Pancreatic Cancer: Current Management and Outcomes
Is There Hope on the Horizon?

110th
Sommer Memorial Lecture Series
Portland, Oregon

Keith D. Lillemoe, M.D.
Chief of Surgery
Massachusetts General Hospital
Background

• 53,670 patients will develop pancreatic adenocarcinoma
• 3rd leading cause of cancer death
• Risk Factors
  • Smoking
  • Pancreatitis
  • Genetics

American Cancer Society . 2017 Facts.
Background

- Presentation
  - 50% metastatic disease
  - 30% locally advanced disease
  - 20% resectable disease

- Median survival
  - 6mo - metastatic
  - 11mo - locally advanced
  - 22mo - resectable
Pancreatic Cancer
Nihilistic Attitude

- Population studies suggest many patients with resectable cancers are not offered surgery
- Social/economic and racial disparities
Health Insurance Expansion and Treatment of Pancreatic Cancer: Does Increased Access Lead to Improved Care?

Andrew P Loehrer, MD, David C Chang, PhD, MPH, MBA, Matthew M Hutter, MD, MPH, FACS, Zirui Song, MD, PhD, Keith D Lillemoe, MD, FACS, Andrew L Warshaw, MD, FACS, Cristina R Ferrone, MD, FACS
Survival for Pancreatic Cancer has improved

- 25 years ago, 5-year survival for pancreatic cancer in the US was 3%
- The most recent statistics show the survival is 8%
- This represents a 166% improvement!

Some reasons for improvement

• Better chemotherapy for patients with metastatic disease
• Better adjuvant treatment after surgery
• Improved outcomes after pancreatic surgery
TREATMENT OF CARCINOMA OF THE AMPULLA OF VATER

ALLEN O. WHIPPLE, M.D., WILLIAM BARCLAY PARSONS, M.D.,
AND CLINTON R. MULLINS, M.D.

NEW YORK, N. Y
FROM THE DEPARTMENT OF SURGERY, COLUMBIA UNIVERSITY

A definite advance has been made in the last five or six years in the surgery of the pancreas, notably in the brilliant cures of hyperinsulinism by the removal of adenomata and more recently by the excision of a large part of the pancreas itself. These cures have been reported by American surgeons with no mortality in the series thus far published.
Pancreatic Cancer

1960’s – 1970’s

- High perioperative morbidity
- Hospital mortality – 25%
- Long term survival for pancreatic cancer – 5%
- Calls to abandon PD for pancreatic cancer
Volume of Pancreatic Resection and Operative Mortality

In-hospital mortality rates as function of volume; 7,558 pts.
Meguid et al, JACS 2008; 206:622-8
FIGURE 1. Survival of patients subjected to pancreatic resection for cancer.
FIGURE 3. Long-term survival of patients who survived the perioperative period (<30 days) after pancreatic resection for cancer.
Hospitals Move to Limit Low-Volume Surgeries
Minimum Volume Standards for Hospitals and Surgeons under the Volume Pledge.

Bariatric surgery refers to the number of “stapled procedures.”
Pancreatic Cancer: Update

Laparoscopic Pancreaticoduodenectomy
Mayo Experience*

- Comparison of Laparoscopic (N=108)
  - vs. Open Pancreaticoduodenectomy (PD)
  - (N=214) for pancreatic ductal carcinoma

Pancreatic Cancer: Update
Laparoscopic Pancreaticoduodenectomy Results

• No difference in use of neoadjuvant therapy, tumor size, LN or margin positivity
• Decreased blood loss, length of stay in Lap PD group (p<0.001) (6 vs 9 days)
• More patients in open PD had delay of >8 weeks or did not receive post-op adjuvant therapy
Pancreatic Cancer: Update
Laparoscopic Pancreateicoduodenectomy Results

- No difference in overall survival
- Progression-free survival was significantly increased in Lap PD group
Da Vinci Robot
Pancreatic Cancer: Update

- Robotic-assisted Pancreatic Resection
  250 cases (132PD*)
- Conversion: 6% (8%*)
- Op Time (PD only): 527 minutes
- Transfusions: 11% of patients
- Complications: Dindo III-IV (20%) (28%*)
  Pancreatic Fistula: 30% (17%*)
- Reoperation: 2% (3%*)
- Perioperative Mortality:
  30 day: .8% (1.5%*)
  90 day: 2.0% (3.8%*)
- Length of Stay: 8 days (10 days*)
- Readmissions: 32% (28%*)

