DO WE NEED RADIATION THERAPY IN PANCREATIC CANCER?

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Dr. Raben does not have any relevant financial relationships with commercial interests to report.

Dr. Raben does not intend to reference off-label/unapproved uses of products or devices in this presentation.
Objectives

- Review current algorithms for pancreatic cancer management
- **Discuss issues and controversies related to adjuvant radiation**
- SBRT? What is it and does it have a role in this disease?
- New science – after all – lets be honest – this is a systemic disease!
Diagnostic tests and Work-up

- Endoscopic US (alone or with ERCP) with biopsy of suspicious nodes if feasible
- CT Abdomen/Chest but I prefer a PET-CT scan
- Labs: please include Ca 19-9 pre-op!! (sensitivity – 90%, specificity- 75% and good marker for follow-up if elevated)
- Laproscopy: optional but I think helpful to prevent unnecessary resections; helps in looking for peritoneal seeding or liver mets
TREATMENT ALGORITHM
NEWLY DIAGNOSED ADENOCARCINOMA OF PANCREAS

Confirm histologic diagnosis (CT or EUS guided needle aspiration)

**Staging evaluation:** CA 19-9 & liver chemistries; Rule out intra-abdominal and chest metastases with CT abdomen/pelvis, possible laparoscopy, chest x-ray

**Exploratory laparotomy:** resection if possible (no encasement of the celiac/superior mesenteric vessels)

Resectable

- **Standard:** EBRT + 5FU or Gemzar based chemo
- **Evaluate:** Neoadjuvant RT + chemo

Unresectable or Borderline Resectable

- **Standard:** EBRT+ 5FU or Xeloda or Gemzar based chemo
- **Evaluate:** Neoadjuvant EBRT + chemo
  - New therapies:
    - EGFR, VEGF Inhibitors
    - mTor inhibitors, Src kinase inhibitors, Akt inhibitors
Adjuvant RT or CRT in pancreatic cancer
So what are we really talking about here?

- ~28,000 cases per year
- ~15% of those are resectable so...~4200 cases in the US each year
- Out of those, at least 15% will have developed metastasis at the time of restaging. **so down to ~3600 cases left**
- ~80% of the resected cases will have regional nodal spread and/or positive margins (3000 cases)...so not big numbers here!
Resected Pancreatic Cancer

High Risk For Local Failure + Distant Metastases
Has adjuvant CRT been effective in other diseases??

- Breast cancer – YES
- Gastric Cancer – YES
- Head and Neck Cancer – Yes
- Lung Cancer – controversial but most say YES in N2 disease
- Rectal cancer – YES (for LC)
- Brain – YES
- Prostate - YES
What do the Europeans say? Dr. Neoptolemos on RT for Pancreatic ca

- Ann Surg (2002): Espac 1 has clearly and unequivocally rejected the survival value of adjuvant chemoradiotherapy

- Clinical Gastroenterology (2002): Adjuvant chemoradiotherapy is of no benefit.

- Expert Opinion (2002): It is not necessary to give chemoradiotherapy when chemotherapy provides as good, if not better results.

- J Surg Oncol Clin N Amer (2004): The standard treatment for pancreatic cancer is now resection and adjuvant chemotherapy

- Br J Ca (2005): Routine use of chemoradiotherapy is not warranted
Here’s the Problem: Patterns Of Failure After Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts.</th>
<th>Local (%)</th>
<th>Peritoneal (%)</th>
<th>Liver (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tepper</td>
<td>26</td>
<td>50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Griffin</td>
<td>36</td>
<td>53</td>
<td>31</td>
<td>44</td>
</tr>
<tr>
<td>Whittington</td>
<td>29</td>
<td>85</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Ozaki</td>
<td>14</td>
<td>86</td>
<td>36</td>
<td>79</td>
</tr>
<tr>
<td>Westerdahl</td>
<td>74</td>
<td>86</td>
<td>-</td>
<td>92</td>
</tr>
</tbody>
</table>
Retroperitoneal margin a major problem
Pancreas Ca: Patterns of Failure After Surgery

MGH: 72 Patients Underwent Resection of Pancreatic Head Carcinoma:

- 37/72 Patients (51%): Tumor Extension to Margins (Retroperitoneum-27, Pancreatic Transection-14, Bile Duct-4)
**Intergroup (RTOG 97-04) Trial**

