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MCW/Froedtert Cancer Center
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Multimodality Management of Localized Pancreatic Cancer

Department of Surgery

- Cardiothoracic Surgery
- Community Surgery
- Education
- Oral Maxillofacial Surgery
- General Surgery
- Pediatric Surgery
- Surgical Oncology
- Transplantation
- Trauma, Critical Care
- Vascular Surgery
Milwaukee late Jan 2009 – July 2011

- Laurie Andrzejewski
- Elaine Babel
- Peter Bapes
- Judith Berndt
- Ze’ev Boim
- Eugene Bojarski
- Charlotte Bouchard
- Richard Broder
- Cassandra Brown
- Thomas Carlisle
- Donald Claesges
- James Cunningham
- Kathleen Daily
- Mildred Donahue
- Richard Drallmeier
- Billie Drath
- Jean Fricke
- Jay Fry
- H. B. Gay
- Cheryl Green
- Donnie Hand
- David Hanschke
- Paul Helgeson
- Jane Hollander
- Rosemary Jacobson
- Harold Kaminski
- James Klein
- Nancy Labott
- Sarah Levin
- Susan Lineberger
- Sharon Lousier
- Donald Macrae
- Earleen McGhee
- Robert Morris
- Thomas Murphy
- Terrance Neary
- Mowaffaq Ousachi
- Donald Panuce
- Eileen Paquin
- Merrie Patch
- James Pauls
- Jay Peck
- Gerald Plost
- Joyce Pratt
- Peter Rillo
- Harriet Russell
- Lillian Rzentkowski
- Gerald Seymour
- Killian Schneider
- Thomas Sullivan
- Marjorie Thome
- Robert Troost
- Norbert Wickman
- Peter Wroblewski
- Ronald Wysocki
- Howard Veldhorst
- Robert Vescio
- Nancy Zabkowicz
49 y.o. woman executive

Dec 2005
- Jaundice
- Taken to surgery, unresectable (double bypass)
- Recovers
- Comes to Houston for another opinion

Can my tumor be removed
## Natural History of Pancreatic Cancer

<table>
<thead>
<tr>
<th>Stage Description</th>
<th>Months From Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>9.3</td>
</tr>
<tr>
<td>Stage I, II (potentially resectable)</td>
<td>15.4</td>
</tr>
<tr>
<td>resected</td>
<td>24.1</td>
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<tr>
<td>not resected</td>
<td>10.3</td>
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<tr>
<td>Stage III (locally advanced)</td>
<td>9.9</td>
</tr>
<tr>
<td>borderline resectable</td>
<td>17.6</td>
</tr>
<tr>
<td>Stage IV (metastatic)</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Katz MHG, Hwang RF, et al. TNM staging of pancreatic adenocarcinoma.
# Postoperative Adjuvant Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Patients</th>
<th>Med. Survival</th>
<th>P-Valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG (1985) 5-FU/XRT</td>
<td>21</td>
<td>20</td>
<td>.03</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>22</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>54</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>No chemo</td>
<td>139</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>CONKO (2008 ASCO) Gem</td>
<td>179</td>
<td>23</td>
<td>.005</td>
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<tr>
<td>Surgery alone</td>
<td>175</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Gem vs 5-FU</td>
<td>201</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>ACOSOG Z5031(2010)</td>
<td>89</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>ESPAC-3 (JAMA 2010) Gem</td>
<td>537</td>
<td>24</td>
<td>.39</td>
</tr>
<tr>
<td>Gem vs 5-FU/LV</td>
<td>551</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>EORTC (JCO 2010)</td>
<td>45</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>*Gem vs Gem/GemXRT</td>
<td>45</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

*Surgery plus something is better than surgery alone

*Treatment started within 8 wks of surgery
POST-OPERATIVE ADJUVANT TREATMENT

Clinical trial preferred or Systemic gemcitabine or 5-FU/leucovorin before or after chemotherapy (fluoropyrimidine- or gemcitabine-based) or Chemotherapy alone:
- Gemcitabine (category 1)
- 5-FU/leucovorin (category 1)
- Capecitabine (category 2B)

Surveillance every 3-6 mo for 2 years, then annually:
- H&P for symptom assessment
- CA19-9 level (category 2B)
- CT scan (category 2B)

Recurrence after resection (See PANC-10)

