Pancreatic cancer: Current Treatment Approaches and Controversies

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Conflict of Interest

No disclosures
Learning Objectives

• Discuss current treatment strategies and approaches to pancreatic cancer
  – Adjuvant therapy
  – Neoadjuvant therapy
  – Definitive chemoradiation
  – Chemotherapy alone

• Future treatment
  – Alternate treatment strategies
  – Radiation technologies
Pancreatic Cancer

• 46,420 estimated cases in 2014
• 39,590 estimated deaths in 2014
• 4th cause of cancer death in the U.S
• 15-20% resectable at presentation
  – 5 yr OS 20%
• 30-40% present with locally advanced/unresectable disease
Patient Presentation

• 61M developed jaundice/pruritus with 20lb weight loss over last 3 months 5/2014
• Labs: Bilirubin 14.8, CT shows lesion in pancreatic head and biliary ductal dilation
• 5/22: ERCP: biliary stricture, stent placed
• 6/1: EUS: 1.1x1.9cm mass pancreatic head, uT1N0
  – FNA: adenocarcinoma
• CA 19-9: 149; CEA: 4.7
“Resectable”

No arterial or venous involvement

15-20% of patients
The Continuum of Resectability

Figure 3. Anatomy and Surgical Resectability of Pancreatic Cancer.
Pancreatic cancers are categorized on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases.
Next Step in Management for Potentially Resectable Pancreatic Cancer

• Upfront Surgery
  – Adjuvant Chemotherapy
  – Adjuvant Chemoradiotherapy

• Preoperative Chemoradiation

• Preoperative Chemotherapy
Whipple procedure
Patterns of Failure after Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts.</th>
<th>Local (%)</th>
<th>Peritoneal (%)</th>
<th>Liver (%)</th>
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<tbody>
<tr>
<td>Tepper</td>
<td>26</td>
<td>50</td>
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<td>Griffin</td>
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<td>Whittington</td>
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<td>Ozaki</td>
<td>14</td>
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<td>Westerdahl</td>
<td>74</td>
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<td>-</td>
<td>92</td>
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</tbody>
</table>
Adjuvant Therapy
Curative resection of pancreatic adenocarcinoma, negative margins (n=43, goal:100)

GITSG (1974-1982)

Randomize

5-FU* + RT

4000cGy total (2000cGy, 2 week break, 2000cGy)

Observation

Primary endpoint: OS

Kalser et al, Arch Surg 1985;120:899
GITSG

2-yr DFS: 11 months vs 9 months (p=0.01)

2-yr OS: 42% CMT vs 15% control (p=0.03)

Kalser et al, Arch Surg 1985;120:899
Resection of T1-2 N0-1 pancreatic head or T1-3 N0-1 periampullary cancer (n=218)
Pancreatic head cancer (n=114)

RANDOMIZE

5-FU* + RT
4000cGy total (2000cGy, 2 week break, 2000cGy)

Observation
No maintenance chemo after treatment

Primary endpoint: OS

EORTC (1987-1995)

EORTC

All patients

2-year OS: 51% vs 41%, (p=.208)
Median OS: 24.5 months vs. 19 months

Pancreatic head

2-year OS: 34% vs 26%, (p=.099), post hoc analysis

EORTC:
Long-term follow-up

No benefit of adjuvant chemoradiation compared to observation

All patients

Pancreatic head

5-year OS: 25% (CRT) vs 22%, (p=.539), HR 0.91 (95% CI, 0.68-1.23)
Median OS: 1.8 yrs vs. 1.6 yrs

Median survival: 1.3 yrs (CRT) vs 1.0 yr (HR 0.76, 95% CI, 0.52-1.12), post hoc analysis

Smeenk et al, Ann Surg, 2007;245:737
ESPAC-1

548 patients screened

7 excluded
1 had not had resection
2 previously had breast cancer
1 had metastases at entry
3 had duplicate records

541 Eligible patients with histologically proven adenocarcinoma of the pancreas having undergone potentially curative resection