Crude data on 538 patients

<table>
<thead>
<tr>
<th>SURGICAL MARGINS</th>
<th>RT + 5-FU</th>
<th>RT + Gemzar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>45%</td>
<td>39%</td>
</tr>
<tr>
<td>Positive</td>
<td>32%</td>
<td>34%</td>
</tr>
<tr>
<td>Unknown</td>
<td>23%</td>
<td>26%</td>
</tr>
</tbody>
</table>
What about around the world?
Pancreatic Adenocarcinoma
Positive Margin Resection

<table>
<thead>
<tr>
<th>Author (YR)</th>
<th>N</th>
<th>Margin</th>
<th>Med S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoptolemos (2001)</td>
<td>101</td>
<td>R1</td>
<td>11</td>
</tr>
<tr>
<td>Benessai (2000)</td>
<td>15</td>
<td>R1/2</td>
<td>9</td>
</tr>
<tr>
<td>Sohn (2000)</td>
<td>184</td>
<td>R1/2</td>
<td>12</td>
</tr>
<tr>
<td>Millikan (1999)</td>
<td>22</td>
<td>R1</td>
<td>8</td>
</tr>
<tr>
<td>Nishimura (1997)</td>
<td>70</td>
<td>R1/2</td>
<td>6</td>
</tr>
<tr>
<td>Sperti (1996)</td>
<td>19</td>
<td>R1/2</td>
<td>7</td>
</tr>
<tr>
<td>Nitecki (1995)</td>
<td>28</td>
<td>R2</td>
<td>9</td>
</tr>
<tr>
<td>Yeo (1995)</td>
<td>58</td>
<td>R1/2</td>
<td>10</td>
</tr>
<tr>
<td>Willett (1993)</td>
<td>37</td>
<td>R1/2</td>
<td>12</td>
</tr>
</tbody>
</table>
Local Failure After Resection

A Significant Clinical Problem: Pain, Obstruction (Biliary, Gastric), and Bleeding
Efforts to Improve Local Control

- Postoperative RT+ChT
- Preoperative RT+ChT
For the surgical residents: Two Important GITSG Studies (1985): The Beginning!!

Resected Pancreatic Ca
   n=43
   Observation
   RT + 5-FU

Resected Rectal Ca
   n=227
   Observation
   RT
   5-FU + MeCCNU
   RT + 5-FU/MeCCNU
Lessons from Rectal Ca Trials (1985-2004)

LC + S Improved by:

- Combined Modality Tx (RT + ChT)
- Modern Tx: Continuous + Higher Dose RT (50-54 Gy) vs Lower Dose (40 Gy)
- PVI vs. Bolus 5-FU with RT
- Sequence: Preop > Postop
- More QA not Less (RT, ChT, Path, Surgery)
- Now using IMRT based approaches with image guidance
Surgeons view of radiation oncology
IMRT and IGRT are becoming standard
Modern Technological Innovations

- Stereotactic targeting
- 3-D conformal avoidance
- IMRT
- 4-D motion assessment
- Motion control
- Image guidance

ALL FACILITATING STEREOTACTIC ABLATIVE AND HYPOFRACTIONATED RADIOTHERAPY
### Adjuvant Pancreatic Ca Trials

#### Table 1: Phase III-studies for adjuvant therapy

<table>
<thead>
<tr>
<th>Group - Study Year</th>
<th>Patients (n)</th>
<th>Inclusion criteria</th>
<th>Treatment arms</th>
<th>Median overall survival (Months)</th>
<th>p-value</th>
<th>Preoperative Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG-1985[18]</td>
<td>49</td>
<td>R0</td>
<td>CRT Observation</td>
<td>21.0 / 10.9</td>
<td>0.005</td>
<td>No</td>
</tr>
<tr>
<td>EORTC-1999[22]</td>
<td>114*</td>
<td>R0</td>
<td>CRT Observation</td>
<td>17.1 / 12.6</td>
<td>0.099</td>
<td>No</td>
</tr>
<tr>
<td>ESPAC-1-2004[17]</td>
<td>289*</td>
<td>R0 or R1</td>
<td>Cx No Cx$^&lt;$</td>
<td>21.6 / 16.9</td>
<td>Not available</td>
<td>No</td>
</tr>
<tr>
<td>CONKO-001-2007[19]</td>
<td>368</td>
<td>R0 or R1</td>
<td>Cx Observation</td>
<td>22.1 / 20.2</td>
<td>0.06</td>
<td>Yes</td>
</tr>
<tr>
<td>RTOG 9704 2008[20]</td>
<td>442$^&lt;$</td>
<td>R0 or R1</td>
<td>CRT + GEM CRT + 5-FU</td>
<td>20.6 / 16.9</td>
<td>0.033</td>
<td>Yes</td>
</tr>
</tbody>
</table>
GITSG (1974): 40 Gy (SC) + Bolus 5-FU
Path QA: Yes
RT QA: Yes