Baseline pretreatment
- CT scan
- CA19-9

See Metastatic Disease (PANC-9)

iSee Principles of Radiation Therapy (PANC-D)

kPatients who have received neoadjuvant chemoradiation or chemotherapy are candidates for additional chemotherapy following surgery. Adjuvant treatment should be administered to patients who have not had neoadjuvant chemotherapy and who have adequately recovered from surgery; treatment should be initiated within 4-8 weeks. If systemic chemotherapy precedes chemoradiation, restaging with a CT scan should be done after each treatment modality.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
12/14/06: Pancreaticoduodenectomy

Surgical pathology:
ductal adenocarcinoma
2.5 x 2.3 x 2.3 cm
8 LN negative/ margins uninvolved

1/29/07: 6 cycles Gemcitabine - 3 weeks on and 1 week off

10/11/10: US guided biopsy - soft tissue near SMA - Pathology: adenocarcinoma
329 consecutive pts / pancreatic resection / min F/U 5 yrs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survival &lt;5 years (n = 241)</th>
<th>Survival ≥5 years (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>No. of patients whose disease recurred</td>
<td>208</td>
<td>21</td>
</tr>
<tr>
<td>Site of first recurrence&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>104 (50)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Lung</td>
<td>37 (18)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Locoregional</td>
<td>38 (18)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>28 (13)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Abdominal wall/dermis</td>
<td>1 (1)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Brain</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Bone</td>
<td>3 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Total local-regional recurrence: 40/329 = 12%

### Hopkins Rapid Autopsy

#### Patterns of Failure

<table>
<thead>
<tr>
<th>Stage at dx</th>
<th>I/II (n=20)</th>
<th>III (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local only</td>
<td>15%</td>
<td>28%</td>
</tr>
<tr>
<td>DM only</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>LR + DM</td>
<td>65%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Iacobuzio-Donahue et al, JCO. 2009;27:1806
Resectable adenocarcinoma of the pancreatic head

SMV

SMA

T
SMA (Retroperitoneal) Margin
AJCC Cancer Staging Manual 7th Edition
**TABLE 2.** Frequency with which surgical margins were evaluated prior to enrollment in as determined by critical review of the pathology reports (n=79)

<table>
<thead>
<tr>
<th>Status</th>
<th>SMA</th>
<th>CBD</th>
<th>Panc</th>
<th>AJCC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluated</td>
<td>37 (47)</td>
<td>74 (94)</td>
<td>79 (100)</td>
<td>36 (46)</td>
</tr>
<tr>
<td>Positive</td>
<td>14 (38)</td>
<td>2 (3)</td>
<td>12 (15)</td>
<td>16 (44)</td>
</tr>
<tr>
<td>Negative</td>
<td>23 (62)</td>
<td>72 (97)</td>
<td>67 (85)</td>
<td>20 (56)</td>
</tr>
</tbody>
</table>

*Cases in which all three margins recommended by the AJCC (sixth edition[11])--SMA, CBD, and Panc--were evaluated. Positive indicates at least one margin of the three AJCC margins was positive; negative indicates all three margins were negative.*

TABLE 3. Frequency with which critical surgical and pathologic factors were documented in operative and pathology reports of patients enrolled on ACOSOG Z5031.

<table>
<thead>
<tr>
<th>Clinical Factor</th>
<th>Reported, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical Factors</strong>*</td>
<td></td>
</tr>
<tr>
<td>Type of resection</td>
<td>80 (100)</td>
</tr>
<tr>
<td>Preoperative clinical stage</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Transfusion requirement</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Search for extrapancreatic disease</td>
<td>77 (96)</td>
</tr>
<tr>
<td>Description of liver</td>
<td>64 (80)</td>
</tr>
<tr>
<td>Description of peritoneum</td>
<td>54 (68)</td>
</tr>
<tr>
<td>Relationship of tumor to SMV</td>
<td>55 (69)</td>
</tr>
<tr>
<td><strong>Technique of SMA dissection</strong></td>
<td>54 (68)</td>
</tr>
<tr>
<td>Marking of SMA margin†</td>
<td>20 (25)</td>
</tr>
<tr>
<td><strong>Absence of residual macroscopic disease</strong></td>
<td>19 (24)</td>
</tr>
<tr>
<td><strong>Pathologic Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>79 (100)</td>
</tr>
<tr>
<td><strong>Inking performed</strong></td>
<td>52 (66)</td>
</tr>
<tr>
<td><strong>Evaluation of SMA margin</strong></td>
<td>37 (47)</td>
</tr>
<tr>
<td>Examination of regional lymph nodes</td>
<td>79 (100)</td>
</tr>
<tr>
<td>Maximum tumor diameter</td>
<td>74 (94)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>79 (100)</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>63 (80)</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>75 (95)</td>
</tr>
<tr>
<td>AJCC TNM stage</td>
<td>39 (49)</td>
</tr>
<tr>
<td>CAP guidelines observed</td>
<td>27 (34)</td>
</tr>
</tbody>
</table>
Surgery-first approach to localized pancreatic cancer