285 in randomisation for both chemoradiotherapy and chemotherapy (two-by-two factorial)
68 in randomisation for chemoradiotherapy only (record whether patient has background chemotherapy or not)
188 in randomisation for chemotherapy only (record whether patient has background chemoradiotherapy or not)

69 assigned observations
70 assigned chemotherapy
74 assigned chemotherapy
72 assigned chemoradiotherapy and chemotherapy
35 assigned no chemotherapy
33 assigned no chemotherapy
96 assigned no chemotherapy
92 assigned chemotherapy

Chemo: Leucovorin (20 mg/m2) followed by bolus 5-FU (425 mg/m2)
RT: 4000cGy total (2000cGy, 2 week break, 2000cGy) + bolus 5-FU

Neoptolemos et al, Lancet, 2001; 358: 1576
Resection of pancreatic adenocarcinoma with no evidence of local/distant spread (n=289)

ESPAC-1: Re-Analysis

1. Observation
2. Chemo/RT\textsuperscript{a}
3. Chemo alone\textsuperscript{b}
4. Chemo/RT\textsuperscript{a} then chemo

\textsuperscript{a} 4000cGy total (2000cGy, 2 week break, 2000cGy) + bolus 5-FU
\textsuperscript{b} Leucovorin (20 mg/m\textsuperscript{2}) followed by bolus 5-FU (425mg/m\textsuperscript{2})

Treatment comparisons
CRT (2,4) vs. no CRT (1,3)
CT (3,4) vs. no CT (1,2)

Neoptolemos et al, NEJM 2004; 350: 1200
ESPAC-1: Re-Analysis

Median survival:

15.9 months CRT vs 17.9 months no CRT (HR for death 1.28 (95% CI, 0.99-1.66; p=.05)

5 yr OS: 10% (CRT) vs 20%

Median survival:

20.1 months Chemo vs 15.5 months no Chemo (HR for death 0.71 (95% CI, 0.55-0.92; p=.009)

5 yr OS: 21% (CT) vs 8%

Randomize

- Gross complete resection (R0 or R1)
- Pancreatic cancer (n=368)
- 80% with R0 resection
- CEA/CA 19-9 <2.5x ULN

- Gemcitabine x 6 cycles

- Observation

Primary endpoint: DFS

Oettle et al, JAMA, 2007; 297:267
CONKO

Median DFS:
13.4 months in Gem group vs 6.9 months in control (p<0.001)

Median OS:
22.1 months in Gem group vs 20.2 months in control (p=0.06)
CONKO Update

A Disease-free survival

B Overall survival

Log-rank P < 0.01

No. at risk
Gemcitabine 179 52 32 25 20 12
Observation 175 26 12 11 8 6

Log-rank P = 0.01

No. at risk
Gemcitabine 179 87 47 31 24 14
Observation 175 70 22 14 9 7

Oettle et al JAMA 2013;310:1473
Gross complete resection (R0 or R1) pancreatic cancer (n=1088)
ESPAC-3

No difference in OS or PFS

Neoptolemos et al, JAMA, 2010; 304:1073
Resected Pancreatic Cancer

United States
• Adjuvant CRT

Europe
• Adjuvant Chemo
GTR pancreatic adenocarcinoma (n=451)

Pancreatic head tumors (n=388)


RANDOMIZE

5-FU 250 mg/m2/day

Gemcitabine 1000 mg/m2/weekly x 3 weeks

XRT + 5-FU

5-FU 250 mg/m2/day

Gemcitabine 1000 mg/m2/weekly

Primary endpoint: OS, OS pancreatic head

Regine et al, JAMA 2008; 299:1019
RTOG 97-04

Pancreatic head tumors: 3-year OS 31% gemcitabine vs. 22% 5-FU

(HR 0.82, 95%CI, 0.65-1.03; p=.09)

On multivariate analysis, HR 0.80, 95%CI, 0.63-1.00; p = .05

Regine et al, JAMA 2008; 299:1019
RTOG 97-04

Overall Survival (%) vs Years after Randomization

Patients at Risk

- RT + 5-FU: 230, 160, 81, 52, 46, 43, 33, 20
- RT + Gemcitabine: 221, 155, 88, 59, 45, 41, 34, 22