Pancreatic Cancer: Update

- Robotic-assisted Pancreaticoduodenectomy
  - “Cancer Outcomes” – 106 patients
- R0 resections – 88%
- Lymph Node Harvest (median) - 19
Actual Overall Survival for MGH Cohort

MGH experience
From 1985 - 2006

499 patients resected

5 year actual survival 19%

10 year actual survival 10%

Ferrone CR et al. Surgery 2012 Sep;152.
Metastatic Pancreatic Adenocarcinoma

- 5-FU
- Gemcitabine
- The ACCORD trial established FOLFIRINOX (%-FU, oxaliplatin, irinotecan) as the standard of care for metastatic pancreatic cancer

Overall Survival and Progression-free Survival

A Overall Survival

Hazard ratio, 0.57 (95% CI, 0.45–0.73)
P<0.001 by stratified log-rank test

B Progression-free Survival

Hazard ratio, 0.47 (95% CI, 0.37–0.59)
P<0.001

No. at Risk
Gemcitabine 171 134 89 48 28 14 7 6 3 2 2 2 1
FOLFIRINOX 171 146 116 81 62 34 20 13 9 5 3 2 2 2

Definition of “Borderline Resectable”

• Currently: Any tumor that is not “cleanly resectable” without vascular resection.

• Venous involvement of any degree

• Patients with focal or non-circumferential involvement of HA or SMA are classified as BD

• The definition is not rigid, and other factors such as age, temporal comorbidity and uncertainty of metastatic spread play a role.
Definition of “Locally-advanced”

- A tumor that involves the celiac axis, or has circumferential or extensive involvement of the hepatic artery or superior mesenteric artery.

- Complete occlusion of the SMV or portal vein.
Contrast between BD and LA tumors

• The distinction is not always clear, but does it really matter
Neoadjuvant Therapy

• Can FOLFIRINOX improve the resectability of locally advanced or borderline resectable PDAC?

• We need an R0 resection.

• The distinction between borderline and locally advanced pancreatic cancer is not always clear.
Neoadjuvant Therapy

• Arguments for:
  • It selects patients who recur early
  • It ensures that patients get treated
  • It may increase R-0 resections

• Arguments against:
  • No proof that it improves survival
  • It may miss the “window of opportunity” in some patients
Reasonable?

41yo female presenting with a 3.6 cm PDAC involving the SMA, Ca19-9 985
After 4 mo of FOLFIRINOX and 50.4Gy of chemoradiation, Ca19-9 37

FINAL PATH: 1.6cm T2N0, negative margins
The impact of FOLFIRINOX on locally advanced and borderline resectable pancreatic adenocarcinoma

C. Ferrone, G. Marchegiani, T. Hong, Dr. Ryan, L. Blazkowsky, D. Ting, D. Dias Santos, J. Allen, A. L. Warshaw, C. Fernandez-del Castillo, and K. Lillemoe

Massachusetts General Hospital
Harvard Medical School

Published in Annals of Surgery, Jan, 2015
Study Design

283 Resections for PDAC

Upfront resection (n=155)

FOLFIRINOX (n=128)

Alone (n=12)

FOLFIRINOX + 50.4Gy (n=100)

FOLFIRINOX + Protons (n=16)

SURGICAL RESECTION
CA 19-9 and size pre vs. post FOLFIRINOX

<table>
<thead>
<tr>
<th></th>
<th>Pre FOLFIRINOX treatment</th>
<th>Post FOLFIRINOX treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 19-9 (U/mL)</td>
<td>Median: 141 (IQR: 28-473) Mean: 567 ($\pm$ 1,325)</td>
<td>Median: 25 (IQR: 9-56) Mean: 102 ($\pm$ 353)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CA 19-9 &lt;37 U/mL</td>
<td>28%</td>
<td>66%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT Tumor size (cm)</td>
<td>Median: 3.2 (IQR: 2.6-4.1) Mean: 3.5 ($\pm$ 1.3)</td>
<td>Median: 2.5 (IQR: 1.6-3.5) Mean: 2.6 ($\pm$ 1.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Clinical and Operative Results