EORTC (1987): 40 Gy (SC) + 5-FU
Path QA: Yes
RT QA: Yes

ESPAC 1 (1996): 40 Gy (SC) + Bolus 5-FU
Path QA: No
RT QA: No
### Adjuvant Pancreas Ca: GITSG (1985)

<table>
<thead>
<tr>
<th>Tx</th>
<th># Pts</th>
<th>MS (mo)</th>
<th>2 Yr. S</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 Gy/5-FU</td>
<td>21</td>
<td>20</td>
<td>43%</td>
</tr>
<tr>
<td>Observation</td>
<td>22</td>
<td>11</td>
<td>18%</td>
</tr>
</tbody>
</table>
Pancreas Adjuvant – GTSG Phase III Study
Probability of Survival by Treatment Group

![Graph showing survival rates for different treatment groups. The graph compares survival probabilities between Chemo + radiotherapy (n = 21) and Operation alone – control (n = 22). The p-value for the difference is P = 0.03.](image)
Pancreas Adjuvant – GTSG Phase III Study
Probability of Survival by Treatment Group
Adjuvant Pancreas / Periampullary Ca: EORTC (1999)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median S (mo)</th>
<th>5 Yr. S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT (40 Gy-SC) + 5-FU</td>
<td>17.1</td>
<td>20</td>
</tr>
<tr>
<td>Observation</td>
<td>12.6</td>
<td>10</td>
</tr>
</tbody>
</table>

P=0.099
PANCREAS CANCER: EORTC PHASE III TRIAL

Survival – Surgery ± EBRT + 5FU

EORTC (1999): Conclusions

- Pancreas Ca: Trend to Improved S with Adjuvant Tx

  Caveats:
  - No Maintenance ChT
  - 20% of “Tx Patients”: **No Tx!!**
  - Underpowered Study
Pancreas Adjuvant – Johns’ Hopkins Survival – Surgery ± Postop EBRT + 5-FU

Pancreas Adjuvant - Johns’ Hopkins Survival - Surgery ± Postop EBRT + 5-FU Tumors ≥3 cm

Pancreas Adjuvant – Johns’ Hopkins
Survival – Surgery ± Postop EBRT + 5-FU
Margin-Negative Patients

Pancreas Adjuvant – Johns’ Hopkins
Survival – Surgery ± Postop EBRT + 5-FU
Node-Positive Patients

ESPAC-1: European Adjuvant Trial

- 541 Pts. With “Macroscopically Resected” Pancreatic Cancer
- Eleven Countries: Austria, Belgium, France, Germany, Greece, Hungary, Italy, Spain, Sweden, Switzerland, UK
- 61 Centers
ESPAC-1: European Adjuvant Trial

Two Main Tx Questions:

- ChemoRT vs. No ChemoRT
- ChT vs. No ChT
ESPAC-1 PHASE III PANCREAS TRIAL: SURGERY ± ADJUVANT

- Randomization methods: 3 separate trials, evaluated as single trial
  - 2x2 factorial (N=285)
    - Surgery alone, EBRT+5FU, 5FU/Leuc, or both
  - Chemoradiotherapy vs none (N=68)
    - Background tx allowed (21/68-unknown)
  - Chemotherapy vs none (N=188)
    - Background tx allowed (61/188-unknown)
- Restaging studies - not performed

Restaging CT Study: Critical Prior to Study Entry

- Verify Quality of Surgery: R0 / R1 vs R2

<table>
<thead>
<tr>
<th>R Designation</th>
<th>Gross Resection</th>
<th>Microscopic Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>complete</td>
<td>negative</td>
</tr>
<tr>
<td>R1</td>
<td>complete</td>
<td>positive</td>
</tr>
<tr>
<td>R2</td>
<td>incomplete</td>
<td>positive</td>
</tr>
</tbody>
</table>