Log-rank p-value = 0.51
HR = 0.933 (0.760, 1.145)

Regine et al, Annals Surgical Oncology 2011; 18:1319
RTOG 97-04: Prospective Quality Assurance of Radiation Therapy Fields

*First Phase III Adjuvant Pancreatic Cancer Trial To Do So*

Abrams et al IJROBP 2012;82:809
RTOG 9704 / US Intergroup Phase III Adjuvant Study
Overall Survival: Per Protocol vs. < Per Protocol

Abrams et al IJROBP 2012;82:809
## Adjuvant Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Treatment Arms</th>
<th>DFS/PFS</th>
<th>Median Survival</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG (74-82)</td>
<td>43</td>
<td>Obs CRT then 5FU</td>
<td>9 mo 11 mo</td>
<td>11 mo 20 mo</td>
<td>2 yr 15% 42%</td>
</tr>
<tr>
<td>EORTC (87-95)</td>
<td>218</td>
<td>Obs 5FU CRT</td>
<td>14.4 mo 18 mo</td>
<td>19.2 mo 21.6 mo</td>
<td>5 yr 22% 25%</td>
</tr>
<tr>
<td>ESPAC-1 (94-00)</td>
<td>289</td>
<td>No CT vs CT No CRT vs CRT</td>
<td>9.4 vs 15.3 mo 15.2 vs 10.7 mo</td>
<td>15.5 vs. 20.1 mo 17.9 vs. 15.9 mo</td>
<td>5 yr 8% vs 21% 20% vs 10%</td>
</tr>
<tr>
<td>CONKO (98-04)</td>
<td>368</td>
<td>Obs Gem</td>
<td>6.7 mo 13.4 mo</td>
<td>20.2 mo 22.8 mo</td>
<td>5 yr 10% 21%</td>
</tr>
<tr>
<td>RTOG 9704 (98-02)</td>
<td>451</td>
<td>5FU, CRT, 5FU Gem, CRT, Gem</td>
<td>No difference</td>
<td>17.1 mo 20.5 mo</td>
<td>5 yr 18% 22%</td>
</tr>
<tr>
<td>ESPAC-3 (07-09)</td>
<td>1088</td>
<td>5FU Gem</td>
<td>14.1 mo 14.3 mo</td>
<td>23 23.6</td>
<td>2 yr 48% 49%</td>
</tr>
</tbody>
</table>
US Future Directions: RTOG 0848

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**Schema**

**First Randomization**

- Arm 1: Gemcitabine x 5 cycles
- Arm 2: Gemcitabine + Erbitux x 5 cycles

**Evaluate to Confirm No Progression**

**Second Randomization**

- Arm 3: 1 cycle of chemotherapy
- Arm 4: 1 cycle of chemotherapy followed by XRT with either capecitabine or 5-FU

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RTOG website: rtog.org
Adjuvant Radiotherapy Planning

• Target Definitions
  – GTV: tumor location on preop imaging
  – CTV: ROI
    • Celiac artery: proximal 1-1.5cm
    • SMA: proximal 2.5-3cm
    • Aorta: from CA/PV/PJ (most superior) to bottom L2 (L3)
    • Portal vein: anterior to IVC (just below bifurcation) to SMV/splenic vein
    • Preoperative GTV
    • Pancreaticojejunostomy

Goodman et al IJROBP 2012;83:901
Adjuvant Radiotherapy Planning

Goodman et al IJROBP 2012;83:901
Adjuvant Radiotherapy Planning

• CTV: ROI expansions
  – Celiac artery: 1-1.5cm expansion
  – SMA: 1-1.5cm expansion
  – Aorta: 2.5-3cm right, 1cm to left, 2-2.5cm anterior, 0.2cm posterior
  – Portal vein: 1-1.5cm expansion
  – Preoperative GTV: 0.5-1cm expansion (or none)
  – Pancreaticojejunostomy: 0.5-1cm expansion