<table>
<thead>
<tr>
<th></th>
<th>No Neoadjuvant N=155</th>
<th>FOLFIRINOX N=128</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>76 (49%)</td>
<td>61 (48%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Age (y)</td>
<td>71 (65-79)</td>
<td>63 (57-69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CA19-9 at resection (U/mL)</td>
<td>123 (26-397)</td>
<td>18 (9-51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT size at resection (cm)</td>
<td>2.2 (1.9-2.8)</td>
<td>2.4 (1.5-3.3)</td>
<td>0.890</td>
</tr>
<tr>
<td>BMI at resection (kg/m²)</td>
<td>26.6 (23.7-30.1)</td>
<td>24.4 (21.7-28.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>OR time (min)</td>
<td>300 (200-362)</td>
<td>377 (315-452)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>425 (275-800)</td>
<td>600 (400-850)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values represent Median (IQR) or N(%)
# Post Operative Results

<table>
<thead>
<tr>
<th></th>
<th>No Neoadjuvant N=155</th>
<th>FOLFIRINOX N=128</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clavien-Dindo ≥3</td>
<td>23 (15%)</td>
<td>17 (13%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Readmission - 90 d</td>
<td>48 (31%)</td>
<td>25 (20%)</td>
<td>0.029</td>
</tr>
<tr>
<td>LOS (d)</td>
<td>7 (5-9)</td>
<td>6 (5-7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Postoperative death - 90 d</td>
<td>3 (1.9%)</td>
<td>2 (1.6%)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Values represent Median (IQR) or N(%)
## Pathologic Results

<table>
<thead>
<tr>
<th></th>
<th>No Neoadjuvant N=155</th>
<th>FOLFIRINOX N=128</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size on pathology (cm)</td>
<td>3.2 (2.5-4.3)</td>
<td>2.5 (1.5-3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N(+)</td>
<td>107 (69%)</td>
<td>46 (36%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R0 (&gt;1mm)</td>
<td>91 (59%)</td>
<td>102 (81%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>96 (62%)</td>
<td>31 (24%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>143 (92%)</td>
<td>81 (64%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values represent Median (IQR) or N(%)
Overall survival from diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Median overall survival from operation (months)</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neoadjuvant</td>
<td>25.1</td>
<td>15.4-N/A</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>43.7</td>
<td>23.2-55.5</td>
</tr>
</tbody>
</table>

p=0.003
Disease-free survival from operation

<table>
<thead>
<tr>
<th></th>
<th>Median DFS from operation (months)</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neoadjuvant</td>
<td>13.4</td>
<td>7.0-22.0</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>19.0</td>
<td>6.8-N/A</td>
</tr>
</tbody>
</table>

p=0.023
FOLFIRINOX: n=159

- Resected (n=128)
- Not-resected (n=31)
FOLFIRINOX: resected vs. not resected

<table>
<thead>
<tr>
<th></th>
<th>Median overall survival from diagnosis (months)</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resected</td>
<td>43.7</td>
<td>23.2-55.5</td>
</tr>
<tr>
<td>Not resected</td>
<td>18.6</td>
<td>14.0-42.5</td>
</tr>
</tbody>
</table>

p<0.001
Results

Locally Advanced

- Resected (34/49) 69%
- R0 (30/49) 61%

Borderline Resectable

- Resected (32/48) 67%
- R0 (31/48) 65%
IORT in Era of Neoadjuvant Chemotherapy


Median Survival
35.1 mo
24.5 mo
24.8 mo
Summary

• Distinguishing between borderline and locally-advanced pancreatic cancers may not be as significant as in the past

• Current neoadjuvant treatments downstage 2/3 of patients with no apparent distinction between BD and LA

• Radiologic imaging is no longer as reliable as it was in the past
Summary

• Longer more complex operations, but no increase in post operative morbidity or mortality

• Significant decrease in LN involvement, perineural invasion and lymphovascular invasion

• After neoadjuvant FOLFIRINOX and chemo/XRT overall survival of locally advanced patients is improved when compared to “clearly” resectable patients

• In the new era of neoadjuvant therapy IORT may still contribute to improved outcomes
Summary

• FOLFIRINOX treated pancreatic cancers have a higher CD8+ T cell infiltration

• FOLFIRINOX treated pancreatic cancers have increased HLA class I expression

• These changes may provide an opportunity for novel immune therapies and check point inhibitors
Locally Advanced Study
FOLFIRINOX with Losartan