Diagnosis, staging and preparation for surgery

Recovery from surgery

OR

1-2 wks

6-10 wks

Adj Therapy

CT

What we know:
Not everyone makes it to Adj Rx

What we do not know:
The biologic impact of surgery first
Adjuvant Therapy for pancreatic cancer

To surgery for Whipple 100

No go
Not resected 10-20

40-60
R0/R1
Recovers and agrees to therapy

Positive restaging
CT/exam:
Early distant recurrence or persistent local disease

Whipple completed 80

Incomplete recovery, patient refusal, R2 resection, etc

? 35-50
Adequate PS
Negative re-staging
All patients do not receive intended adjuvant therapy

- Treatment related: surgery complications, delayed recovery
- Disease related: disease progression
- Patient related: age, preoperative PS, medical co-morbidities, patient refusal

35% did not receive adjuvant therapy: MDACC
Received intended adjuvant therapy

Corsini, JCO 2008;26:3511-3516-3502 (Mayo) 60%
Herman JCO 2008;26:3503-3510 (Hopkins) 44%
Simons Cancer 2010;116:1681-90 (SEER) 48%
Merchant J Am Coll Surg 2009:208:829-841 50%
The operating surgeon must document in the operative note that a complete gross excision of the primary tumor was achieved. The pathology report must include documentation of the margin status and the size of the tumor.

Abdominal/pelvic CT scan with contrast and chest CT/x-ray (CT of chest preferred) within 31 days of registration on study.
Survival after Resection of Pancreatic Adenocarcinoma: Results from a Single Institution over Three Decades

Jordan M. Winter, MD\textsuperscript{1}, Murray F. Brennan, MD\textsuperscript{1}, Laura H. Tang, MD\textsuperscript{2}, Michael I. D’Angelica, MD\textsuperscript{1}, Ronald P. DeMatteo, MD\textsuperscript{1}, Yuman Fong, MD\textsuperscript{1}, David S. Klimstra, MD\textsuperscript{2}, William R. Jarnagin, MD\textsuperscript{1}, and Peter J. Allen, MD\textsuperscript{1}

Ann Surg Oncol
DOI 10.1245/s10434-011-1900-3

FIG. 3 Long-term survival after pancreatectomy for pancreatic cancer (1-year survivors). 1980s, median = 23.2 months; 1990s, median = 25.6 months; 2000s, median = 24.5 months. \(P\) values compare the specified decade to the 1980s.

The lack of improvement in long-term survival observed in this study in patients with resected pancreatic cancer underscores the need for improved early detection and novel treatment strategies for this aggressive disease.
Advantages of the neoadjuvant approach

• Provides early treatment of micrometastatic disease (80-90% of “resectable” patients))

• Patients with rapidly progressive disease will not be subjected to surgery

• A logical strategy for the high incidence of positive margins

• Delayed recovery not an issue as the patient is preop
Development of a Clinical Protocol
neoadjuvant therapy for pancreatic cancer

1. Write the eligibility section
   Objective definition of resectability

Confirmation the diagnosis of cancer:
   FNA (CT evolved to EUS)
   Endobiliary stents (plastic evolved to metal)

Review patient eligibility
   Multidisciplinary Conference
Definitions

Resectable:
no extension to celiac, CHA, SMA
patent SMV-PV confluence
stage I, II (T1-3, Nx, M0)

Locally Advanced:
celiac, SMA encasement (> 180°)
stage III (T4, Nx, M0)

Borderline:
arterial abutment (≤ 180°)
stage III (minimal T4)
Resectable adenocarcinoma of the pancreatic head
Resectable: likely to require venous resection
Borderline Resectable


Locally Advanced (Stage III)
Imaging Template for Pancreatic Cancer

- Tumor size and location
- Tumor - vein relationship: SMV, portal vein and splenic vein
- Tumor - artery relationship: SMA, celiac axis, common hepatic artery
- Presence or absence of distant metastases: liver, lung, peritoneum
CRITERIA DEFINING RESECTABILITY STATUS

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

Tumors considered borderline resectable include the following:
- No distant metastases
- Venous involvement of the SMV/portal vein demonstrating tumor abutment with 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 suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
- Gastroduodenal 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.
- Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall.