• PTV: 0.5cm in all directions
Adjuvant Radiotherapy Planning

Goodman et al IJROBP 2012;83:901
Adjuvant Radiotherapy Planning
Pancreas & Periampullary

~1400 pts
12 weeks post curative surgery

Europe Future Directions: ESPAC-4

Randomize

Gemcitabine

Gem/Capecitabine

Enrollment started 2008
Anticipated completion 2014
Neoadjuvant therapy
Rationale for Neoadjuvant CRT

• Increase likelihood R0 tumor resection
• Eliminating micro-metastatic disease
• Improving tumor related symptoms
• Minimize delays in treatment
• Smaller treatment fields
• Determining if tumor sensitive to therapy
• Allows biology to declare self- i.e. avoid unnecessary surgery
## Neoadjuvant CRT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>N</th>
<th>Treatment Arms</th>
<th>Complete Resection</th>
<th>Median Survival, OS (Entire Cohort)</th>
<th>Median Survival, OS (Resected OS Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisters et al[35]</td>
<td>1998</td>
<td>35</td>
<td>5-FU CRT (30 Gy) + IORT</td>
<td>20 (57%)</td>
<td>-</td>
<td>25 mo; 3-yr, 23%</td>
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<tr>
<td>Hoffman et al [36]</td>
<td>1998</td>
<td>53</td>
<td>MMC/5-FU CRT (50.4 Gy)</td>
<td>24 (45%)</td>
<td>9.7 mo</td>
<td>15.7 mo; 2-yr, 27%</td>
</tr>
<tr>
<td>Pisters et al[37]</td>
<td>2002</td>
<td>37</td>
<td>Paclitaxel CRT (30 Gy) + IORT</td>
<td>20 (54%)</td>
<td>12 mo; 3-yr, 14%</td>
<td>19 mo; 3-yr, 28%</td>
</tr>
<tr>
<td>Evans et al[25]</td>
<td>2008</td>
<td>86</td>
<td>Gem CRT (30 Gy)</td>
<td>64 (74%)</td>
<td>22.7 mo; 5-yr, 27%</td>
<td>34 mo; 5-yr, 32% (est)</td>
</tr>
<tr>
<td>Varadhachary et al[26]</td>
<td>2008</td>
<td>90</td>
<td>Gem/CDDP CT, gem CRT (30 Gy)</td>
<td>52 (58%)</td>
<td>17.4 mo</td>
<td>31 mo</td>
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<tr>
<td>Le Scodan et al[38]</td>
<td>2009</td>
<td>41</td>
<td>Gem/CDDP CRT (50 Gy)</td>
<td>26 (63%)</td>
<td>9.4 mo</td>
<td>12 mo; 2-yr, 32%</td>
</tr>
</tbody>
</table>

5-FU = fluorouracil; CDDP = cisplatin; CRT = chemoradiotherapy; CT = chemotherapy; gem = gemcitabine; IORT = intraoperative radiotherapy; MMC = mitomycin-C; OS = overall survival.
Neoadjuvant CRT

74 pts
Resectable pancreas head adenocarcinoma

Randomize

R0
Surgery: 67%
CRT: 90%
mOS (NS)
Surgery: 14.4 mo
CRT: 17.4 mo
“Borderline Resectable”

Involvement of SMV/PV
SMA abutment <180°
Borderline Resectable

• NCCN
  – No distant metastases
  – Venous involvement of the SMV/PV (resection/replacement possible)
  – GD artery encasement up to hepatic artery (no celiac involvement)
  – \( \leq 180^\circ \) involvement of SMA

