robotic Pancreas Program

• Major objectives
  – Reproduce open technique and outcomes
  – Widely applicable
  – Quality Assurance

• Rule out Disadvantages
  – Equivalent safety?
  – Learning curve and time investment

• Explore Potential Advantages
  – Decrease peri-operative morbidity/blood transfusions
  – Earlier adjuvant chemotherapy
### Table 3. Perioperative outcomes following laparoscopic and robotic-assisted distal pancreatocemy

<table>
<thead>
<tr>
<th>Outcome Parameter</th>
<th>LDP N=94</th>
<th>RDP N=30</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure duration (min ± SD)</td>
<td>372 ± 141</td>
<td>293 ± 93</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Planned splenectomy (%)</td>
<td>77 (82)</td>
<td>28 (93%)</td>
<td>0.157</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>150 (100, 300)</td>
<td>150 (100, 300)</td>
<td>0.688</td>
</tr>
<tr>
<td>Frequency of blood transfusion (%)</td>
<td>12 (13)</td>
<td>3 (10%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Average units transfused</td>
<td>2.23 ± 1.36</td>
<td>2.31 ± 0.38</td>
<td>0.921</td>
</tr>
<tr>
<td>Median EBL (ml) in upper quartile (75th percentile for blood loss)</td>
<td>550 (400, 650)</td>
<td>375 (300, 550)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Converted to open</td>
<td>15 (16)</td>
<td>0 (0%)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Postoperative admission to ICU</td>
<td>31 (33)</td>
<td>7 (23)</td>
<td>0.370</td>
</tr>
<tr>
<td>Pancreatic fistula</td>
<td>39 (41)</td>
<td>14 (46)</td>
<td>0.676</td>
</tr>
<tr>
<td>ISGPF Grade A</td>
<td>23 (24)</td>
<td>6 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>ISGPF Grade B</td>
<td>11 (12)</td>
<td>4 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>ISGPF Grade C</td>
<td>5 (5)</td>
<td>4 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>90-day morbidity</td>
<td>0.658</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor (Clavien 1/2)*</td>
<td>47 (50)</td>
<td>14 (46)</td>
<td></td>
</tr>
<tr>
<td>Major (Clavien 3/4)*</td>
<td>13 (14)</td>
<td>6 (20)</td>
<td></td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>7.1 ± 4.0</td>
<td>6.1 ± 1.7</td>
<td>0.183</td>
</tr>
<tr>
<td>90-day readmission</td>
<td>22 (23)</td>
<td>11 (37)</td>
<td>0.162</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1 (1.1)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Normally-distributed values are expressed as mean ± SD or n (%); otherwise: median (25th, 75th percentile) as interquartile range (IQR).

*Clavien classification of surgical complications.¹⁶


### LDP vs RDP: Pathologic Outcomes

#### Table 4. Pathologic outcomes following distal pancreatocemy for pancreatic ductal adenocarcinoma (PDA)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LDP</th>
<th>RADP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (n, %)</td>
<td>14 (19)</td>
<td>13 (43)</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>3.4 ± 1.6</td>
<td>3.1 ± 1.2</td>
<td>0.604</td>
</tr>
<tr>
<td>R1 margin status</td>
<td>7 (50)</td>
<td>0 (0)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Nodal harvest (median, IQR)</td>
<td>9 (7, 11)</td>
<td>19 (17, 24)</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Normally-distributed values are expressed as mean ± SD or n (%); otherwise: median (25th, 75th percentile) as interquartile range (IQR).