• **Advanced non-small cell lung cancer**¹:
  3.1 month median survival advantage among ACE-I or ARB recipients -- 11.7 vs 8.6 months, HR 0.56, p=0.03) (n=287 patients)

• **Locally advanced/metastatic pancreatic cancer**²:
  8.7 month median PFS among patients receiving ACE-I or ARB therapy (n=27) versus 4.5 months in a cohort receiving other antihypertensive therapy (n=25) versus 3.6 months in a cohort not receiving any antihypertensive therapy (n=103) (p=0.032).

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Pancreatic cancer and Renin-angiotensin system

<table>
<thead>
<tr>
<th>Stage Type</th>
<th>Percentage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic</td>
<td>60%</td>
<td>93/155</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>40%</td>
<td>62/155</td>
</tr>
<tr>
<td>Metastatic</td>
<td>50%</td>
<td>7/14</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>50%</td>
<td>7/14</td>
</tr>
<tr>
<td>Metastatic</td>
<td>71%</td>
<td>25/35</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>29%</td>
<td>10/35</td>
</tr>
</tbody>
</table>

Significant benefit of PFS and OS

Borderline but benefit not significant
Angiotensin antagonism modulates the PDAC TME

Jain, Boucher, Duda (MGH)
Losartan affects TGF-β

B. Diop-Frimpong et al, PNAS (2011)
Losartan can decrease Collagen I and HA

Control

Losartan

B. Diop-Frimpong et al, PNAS (2011)
Collagen and HA Depletion Increases Tumor Perfusion

Pre-Losartan

Post-Losartan

vessels

matrix (collagen)

Chauhan, Martin et al., Nature Communications (2013)
Losartan decompresses vessels

Chauhan, Martin et al., Nature Communications (2013)
Losartan improves delivery of drugs and oxygen

Chauhan, Martin et al., Nature Communications (2013)
Univariate model showed that Chronic ASI use is associated with longer survival in resected patients and a trend towards longer survival in locally advanced patients.
Resected PDAC: ASI exposure is correlated with longer overall survival in the propensity score matched analysis.

Median Survival: ASI +: 36.3 m  
ASI -: 17.1 m  
p=0.002

• 56 Y.O. Female diagnosed with pancreatic cancer on 10/2016
• 1/11/17 Started FOLFIRINOX losartan
• 4/26/17 FOLFIRINOX losartan Cycle 8
• 5/29/17 Week 1 Chemo RT
• 7/7/17 Completed Chemoradiation
• CA 19-9 was 167 pre-treatment, normalized by cycle 6, and was 13 in 8/17
• Patient underwent extended distal pancreatectomy and splenectomy on 9/6/17

• Final Path: Single focus of residual adenocarcinoma measuring 1.5 mm; margins negative; 18 lymph nodes negative.
MGH Study 13051: Folfirinox x 8 + Losartan followed by chemoradiation in Locally-advanced Pancreatic Cancer

- 50 patients enrolled; 40 have completed treatment; 3 developed metastasis or progression (15%)
- 34/40 patients who were taken to surgery underwent resection (85%)
- 88% underwent R0 resection with complete pathologic response in 9%
- Of all evaluable patients (N=49)
  - mPFS = 19.9 months
  - mOS = 31.4 months
- Of all resected patients (N=34)
  - mPFS = 27.6 months
  - mOS = 33.0 months
  - 1 year PFS = 96.0%
  - 2 year PFS = 60.6%
Conclusions

• Although the prognosis for pancreatic cancer continues to be grim, overall survival has increased over the last 3 decades.

• There is better chemotherapy for patients with metastatic disease.

• For resectable patients, mortality from surgery has improved (when performed in high-volume centers), and there is better adjuvant treatment.

• Patients with borderline and locally-advanced pancreatic cancer can be down-staged, and some of them can undergo surgery and have a possibility of cure.

• Promising therapies are in the horizon
Post-FOLFIRINOX pathology

≤1 mm residual tumor in 9 patients
Pancreatic Cancer
Does pCR Equal Care?