• No randomized data
Recommend clinical trial: chemo/chemoradiation
### Studies of neoadjuvant treatment in borderline resectable pancreatic cancer (2010 to present)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Neoadjuvant regimen</th>
<th>Number resected (percent)</th>
<th>Number completely (R0) resected (percent)</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td>Leone F, 2013</td>
<td>15</td>
<td>GEMOX then Gem-RT</td>
<td>9 (60)</td>
<td>NR</td>
<td>Median 28 months</td>
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<tr>
<td>Takaahashi H, 2013</td>
<td>80</td>
<td>Gem-RT</td>
<td>43 (54)</td>
<td>42 (98)</td>
<td>5-year: 34 percent</td>
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<tr>
<td>Kim E, 2013</td>
<td>39</td>
<td>GEMOX-RT</td>
<td>24 (62)</td>
<td>NR</td>
<td>Median 18.4 months</td>
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<td>Motto F, 2013</td>
<td>16</td>
<td>Gem-S-1</td>
<td>NR</td>
<td>NR</td>
<td>2-year: 31.5 percent</td>
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<tr>
<td>Mahaseth H, 2012</td>
<td>2</td>
<td>FOLFRINOX then CRT</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>NR</td>
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<td>Kharofo J, 2012</td>
<td>12</td>
<td>FOLFRINOX then CRT</td>
<td>7 (58)</td>
<td>7 (100)</td>
<td>Median survival not reached at 13 months</td>
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<tr>
<td>Peddi P, 2012</td>
<td>4</td>
<td>FOLFRINOX</td>
<td>4 (100)</td>
<td>NR</td>
<td>NR</td>
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<td>Hosein P, 2012</td>
<td>4</td>
<td>FOLFRINOX</td>
<td>3 (75)</td>
<td>3 (100)</td>
<td>NR</td>
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<tr>
<td>Lee J, 2012</td>
<td>18</td>
<td>Gem-Cape</td>
<td>11 (61)</td>
<td>9 (82)</td>
<td>NR</td>
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<td>Kang C, 2012</td>
<td>32</td>
<td>Gem with or without Cis-RT</td>
<td>32 (100)</td>
<td>28 (88)</td>
<td>NR</td>
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<td>Chuong M, 2011</td>
<td>14</td>
<td>GTX then CRT</td>
<td>14 (100)</td>
<td>12 (86)</td>
<td>NR</td>
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<td>Barugola G, 2012</td>
<td>27</td>
<td>Various</td>
<td>27 (100)</td>
<td>NR</td>
<td>NR</td>
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<td>Stokes J, 2011</td>
<td>40</td>
<td>Cape-RT</td>
<td>16 (40)</td>
<td>12 (75)</td>
<td>NR</td>
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<tr>
<td>Sahara K, 2011</td>
<td>12</td>
<td>Gem-Tax</td>
<td>4 (33)</td>
<td>NR</td>
<td>NR</td>
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<td>Chun Y, 2010</td>
<td>74</td>
<td>Various</td>
<td>74 (100)</td>
<td>44 (60)</td>
<td>Median 21 months</td>
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<tr>
<td>Mcclaine R, 2010</td>
<td>29</td>
<td>Various</td>
<td>12 (41)</td>
<td>8 (75)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Cap: capecitabine; Cis: cisplatin; CRT: chemoradiotherapy; FOLFRINOX: short-term infusional fluorouracil plus leucovorin, irinotecan, and oxaliplatin; Gem: gemcitabine; GEMOX: gemcitabine plus oxaliplatin; GTX: gemcitabine, docetaxel, plus capecitabine; NR: not reported; RT: radiation therapy; Tax: taxane.

Unresectable/Locally Advanced Disease
Patient Presentation

• 63M developed 10/10 abdominal pain radiating to his back with several days of nausea and vomiting 5/2014
• ED for evaluation
• CT performed......
The Continuum of Resectability

Figure 3. Anatomy and Surgical Resectability of Pancreatic Cancer.
Pancreatic cancers are categorized on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases.