- Identify patients (25%) who develop metastatic disease after CT restaging
PANCREAS CA: ESPAC-1
Randomization Method, 3 Trials

541 eligible patients: Bx (+) ACA pancreas; gross total resection

Physician Selection

285 pts randomized for both chemoRT and adjuvant chemo
(2X2 factorial)

68 pts randomized for chemoRT only;
(record background chemo or not)

188 pts randomized for adjuvant chemo only
(record background chemoRT or not)
ESPAC-1: Pooled Data Results

- Improved MS in Pts. Receiving 5-FU/Leuc (19.7 mo) vs Pts. Not Receiving ChT (14.0 mo)
- No Difference in MS Between ChT/RT Pts. (15.5 mo) and Non-ChT/RT Pts. (16.1 mo)

ESPAC-1 PHASE III PANCREAS ACA TRIAL  Patient Group and Randomization Methods*

- Eligible patients: ACA pancreas, gross total resection
- Randomization methods: 2x2 factorial design (N=289)
  - Surgery alone (N=69)
  - Postop EBRT+5FU (N=73)
  - Adjuvant 5FU/Leucovorin (N=75)
  - EBRT+5FU, 5FU/Leucovorin (N=72)
- Statistical analysis: Analyzed by intent to treat
  - Adjuvant chemotherapy (N=147) vs none (N=142)
  - Postop EBRT+5FU (N=145) vs none (N=144)

Neoptolemos JP et al, NEJM 350:1200-10, 2004
PANCREAS CA: ESPAC-1
Randomization Method, 3 Trials

541 eligible patients: Bx (+) ACA pancreas; gross total resection

Physician Selection

- 289 pts randomized for both chemoRT and adjuvant chemo (2X2 factorial)
- 68 pts randomized for chemoRT only; (record background chemo or not)
- 188 pts randomized for adjuvant chemo only; (record background chemoRT or not)
PANCREAS CANCER: ESPAC-1 TRIAL

2x2 Factorial Design

289 patients histologically proven ACA of the pancreas potentially curative resection

- 69 assigned to observation
- 73 assigned to chemoRT
- 75 assigned to adjuv chemo
- 72 assigned to chemoRT and adjuvant chemo

Treatment comparison

- ChemoRT vs No chemoRT (145 vs 144)
- Adjuvant chemo vs No adjuvant chemo (147 vs 142)

Neoptolemos et al, NEJM 350:1202, 2004
ESPAC-1 PHASE III PANCREAS ACA TRIAL*
Tx Methods – Surgery & Adjuvant Therapy

- **Surgery**
  - Pancreatoco-duodenectomy (head lesions) or total pancreatectomy
  - Positive resection margins, 18% of patients

- **Adjuvant chemotherapy**
  - 5FU (425 mg/m²) Leucovorin (20 mg/m²)
  - 5 consecutive days every 28 d for 6 cycles

- **EBRT+5FU**
  - 40 Gy/6 wks split course
  - No defined fields, no central audit !!! (dealer’s choice)
  - Each center used its own QA standards
  - Concurrent bolus chemo, 5FU 500 mg/m² d 1-3, wk 1 and 3 EBRT

ESPAC 1: ChemoRT vs. No ChemoRT

<table>
<thead>
<tr>
<th></th>
<th># Pts</th>
<th>MS (mo)</th>
<th>2 Yr S (%)</th>
<th>5 Yr. S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChemoRT</td>
<td>145</td>
<td>15.9</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>No ChemoRT</td>
<td>144</td>
<td>17.9*</td>
<td>41</td>
<td>20</td>
</tr>
</tbody>
</table>
# ESPAC 1: ChT vs. No ChT

<table>
<thead>
<tr>
<th></th>
<th># Pts</th>
<th>MS (mo)</th>
<th>2 Yr S (%)</th>
<th>5 Yr. S (%)</th>
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<tbody>
<tr>
<td>ChT</td>
<td>145</td>
<td>20.1*</td>
<td>40</td>
<td>21</td>
</tr>
<tr>
<td>No ChT</td>
<td>144</td>
<td>15.5</td>
<td>30</td>
<td>8</td>
</tr>
</tbody>
</table>
ESPAC-1