Tumors considered to be unresectable demonstrate the following:
- HEAD
  - Distant metastases
  - Greater than 180 degrees SMA encasement, any celiac abutment
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion or encasement
- BODY
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- TAIL
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
  - Nodal status
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable.
Preop Clinical Trials
investigator initiated – industry supported

Protocol-based preop chemoradiation
- 88-004  50.4 Gy/ 5-FU 300mg/m²
- 92-002  wide field liver irradiation
- 93-007  30 Gy/ 5-FU 300mg/m²
- 95-224  30 Gy/paclitaxel 60mg/m²/wk
- 98-020  30 Gy/Gem 400mg/m²/wk
- 01-341  Gem/Cis, 30 Gy/Gem
- 05-0784 Gem/Bev, 50.4 Gy
- 08-0459 Gem/Erlotinib +/- XRT
Gem-XRT

7 wks  3-4 wks

XRT: 30 Gy (3Gy/F; M-F)

Chemo: Gemcitabine (400)

Staging CT

3 months

Staging CT

JCO 2008;26:3496-3502
Median survival for all 86 patients = 23 months
Local recur = 11% (all neg SMA margin; isolated LR 2/7)
Is a window of opportunity lost with the neoadjuvant approach?

• Local progression during neoadjuvant therapy
  - No (but chemo alone without postop chemoXRT untested)
    JCO 2008;26:3496-3502
    JCO 2008;26:3487-3495
    (1/176 patients (0.6%)

• Distant metastases develop during neoadjuvant therapy?
  - Already there in the majority of patients
  - Small volume disease may be more responsive to systemic therapy (improved survival in resected patients)
Resectable\textsuperscript{d,e} → Consider staging laparoscopy\textsuperscript{f} in high risk patients or as clinically indicated → Laparotomy

Surgical resection

Unresectable at surgery\textsuperscript{g} → Biopsy confirmation of adenocarcinoma, if not performed previously

See Adjuvant Treatment and Surveillance (PANC-6)

See Locally Advanced Unresectable (PANC-7)

See Metastatic Disease (PANC-9)

\textsuperscript{d} See Criteria Defining Resectability Status (PANC-B).
\textsuperscript{e} Consider neoadjuvant therapy on clinical trial. This requires biopsy confirmation of adenocarcinoma, and for patients with biliary obstruction, durable biliary decompression.
\textsuperscript{f} See Principles of Diagnosis and Staging \textsuperscript{g} (PANC-A).
\textsuperscript{g} See Principles of Palliation and Supportive Care (PANC-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
ACOSOG Z5041: phase II (operable pancreatic adenocarcinoma)  
2008  
preop / postop Gem / Tarceva surgery

Patients with Stage I-II (T1-T3, Nx) adenocarcinoma of the pancreatic head or unicate process, resectable by CT

Preoperative Gemcitabine & Erlotinib  
whipple  
Postoperative Gemcitabine & Erlotinib

2 months  
2 months

Accrual goal = 91  
Central review of CT / path  
Protocol-specific operative summary

Pisters PWT, et al
SURGICAL MARGINS:
All negative
Superior mesenteric artery margin - Negative, tumor distance from bed margin 0.6 cm (Slide G4)

PRIMARY TUMOR (pT):  pT3:

LYMPH NODES:
Total number of lymph nodes involved: 0
Total number of lymph nodes examined: 43
Chemoradiation: March, 2011
SURGICAL MARGINS:
All surgical margins are free of tumor
Distance of invasive carcinoma from SMA margin: 10.0 mm
PRIMARY TUMOR (pT): pT3
LYMPH NODES:
Total number of lymph nodes involved: 0
Total number of lymph nodes examined: 22
BORDERLINE RESECTABLE\textsuperscript{c,d} NO METASTASES, PLANNED NEOADJUVANT THERAPY