Robotic Pancreaticoduodenectomy

Pathologic Outcomes

Table 4: Pathologic outcomes following RAPD for invasive periampullary adenocarcinoma

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PDA, Amp, CCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>TNM* (n=25)</td>
<td></td>
</tr>
<tr>
<td>T1N0</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>T2N0</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>T2N1</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>T3N0</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>T3N1</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>T4N1</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>AJCC Stage</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>IB</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>IIA</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>IIB</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Tumor Size (cm)</td>
<td>2.7 cm, IQR 0.7</td>
</tr>
<tr>
<td>Lymph nodes harvested</td>
<td>18, IQR 5</td>
</tr>
<tr>
<td>R0 margin</td>
<td>33 (89%)</td>
</tr>
<tr>
<td>R1 margin</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Adjuvant tx indicated (n=15)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Adjuvant tx duration (wks)</td>
<td>11.5 (8.8–12.5)</td>
</tr>
</tbody>
</table>

Data presented as median (IQR), or n (%) for PDA, AMP, and CCA only.

The need for VR had no impact on survival duration.

In conclusion, properly selected patients with adenocarcinoma of the pancreatic head who require VR have a median survival of approximately 2 years, which does not differ from those who undergo standard PD and is superior to historical patients believed to have locally advanced disease treated nonoperatively.

Genomic Advances
Exome of 100 PDAC tumors Sequenced

- Significantly mutated gene list (16)
- Multiple genes (average 26)/variability
- DNA Damage repair, Chromatin Modification and Axon guidance pathway genes


Circulating DNA
Early Diagnostic Test

- Can we detect circulating tumor DNA in patients with PDAC? Could this be used as an early diagnostic test?
- Does the presence or quantity of circulating tumor DNA correlate with prognosis, response to treatment, disease recurrence?
- One such approach is through a **LIQUID BIOPSY**, where the genetic makeup of the tumor can be assessed through a biofluid sample.
- Liquid biopsies have the potential to help clinicians:
  - screen for disease,
  - stratify patients to the best treatment
  - monitor treatment response and resistance mechanisms in the tumor.
- A liquid biopsy can be used for molecular characterization of the tumor and its non-invasive nature allows repeat sampling to monitor genetic changes over time without the need for a tissue biopsy.
- Three approaches in the liquid biopsy field:
  - circulating tumor cells (CTCs),
  - cell free DNA (cfDNA)
  - exosomes.

Immunotherapy

- Wide range of vaccines
- Immune antibodies
- Chimeric antigen receptors (CARs) are recombinant receptors that combine the specificity of an antigen-specific antibody with the activating functions of T cells
- Adoptive cell transfer approach, T cells are removed from the tumor tissue (tumor-infiltrating lymphocytes), expanded ex vivo, and reinfused back to the patient at cell doses of approximately $1 \times 10^9$ cells following a nonmyeloablative lymphocyte-depleting preparative regimen.

<table>
<thead>
<tr>
<th>Table 1. Vaccine trials in progress</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigator/institution</strong></td>
</tr>
<tr>
<td>Multinational</td>
</tr>
<tr>
<td>Le. Dong + John Hopkins</td>
</tr>
<tr>
<td>Lebera, Decurtins + John Hopkins</td>
</tr>
<tr>
<td>Czerwinski, Emansson East Carolina</td>
</tr>
<tr>
<td>Le. Dong + John Hopkins</td>
</tr>
<tr>
<td>Goriti, Minakawa Tokiohaus</td>
</tr>
<tr>
<td>Pego, Elizabeth CMIMT</td>
</tr>
<tr>
<td>Bond, Philip CMIMT</td>
</tr>
</tbody>
</table>
Genetic Analysis of Pancreatic Cyst Fluid

Where do we go from here?
Final Conclusions

• Surgery for resectable disease is still considered the standard of care

• We are improving with chemotherapeutic regimens
  – FOLFIRINOX and ABRAXANE in the adjuvant and neoadjuvant setting
  – Improved pathologic response in neoadjuvant FOLFIRINOX
  – New targets from genetic characterization

• Earlier surgery for premalignant lesions

• Patient selection will be KEY
  – Personalized therapy based on molecular and genetic characteristics
  – Who should have aggressive surgery?

• Early detection
  – Better stratification of cystic lesions
  – Development of a blood test

• There is still work to be done!

George Van Bure, II, MD
Assistant Professor of Surgery
Elkins Pancreas Center
Baylor College of Medicine
George.vanbure@bcm.edu
Clinic: 713-798-2262