- **2x2 factorial** 289

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Data available</td>
<td>122</td>
<td>(83%)</td>
</tr>
<tr>
<td>Received all chemo</td>
<td>61</td>
<td>(41%)</td>
</tr>
<tr>
<td>Received &lt; 6 cycles</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Received none</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChemoXRT</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>Data available</td>
<td>128</td>
<td>(88%)</td>
</tr>
<tr>
<td>Received 40 Gy</td>
<td>90</td>
<td>(62%)</td>
</tr>
<tr>
<td>Received +/- 40 Gy</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Received none</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>
Protocol Compliance

<table>
<thead>
<tr>
<th></th>
<th>German Rectal CAO/ARO/AIO-94 (n=421)</th>
<th>Espac-1 ChemoRT (n=145)</th>
<th>Espac-1 ChT (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unavailable Data</td>
<td>&lt; 2%</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>RT Dose per Protocol</td>
<td>92%</td>
<td>62%</td>
<td>-</td>
</tr>
<tr>
<td>ChT per Protocol</td>
<td>89%</td>
<td>-</td>
<td>41%</td>
</tr>
<tr>
<td>No Tx</td>
<td>3% RT</td>
<td>7% RT</td>
<td>14% ChT</td>
</tr>
<tr>
<td></td>
<td>4% ChT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Local Recurrence: The Unexplained Problem

- First site of recurrence local
  - 35% Local
  - 27% Local + distant
- No QA: path, surgical, RT, diagnostic imaging
- Margins + reported to be 18% overall

ESPAC-1/Neoptolemos, NEJM, 2004
ESPAC-1 PHASE III PANCREAS ADJUVANT
Major Flaws in Study Design

- Randomization methods:
  - 3 separate trials, evaluated as single trial
  - Background therapy allowed 2 of 3 trials

- Restaging studies - not performed

- EBRT+5FU
  - 40 Gy/6 wks split course
  - No defined fields, no central audit
  - Each center used its own QA standards

# Pancreas Ca: Adjuvant Phase III Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy of 40 Gy (S.C.) + 5-FU</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG (1985)</td>
<td>Yes</td>
<td>- Small #’s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Slow accrual</td>
</tr>
<tr>
<td>EORTC (1999)</td>
<td>No</td>
<td>- Underpowered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Periampullary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 20% Not tx</td>
</tr>
</tbody>
</table>
PANCREATIC CANCER

Phase III U.S. GI Intergroup Adjuvant Trial

- RTOG was the Coordinating group of the Intergroup Phase III postop study:

**RTOG 9704**

5-FU ⇒ Chemo RT (5-FU) ⇒ 5-FU

vs

GEM ⇒ Chemo RT (5-FU) ⇒ GEM
RESECTED PANCREATIC CANCER

Phase III U.S. GI Intergroup, RTOG 9704

- Initial accrual goal of 330 pts was increased due to excellent accrual (11/mo); **538 pts accrued from Jul 98-Jul 2002**
- Restaging studies were performed after recovery from surgery
- Chemoradiation (CRT)
  - **EBRT**, 50.4 Gy in 28 Fx over 5.5 wks, boost after 45 Gy
  - **PVI 5FU**, 250 mg/m2/d during EBRT
- Pre and Post-CRT Chemotherapy
  - **Arm 1**: 3 wks of PVI 5-FU (250 mg/m2/d) before CRT and 2 cycles after CRT (cycle = 4 wk PVI 5FU 250 mg.m2/d; 2 wk rest)
  - **Arm 2**: 1 cycle of gemzar before CRT and 3 cycles after CRT (cycle = 3wks of gemzar @ 1000 mg/m2; 1 wk rest)
Results of RTOG 97-04

- On multivariate analysis 3 parameters reached statistical significance:
  - treatment arm ($p = 0.025$),
  - nodal status ($p = 0.003$)
  - maximal tumor diameter ($p = 0.03$).
- Benefits with Gem seen in HOP cancers
- Compared to ESPAC-1, RTOG 97-04 included patients with a more unfavourable distribution of risk factors (resection status, pN-category and largest tumor diameter) but nevertheless resulted in longer survival.
Oh...and one more thing

- The improved radiotherapy technique employed in the RTOG trial is reflected in the reduction of local recurrence rates being
  - 25% in the RTOG trial compared to
  - 47% in the GITSG trial
  - And 62% overall in the ESPAC-1 trial.