WORKUP

- Biopsy positive → Neoadjuvant therapy (category 2B)\textsuperscript{j}
- Biopsy negative → Repeat biopsy
- Biopsy, EUS-directed biopsy preferred\textsuperscript{1}
- Staging laparoscopy\textsuperscript{f} (category 2B)
- Placement of temporary stent if biliary ductal obstruction is present

Planned neoadjuvant therapy\textsuperscript{h}

Surgical resection

- Unresectable at surgery\textsuperscript{g}
- Disease progression precluding surgery\textsuperscript{g}
- No jaundice
- Jaundice

TREATMENT

- See Adjuvant Treatment and Surveillance (PANC-6)
- See Locally Advanced Unresectable (PANC-7)
- See Metastatic Disease (PANC-9)

- Stenting or biliary bypass
- ± duodenal bypass (category 2B for prophylactic duodenal bypass)
- ± open ethanol celiac plexus block (category 2B)

\textsuperscript{c}See Principles of Diagnosis and Staging (PANC-A).
\textsuperscript{d}See Criteria Defining Resectability Status (PANC-B).
\textsuperscript{e}See Principles of Diagnosis and Staging #5 (PANC-A).
\textsuperscript{f}See Principles of Palliation and Supportive Care (PANC-C).
\textsuperscript{g}See Principles of Palliation and Supportive Care (PANC-C).
\textsuperscript{h}Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
\textsuperscript{1}See Principles of Diagnosis and Staging #1 and #5 (PANC-A).
\textsuperscript{i}See Principles of Radiation Therapy (PANC-D).
67 woman
Presented with painless jaundice
Initial CT: July 12, 2010
A preoperative CT scan had documented several enlarged lymph nodes.

Further exploration of the porta hepatis and hepatoduodenal ligament identified a enlarged lymph node. A biopsy of this lymph node documented metastatic adenocarcinoma consistent with a pancreatic primary. This lymph node was outside the margins of a pancreatoduodenectomy and, therefore, a Whipple procedure was not performed.

Date of operation: 7-18-2010 (dictated 7-26-2010)
Postop / Pre-chemo CT, Aug 17, 2010:

Mesenteric venous anatomy and tumor involvement: Tumor abuts the proximal anterior/lateral aspect of the main SMV trunk without encasement. The first jejunal branch courses normally under the SMA and there is tumor abutment with mild narrowing at the origin of the first jejunal branch (series 5, image 185; series 457, image 23). The ileal branches are free of disease.

Referred to MCW medical oncology (Dr. Ritch)
Aug 10, 2010
Surgery July 17

Restaging CT
Aug 17, 2010

Restaging CT
Nov 15, 2010

Restaging CT
Feb 9, 2011

July 13, 2010
CA19-9: 299
Bili elevated

FOLFIRINOX
Aug 24
PreRx CA19-9: 39
Paul Ritch

Cape-XRT
Nov 29 – Jan 7, 2011
50.4 Gy
Beth Erickson
preRx CA19-9: 29

Reoperative Whipple
March 9, 2011
Preop CA19-9: 16

KM 09463789
Tumor Characteristics:
G: Whipple Resection, Pancreas (Exocrine)

TUMOR SITE: Pancreatic head
TUMOR SIZE: Greatest dimension: 3.2 cm
HISTOLOGIC TYPE: Ductal adenocarcinoma
HISTOLOGIC GRADE: Moderately differentiated
MITOTIC ACTIVITY: Absent
IN SITU CARCINOMA: In situ carcinoma is also present
EXTRAPANCREATIC EXTENSION: No extrapancreatic extension is identified
DIRECT EXTENSION: The tumor does not extend into the adjacent structures
VASCULAR INVASION: Absent
PERINEURAL INVASION: Absent
SURGICAL MARGINS: All surgical margins are free of tumor
Distance of invasive carcinoma from closest margin: 4mm (SMA)

PRIMARY TUMOR (pT):
pT2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
LYMPH NODES:
Total number of lymph nodes involved: 0
Total number of lymph nodes examined: 16
TREATMENT SCHEMA: Pre-op Gem-XRT

Medical College of Wisconsin
Pancreatic Cancer Program: off-protocol therapy of resectable pancreatic cancer