Johns Hopkins Experience

- 186 patients with borderline/locally advanced PDAC
- 19 patients (10%) had a “Complete Response or pCR”


<table>
<thead>
<tr>
<th></th>
<th>pCR (19 patients)</th>
<th>Near CR (29 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS (median)</td>
<td>26 mos</td>
<td>12 mos (p&lt;0.019)</td>
</tr>
<tr>
<td>OS</td>
<td>&lt;60 mos</td>
<td>27 mos (p=0.003)</td>
</tr>
</tbody>
</table>

pCR was an independent predictor of DFS and OS on multivariable analysis

Pancreatic Cancer Interception Grant
Losartan in Locally Advanced Panc Can

• PIs: Alec Kimmelman and David Ryan
SU2C Trial

• Clinical Trial PI: Ted Hong, MD MGH
• Clinical Trial Steering Committee: Alec Kimmelman (NYU), David Ting (MGH), David Ryan (CHAIR – MGH), Joe Herman (MDACC), Richard Burkhart (Hopkins), Dan Laheru (Hopkins), Carlos Fernandez del Castillo (MGH), Wells Messerchmitt (Colorado)
SU2C Trial

Primary Objective
Determine if the addition of losartan, or combination of losartan and immunotherapy (nivolumab) to FOLFIRINOX followed by SBRT and surgery will result in an R0 resection rate >65%

Stratify by

Borderline Resectable
Locally Advanced

Localized Pancreatic Cancer

FOLFIRINOX x 8
N=40

SBRT
Surgery
F/u off therapy

FOFLIRINOX x 8
Losartan
N=40

SBRT
Losartan
Surgery
Losartan X 6 months

FOLFIRINOX x 8
Losartan
N=40

SBRT
Nivolumab
Losartan
Surgery
Nivolumab Losartan X 6 months

CURE Pancreatic Cancer
Lustgarten Foundation
Clinical Trial

Primary Objectives

• Evaluate the ability of losartan when added to FOLFIRINOX with or without immunotherapy (nivolumab) to increase the R0 resection rate of borderline resectable or locally advanced pancreatic cancers.
Clinical Trial

Secondary Objectives

• Determine if the addition of losartan to FOLFIRINOX followed by SBRT, or combination of losartan and immunotherapy (nivolumab) to SBRT and surgery will improve progression-free survival.

• Determine if the addition of losartan to FOLFIRINOX followed by SBRT, or combination of losartan and immunotherapy (nivolumab) to SBRT and surgery will improve overall survival.

• Evaluate pathologic complete response (pCR) at time of surgical resection on each protocol arm. pCR is defined by no residual cancer in the pancreatic tissue.
Exploratory Objectives

• Explore whether the addition of immunotherapy (nivolumab) to FOLFIRINOX followed by SBRT and surgery for patients already on ACE/ARB therapy is associated with different outcomes compared to the combination of losartan and immunotherapy in patients not exposed to ACE/ARB.

• Characterize relationships between immune infiltrates and extracellular matrix (ECM)

• Explore the ability of pancreatic cancer organoids to predict the clinical outcomes of individual patients including response and survival

• Explore the ability of blood-based biomarkers (ctDNA, CTCs, exosomes) to detect pancreatic cancer before and after surgery

• Explore the impact of FOLFIRINOX, ACE/ARB and immunotherapy on systemic and tumor metabolites

• Determine if losartan changes the pancreatic tumor micro-environment
Great Debates I: Friday, March 4
2:00-3:00 pm

Resectable Pancreatic Head Adenocarcinoma: Resect First

PRO: Keith D. Lillemoe, MD
CON: Douglas B. Evans, MD
Pancreatic Cancer - Controversies

- Many controversies continue to exist in the treatment of pancreatic cancer
- Most will never be resolved to the “satisfaction” of all
- Perhaps such controversy has been healthy for the advancement of care for this disease
Pancreatic cancer in 1992
Pancreatic cancer in 1992

Pancreatic cancer in 2017
THANK YOU

Cristina Ferrone
Carlos Fernandez-del Castillo

Motaz Qadan
Andrew L. Warshaw
Andrew Liss

Ted Michelakos
Lei Cai
Ilaria Pergolini
Kim Honselmann
Zhi Fong

Theodore Hong
Jennifer Wo
Dushyant Sahani
Deb Gervais
Avinash Kambadakone

William Brugge
David Forcione
Brenna Casey
Peter Kelsey