- In other words ...when we do our job correctly, use IMRT and image guidance, we have less toxicity and better outcomes
Adjuvant Therapy: Pancreas Ca

The value of postoperative EBRT 40 Gy (S.C.) with concurrent ± maintenance 5-FU: Conflicting Results
Adjuvant Therapy: Pancreas Ca

Given this data, what is appropriate tx for patients with potentially resectable pancreatic cancer?
Rationale: Adjuvant Radiation Therapy + ChT

- LF - Significant clinical problem: Effective Tx is critical
- Locally Advanced Pancreas Ca: 3 Positive Trials for EBRT+ChT
- Well Conducted Adjuvant Trials in Gastric and Rectal Ca: Improved LC and S
- Trials: Contemporary Techniques and Doses (EBRT+ChT)
<table>
<thead>
<tr>
<th>Study</th>
<th># Pts.</th>
<th>EBRT (Gy)</th>
<th>ChT</th>
<th>5 Yr.S (%)</th>
<th>LC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginia Mason (2003)</td>
<td>43</td>
<td>45-54</td>
<td>5-FU CDDP Interferon</td>
<td>55</td>
<td>-</td>
</tr>
<tr>
<td>Hopkins (2000)</td>
<td>366</td>
<td>40-57.6</td>
<td>5-FU ± L</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Mayo (1993)</td>
<td>29</td>
<td>45-54</td>
<td>5-FU</td>
<td>17</td>
<td>93</td>
</tr>
<tr>
<td>U. Penn (1991)</td>
<td>20</td>
<td>&gt;45</td>
<td>5FU+Mit-C</td>
<td>43 #</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>35 #</td>
<td>15</td>
</tr>
</tbody>
</table>
Resectable Pancreas Cancer

Phase II/III Trials: Optimize Local Control by Integrate EBRT (Contemporary Techniques and Doses) with Newer Cytotoxics and Target Agents
EORTC (40013-22011): Adjuvant Pancreas Phase II Trial

Resection:
- Gemcitabine + EBRT (50.4 Gy) with Gemcitabine
- Gemcitabine

- Better local control with CRT after Gem, only RO patients entered, good QA

- **RTOG 0848/EORTC Phase III study** will seek to clarify the role of adjuvant CRT, following delivery of full-course gemcitabine-based chemotherapy.
### Selected Adjuvant Pancreatic Protocols

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Intergroup</td>
<td>Randomized phase II (Adjuvant/</td>
<td>Gem + C-225</td>
</tr>
<tr>
<td></td>
<td>Post-op)</td>
<td>Cape + C-225 + XRT (50.4 Gy / 5.5 weeks)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gem + C-225</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gem + Bev</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cape + Bev + XRT (50.4 Gy / 5.5 weeks)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gem + Bev</td>
</tr>
<tr>
<td>ACOSOG Z05031</td>
<td>Phase II</td>
<td>XRT (50.4 Gy / 5.5 weeks) + PVI 5-FU + IFN + CDDP weekly</td>
</tr>
<tr>
<td>ACOSOG</td>
<td>Phase II (Neoadjuvant/ Pre-op)</td>
<td>Gem + Bev</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cape + XRT (45 Gy / 5 weeks) + Bev</td>
</tr>
</tbody>
</table>
Summary

- GITSG/EORTC/ESPAC: Conflicting Results
- Strong Rationale and Support for Adjuvant RT and ChT (Concurrently and Maintenance)
- Phase III Trials: Results Pending
- Dr. Neoptolemos (2005): “There may be scope for future studies to investigate more modern chemoradiation techniques”...ya think!!
Neoadjuvant CRT – can’t we just get along??