XRT: 50.4 Gy; 1.8 Gy/fraction, Mon-Fri

ChemoXRT

wk1  2   3   4   5   6   7   8   9   10  11

Gem  Gem  Gem  Gem  Gem  Gem  Gem

Sat or Mon

4 Weeks rest

Surgery

Restaging

Pretreatment
Staging Evaluation

Gem: 400 mg/m² over 40 min
Extra-hepatic obstruction of the bile duct on CT with a pancreatic mass

Positive for adenocarcinoma

Discuss at multidisciplinary conference

Resectable
Borderline Resectable
Locally Advanced

Metastatic

Clinical Trial when possible
Neoadjuvant therapy favored

Metal stent regardless of stage of disease / resectability status (as surgery will not be the first treatment)

Be sure this is a good quality CT!!
Criticisms of Neoadjuvant Therapy for Resectable Pancreatic Cancer

Only real “shot” for the patient is surgery – other therapies largely ineffective

Treatment sequencing does not matter – can reliably give chemotherapy and radiation after surgery (at which time one has a tissue dx and stent not an issue)

Window of resectability may be lost (local and distant)
SMV Anatomy

PV

Splenic V

SMV

IMV may enter spl vein or SMV

SMA

Ileal branch

Jejunal branch
Jejunal branch of the SMV has been divided and the involved segment of the ileal branch is resected and an IJ interposition graft used to reconstruct the SMV.
SMV Anatomy

PV

Splenic V

SMV

IMV may enter spl vein or SMV

SMA

Ileal branch

Jejunal branch
Hepatic duct
PV
IJ interposition
SMV
SMA
LRV
Spl V
CHA
Spl A
Tseng, J Gastroint Surg 2004;8:935.
## Pancreatic Adenocarcinoma

**VR vs. standard PD (univariate analysis)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. patients</th>
<th>Median survival (mo)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>291</td>
<td>24.9</td>
<td>21.40-28.46</td>
<td>--</td>
</tr>
<tr>
<td>Male</td>
<td>175</td>
<td>23.1</td>
<td>19.05-27.15</td>
<td>.47</td>
</tr>
<tr>
<td>Female</td>
<td>116</td>
<td>27.0</td>
<td>22.43-31.50</td>
<td></td>
</tr>
<tr>
<td>Standard PD</td>
<td>181</td>
<td>26.5</td>
<td>21.1-31.89</td>
<td>.18</td>
</tr>
<tr>
<td>PD with VR</td>
<td>110</td>
<td>23.4</td>
<td>19.50-27.37</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>25</td>
<td>30.8</td>
<td>16.61-44.92</td>
<td>.22</td>
</tr>
<tr>
<td>T2</td>
<td>56</td>
<td>25.9</td>
<td>20.2-31.46</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>206</td>
<td>23.7</td>
<td>19.94-27.46</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>146</td>
<td>31.9</td>
<td>24.57-39.30</td>
<td>.005</td>
</tr>
<tr>
<td>N1</td>
<td>145</td>
<td>21.1</td>
<td>17.40-24.73</td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>246</td>
<td>26.5</td>
<td>22.29-30.71</td>
<td>.14</td>
</tr>
<tr>
<td>R1</td>
<td>45</td>
<td>21.4</td>
<td>17.05-25.68</td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>209</td>
<td>25.1</td>
<td>21.42-28.85</td>
<td>.92</td>
</tr>
<tr>
<td>No adjuvant therapy</td>
<td>29</td>
<td>18.5</td>
<td>9.48-27.52</td>
<td></td>
</tr>
</tbody>
</table>

Tseng, J Gastroint Surg 2004;8:935.
## Pancreatic Adenocarcinoma

VR vs. standard PD (multivariate analysis)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender</td>
<td>0.925</td>
<td>0.665-1.286</td>
<td>0.642</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.008</td>
<td>0.991-1.026</td>
<td>0.351</td>
</tr>
<tr>
<td>Reoperative PD</td>
<td>1.094</td>
<td>0.722-1.66</td>
<td>0.671</td>
</tr>
<tr>
<td><strong>Vascular resection</strong></td>
<td>1.132</td>
<td>0.789-1.625</td>
<td><strong>0.499</strong></td>
</tr>
<tr>
<td>Operative blood loss</td>
<td>1.0</td>
<td>1.0-1.0</td>
<td>0.445</td>
</tr>
<tr>
<td>Tumor size</td>
<td>0.953</td>
<td>0.818-1.11</td>
<td>0.537</td>
</tr>
<tr>
<td>RP margin positive</td>
<td>1.164</td>
<td>0.772-1.755</td>
<td>0.469</td>
</tr>
<tr>
<td>T stage (AJCC)</td>
<td></td>
<td></td>
<td>0.730</td>
</tr>
<tr>
<td>Nodal metastasis</td>
<td><strong>1.502</strong></td>
<td><strong>1.10-2.05</strong></td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Any adjuvant treatment</td>
<td>0.962</td>
<td>0.412-2.244</td>
<td>0.929</td>
</tr>
<tr>
<td>Neoadjuvant treatment</td>
<td>1.176</td>
<td>0.615-2.248</td>
<td>0.623</td>
</tr>
<tr>
<td>Postop treatment</td>
<td>0.946</td>
<td>0.538-1.663</td>
<td>0.846</td>
</tr>
</tbody>
</table>