- Kill the microscopic areas of the cancer, get more RO resections and decreased LN metastasis
- Don’t have the problems related to hypoxia and long post-op delays
- Less injury as we aren’t worried about surgical anastomosis
- Better selection of patients, imaging, biomarkers to tell us which way to go (ca 19-9)
# Pancreas Ca: NeoAdjuvant Tx

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts.</th>
<th>EBRT (Gy)</th>
<th>ChT</th>
<th>4 Y.S (%)</th>
<th>LC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDAH (2002)</td>
<td>20</td>
<td>30/10 Fx</td>
<td>Paclitaxel</td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>MDAH (1999)</td>
<td>35</td>
<td>30/10 Fx</td>
<td>5-FU</td>
<td>23</td>
<td>90</td>
</tr>
<tr>
<td>MDAH (1996)</td>
<td>39</td>
<td>30-50.4</td>
<td>5-FU</td>
<td>17</td>
<td>93</td>
</tr>
<tr>
<td>F.C.C. (1995)</td>
<td>11</td>
<td>50.4</td>
<td>5FU+Mit-C</td>
<td>40</td>
<td>91</td>
</tr>
</tbody>
</table>
Stereotactic Body Radioablation or SBRA (or SBRT) for LAPC
Reality of Stereotactic Ablation

- Historically, rarely feasible
  - Requires very high dose delivery
  - Toxicity would typically prohibit ablation
  - Only BRACHYTHERAPY techniques

- Historically, required a special circumstance
  - Inherent uptake of iodine by thyroid-like tissue
  - Implantable tumors

- Ablation with radiation was **NOT** feasible – simply didn’t have the “soft” or “hard” technology (or QA and expertise not there...aka..ESPAC!!)
SBRT: operational definition

- Stereotactically localized, ultra-high-dose radiotherapy
  - Given to discrete tumor nodules in extracranial locations
  - Within a hypofractionated regimen (1-5 treatments)
  - Unlike typical 6-7 week course of radiotherapy
  - Analogous to cranial stereotactic radiosurgery (SRS)

Head frame-based cranial SRS  Body frame-based cranial SRS
SBRT-friendly systems now widely available
Spectrum of potential applications of SBRT

- Intensified treatment to a primary cancer
  + Stage I lung cancer
  + Primary HCC
  + Pancreas cancer
  + Prostate cancer
- Palliation/control for challenging sites of recurrence
  + Spinal
  + Retroperitoneal
  + Previously irradiated volumes
- Adjuvant systemic cytoreductive therapy
  + “Radical” treatment for isolated liver, lung, spine, and other mets
High Dose: Conventional Radiation vs. SABR

Postage Stamp

6000 cGy (script dose)

THIS IS A PARADIGM CHANGING DIFFERENCE
Treatment: 60 Gy/3 fractions
Characteristic radiographic findings

- Baseline
- 4 mos, CR
- 8 mos, subtle fibrosis
- 12 mos, mature fibrosis
- 18 mos, NED
Benefits of Stereotactic Ablative Radiotherapy

- Outpatient
- 20-60 Minutes Per Treatment
- Entire course of Rx in 1-2 weeks
- No Sedation or Anesthesia (painless)
- 1-5 Treatments qd or qod
- Immediate Return To Activities
Can we do this with LAPC?
Stereotactic Radiotherapy for Unresectable Adenocarcinoma of the Pancreas

Daniel T. Chang, MD, Devin Schellenberg, MD, John Shen, BS, Jeff Kim, BS, Karyn A. Goodman, MD, George A. Fisher, MD, PhD, James M. Ford, MD, Terry Desser, MD, Andrew Quon, MD, and Albert C. Koong, MD, PhD

**FIGURE 1.** Typical isodose distribution for patients receiving stereotactic body radiotherapy. Twenty-five grays (Gy) are prescribed to the line that completely encompasses the planning target volume. The 12.5-Gy line is kept away from the distal wall of the duodenum and stomach.

**FIGURE 3.** Actuarial curve of overall survival calculated from date of stereotactic body radiotherapy.
Can it be done safely?

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel ulcer</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel ulcer</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Duodenal stricture</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Biliary stricture</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Small bowel perforation</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6 (8)</strong></td>
<td><strong>7 (9)</strong></td>
<td><strong>1 (1)</strong></td>
<td><strong>14 (18)</strong></td>
</tr>
</tbody>
</table>
Bottom line – volume of duodenum getting high dose is the key!

Fig. 3. Maximum dose predicts duodenal toxicity. Kaplan-Meier analysis of toxicity according to the maximum dose to 1 cm³ of duodenum (D_{max}).
Adapt based on location of cancer

<table>
<thead>
<tr>
<th>800 cGy x 3</th>
<th>1000 cGy x 3</th>
<th>1200 cGy x 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(total dose 2400 Gy)</td>
<td>(total dose 3000 Gy)</td>
<td>(total dose 3600 Gy)</td>
</tr>
</tbody>
</table>

Fig. 1. Adaptive tolerance-based stereotactic body radiotherapy dose prescription showing graphic depiction of relationship between duodenum and pancreatic tumor (red) used to determine each of three prescribed doses.

Anand Mahadevan, M.D.
Can we use Ca-19-9 after SBRT?

(a) Effect of CA19-9 levels at Diagnosis on Survival

(b) Effect of Achieving a Normal CA19-9 on Survival

Devlin Schellenberg, M.D.

And finally...where does biologics come in to play?

- Tarceva FDA approved with gemzar – not very active
- Src kinase inhibitors
- mTOR inhibitors
- DNA repair inhibitors (PARP)
- Protease inhibitors
- Akt/Pl3-K inhibitors
SRC-family kinases in signal transduction

Growth factors (EGF, PDGF, HGF)

RTKs (EGFR, PDGFR, c-Met)

Integrins

Actin cytoskeleton

Adapter and structural proteins

Survival

Cellular transformation

Mitogenesis

Migration/morphogenesis
SFK roles in cytoskeletal function

Central role of c-Src in cellular morphology, motility, adhesion, membrane ruffling, and invasive phenotype ('epithelial-to-mesenchymal transition')
Dasatinib, a src kinase inhibitor blocks metastatic process

Table 2. Effects of c-Src Targeted siRNA or the Src Family Kinase Selective Inhibitor BMS-354825 on In Vivo Growth and Progression of Pancreatic Adenocarcinoma Cells

<table>
<thead>
<tr>
<th></th>
<th>Primary Pancreatic Tumors</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>Mass (mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>9/9</td>
<td>1486</td>
</tr>
<tr>
<td>BMS-354825</td>
<td>7/7</td>
<td>754*</td>
</tr>
</tbody>
</table>

L3.6pl cells were injected into the pancreas of nude mice (5 x 10^5 cells/mouse) on Day 0. On Day 14, 200 μl BMS-354825 (15 mg/kg) or an equal volume of citrate buffer vehicle was administered by oral gavage. Treatments continued daily for 28 days. Mice were sacrificed on Day 42 and evaluated for primary pancreatic tumors and liver and lymph node metastases.

* = P<0.05, relative to controls

... so does the AZD Src inhibitor

Fig. 7  Dose-dependent inhibition of L3.6pl human pancreatic cancer cell migration by AZM475271 (modified Boyden chamber assay). *, $P < 0.001$; **, $P < 0.0004$ (versus fibronectin stimulation).

Table 1  In vivo Efficacy of AZM475271 +/− Gemcitabine for Human Pancreatic Cancer in Nude Mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pancreatic tumor</th>
<th>Metastases† (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor incidence † (N)</td>
<td>Median (range) tumor volume (mm$^3$)</td>
</tr>
<tr>
<td>Gemcitabine (twice weekly, 100 mg/kg)</td>
<td>5/5</td>
<td>393 (297–471); $P &lt; 0.0004$ ‡</td>
</tr>
<tr>
<td>AZM475271 (50 mg/kg/d)</td>
<td>9/9</td>
<td>827 (603–879); $P &lt; 0.002$ ‡</td>
</tr>
<tr>
<td>AZM475271 (50 mg/kg/d) + gemcitabine (twice weekly, 100 mg/kg)</td>
<td>8/8</td>
<td>124 (63–363); $P &lt; 0.0001§; P &lt; 0.002$ §</td>
</tr>
</tbody>
</table>

* Data represent number of mice with tumors/number of mice receiving injections.
† Data represent number of mice with metastases/number of mice receiving injections.
‡ Compared with controls.
§ Compared with gemcitabine alone (unpaired Student’s t test).
c-Src overexpression was found in 13 of 13 clinical samples of pancreatic cancer (but not in normal tissues) and in 14/17 cell lines

So...how could we use it?

Surgical Resection
Stratify based on R0 vs R1
LN mets
Ca-19-9

CRT

CRT + Src kinase
Still a ways to go – but he who dares...wins!
Thanks
Impossible is nothing