Tseng, J Gastroint Surg 2004;8:935.
1. Neoadjuvant treatment sequencing used to:
   • select those with favorable biology for the larger, high risk operations
   • treat radiographically occult M1 disease
   • enhance the chance of a complete (R0, R1) resection

2. Outcome for R1 different than R2 (ie, better)
Borderline Resectable
Katz / M. D. Anderson Classification

- Type A: Anatomically *borderline* resectable tumor
- Type B: *Indeterminant* extrapancreatic metastasis
- Type C: Patient of *marginal* performance status


Stage Specific Therapy

Resectable: preop or postop chemo / chemoradiation

Borderline Resectable (A/B):
  preop chemo (2 mon) – chemoradiation - surgery

Borderline Resectable (C):
  preop chemo / chemoradiation - surgery

Locally Advanced: chemo (4-6 mon) - chemoradiation
Borderline Resectable Panc CA Treatment Approach

Consider an additional 2 months of chemo only when a significant response occurs.

Chemo:
gem doublet FOLFIRINOX

Staging CT

S staged as Borderline

Borderline Resectable
Katz / M. D. Anderson Classification

- Type A: Anatomically *borderline* resectable tumor
- Type B: *Indeterminant* extrapancreatic metastasis
- Type C: Patient of *marginal* performance status

1. Neoadjuvant treatment sequencing used to:
   - select those with favorable biology
   - treat radiographically occult M1 disease
   - enhance the chance of a complete (R0, R1) resection

2. Outcome for R1 different than R2 (ie, better)
Accurate Pathology and Multimodality Therapy
Pancreaticoduodenectomy: Ductal Adenocarcinoma
M D Anderson (N = 360)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. Pts</th>
<th>Med Sur</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>360</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>174</td>
<td>32</td>
<td>.002</td>
</tr>
<tr>
<td>N1</td>
<td>186</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>300</td>
<td>28</td>
<td>.03</td>
</tr>
<tr>
<td>R1</td>
<td>60</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Maj Comp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>263</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>93</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

R0   17 mo  
R1   11 mo  

ESPAC-1
Ann Surg 2001

Raut, Ann Surg 2007;246:52-60
Local Failure (All pts) 8%
The Importance of Neoadjuvant Therapy
Pancreaticoduodenectomy: Ductal Adenocarcinoma
M D Anderson (N = 360)

<table>
<thead>
<tr>
<th>Preoperative Therapy</th>
<th>R1 Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>13%</td>
</tr>
<tr>
<td>NO</td>
<td>19%</td>
</tr>
</tbody>
</table>

Raut, Ann Surg 2007;246:52-60
Local Failure (All pts) 8%
Borderline Resectable PC Treatment Sequencing

Treatment phase
~ 6 wks

Break
~ 6 wks

- CTX
- gem combo
- Chemo-XRT

Restaging
Dropout

Classification as Borderline
Staging CT

OR

## Rates of Resection, Path Response, Survival

160 Patients with Borderline Resectable PC

<table>
<thead>
<tr>
<th>MDACC Type</th>
<th>No. of Patients (%)</th>
<th>Median Survival (Mos)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Resected</td>
<td>Path Resp. IIb, III, IV</td>
</tr>
<tr>
<td>A</td>
<td>84 (53)</td>
<td>32 (38)</td>
<td>19 (59)</td>
</tr>
<tr>
<td>B</td>
<td>44 (28)</td>
<td>22 (50)</td>
<td>13 (59)</td>
</tr>
<tr>
<td>C</td>
<td>32 (20)</td>
<td>12 (38)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Total</td>
<td>160</td>
<td>66 (41)</td>
<td>37 (56)</td>
</tr>
</tbody>
</table>

*p: comparison of median survival between resected and unresected patients of each type

Definitions: AHPBA / SSO 2008

Resectable (stage I, II (T1-3NxM0): no extension to celiac, CHA, SMA, SMV-PV confluence

Borderline (*should not go straight to surgery*): a) venous abutment or encasement (with option for reconstruction) b) arterial abutment (≤ 180°)

Locally Advanced (stage III (T4NxM0): celiac, SMA encasement (> 180°)

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy</th>
<th>Duration of chemotherapy</th>
<th>Chemoradiation</th>
<th>No. Patients Assessed for Survival Analysis</th>
<th>Did not receive any of the intended treatment</th>
<th>Received salvage chemotherapy</th>
<th>Margin status pos or unknown</th>
<th>Overall Survival</th>
<th>Overall survival for panc head</th>
<th>Local Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 97-04</td>
<td>Infusional 5-FU before and after chemoradiation</td>
<td>3 weeks pre- and 3 months post-chemoXRT</td>
<td>Infusional 5-FU and 50.4 Gy (28 fractions, 5 days per week)</td>
<td>230</td>
<td>0</td>
<td>95 (41%)</td>
<td>128 (56%)</td>
<td>Not provided</td>
<td>17.1</td>
<td>61 (27%)</td>
</tr>
<tr>
<td>Gemcitabine before and after chemoradiation</td>
<td>3 weeks pre- and 3 months post-chemoXRT</td>
<td>Infusional 5-FU and 50.4 Gy (28 fractions, 5 days per week)</td>
<td>221</td>
<td>0</td>
<td>77 (35%)</td>
<td>135 (61%)</td>
<td>Not provided</td>
<td>20.5</td>
<td>49 (22%)</td>
<td></td>
</tr>
<tr>
<td>EORTC</td>
<td>Gemcitabine then GemXRT</td>
<td>4 months</td>
<td>Gem (300 mg/m² weekly) and 50.4 Gy</td>
<td>45</td>
<td>2 (Gem) 9 (XRT) (20%)</td>
<td>Not provided</td>
<td>0</td>
<td>24.3</td>
<td>***24.3</td>
<td>14 (31%)</td>
</tr>
<tr>
<td>Gem</td>
<td>4 months</td>
<td>None</td>
<td>50.4 Gy</td>
<td>45</td>
<td>3 (7%)</td>
<td>Not provided</td>
<td>0</td>
<td>24.4</td>
<td>***24.4</td>
<td>17 (37%)</td>
</tr>
<tr>
<td>ESPC-3</td>
<td>Bolus 5-FU and Folinic Acid</td>
<td>6 months</td>
<td>None</td>
<td>551</td>
<td>65 (12%)</td>
<td>Not provided</td>
<td>195 (35%)</td>
<td>•23.0 From date of surg</td>
<td>Not provided</td>
<td>Not provided</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>6 months</td>
<td>None</td>
<td>None</td>
<td>537</td>
<td>59 (11%)</td>
<td>Not provided</td>
<td>189 (35%)</td>
<td>•23.6</td>
<td>Not provided</td>
<td>Not provided</td>
</tr>
<tr>
<td>CONKO-001</td>
<td>Gemcitabine</td>
<td>6 months</td>
<td>None</td>
<td>179</td>
<td>18 (10%)</td>
<td>“Some patients”</td>
<td>34</td>
<td>•22.1</td>
<td>Not provided</td>
<td>45 (25%)</td>
</tr>
<tr>
<td>Control (surgery only)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>175</td>
<td>NA</td>
<td>“Almost all patients”</td>
<td>27</td>
<td>20.2</td>
<td>Not provided</td>
<td>66 (38%)</td>
</tr>
</tbody>
</table>
General Consensus: Adj Rx Pancreas CA

• Positive margin resections are common (25%-50%) and confound the results of adjuvant therapy trials

• Chemoradiation delivered to persistent (macroscopic), incompletely resected disease (R2) is not adjuvant therapy

• Pathologists cannot tell the difference between an R1 and an R2 resection

• Operative notes rarely contain information on the completeness of resection (ACOSOG Z5031: 24%)

• If adjuvant chemoradiation is delivered, it should follow systemic therapy