Ryan et al, NEJM 2014;371:1039
Unresectable/Locally Advanced

• NCCN
  – Distant metastases
  – >180° involvement of SMA or celiac abutment
  – Unreconstructable SMA/portal occlusion
  – Aortic invasion or encasement
Treatment Options for Unresectable Pancreatic Cancer

• Chemoradiotherapy
• Chemotherapy alone
Locally unresectable pancreatic adenocarcinoma (n=43)

Randomize

SMF* x 2 years
*Streptozocin, mitomycin-C (q 8 weeks), 5-FU

5-FU + 54 Gy RT**
**Followed by SMF chemo

Primary end point: Overall survival

Trial closed due to poor accrual

GITSG: Chemo vs. Chemoradiation

GITSG, JNCI (80), 1988
GITSG: Chemo vs. Chemoradiation

OS (1): 41% CMT vs. 19% CT (p<.02)

At 18 months, OS 18% CMT vs. 0%

Toxicity higher in CMT arm → 50% of patients had “severe” toxicity
ECOG: 5-FU vs 5-FU + RT

Unresectable gastric adenocarcinoma (n=57) and pancreatic adenocarcinoma# (n=91) (n=148 evaluable)

∥Patients with residual disease after resection also included

RANDOMIZE

5-Fluorouracil*
N=44 (pancreas)
*600 mg/m² weekly until disease progression

5-FU** + RT
N=47 (pancreas)
40 Gy in 20 x 20 cm field max
**600 mg/m² days 1-3, then weekly after RT

Klaassen, J Clin Oncol (3), 1985
ECOG: 5-FU vs 5-FU + RT

Time to recurrence (pancreas)  Overall survival (pancreas)

No difference in local-regional recurrence each arm (32%)
Locally advanced pancreatic cancer (n=119)

RANDOMIZE

Gemcitabine*
*1000 mg/m² weekly x 7 weeks then maintenance

RT (60 Gy) + 5-FU + CDDP**
**5-FU: 300 mg/m² days 1-5 and CDDP: 20 mg/m² days 1-5 during weeks 1 and 5

Primary end point: Overall survival

Chauffert, Ann Oncol (19), 2008
FFCD: Gem vs. Chemoradiation

**Overall Survival (ITT)**

- Median OS: **13.0 mths** Gem (99% CI 8.7-18.1) vs. **8.6 mths** CRT (99% CI 7.1-11.4)
- OS (1): 53% vs. 32%

**Progression-Free Survival**

- PFS (1): 32% Gem vs. 14% CRT
- 73% vs. 42% completed >75% of planned tx. Higher grade 3-4 tox in CRT (65% vs 40%)
Chemo vs. CRT for LAPC: ECOG

74 pts
Unresectable pancreas
ECOG 0-2

Primary endpoint: OS

Randomize

Gemcitabine
N=37
*1000 mg/m2 weekly x 6 weeks then maintenance

Gem/RT
N=34
**Gem: 600 mg/m2 weeks 1-5 then maintenance Gem 1000 mg/m2 x 5 cycles

Loehrer et al JCO 2011;29:4105
Chemo vs. CRT for LAPC: ECOG

Median OS 9.2 months Gem (95% CI 7.9-11.4) vs. 11.1 months Gem-RT (95% CI 7.6-15.5) (p=.017)
No difference in PFS
Local recurrence (first site of met): 11 patients Gem vs. 4 patients Gem-RT (NS)
## CRT vs. Chemotherapy

<table>
<thead>
<tr>
<th>Trials</th>
<th>N</th>
<th>Chemo</th>
<th>LF</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG CRT (54Gy) CT</td>
<td>22</td>
<td>5FU/SMF</td>
<td>45%</td>
<td>9.7 mo</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>SMF</td>
<td>48%</td>
<td>7.4 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.02</td>
<td></td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>ECOG CRT (40Gy) CT</td>
<td>47</td>
<td>5FU</td>
<td>32%</td>
<td>8.3 mo</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>5FU</td>
<td>32%</td>
<td>8.2 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFCD/SFRO CRT (60Gy) CT</td>
<td>59</td>
<td>5FU/CDDP</td>
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<td>8.6 mo</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>Gem</td>
<td></td>
<td>13 mo</td>
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<tr>
<td></td>
<td></td>
<td>p=0.03</td>
<td></td>
<td>p=0.03</td>
</tr>
<tr>
<td>ECOG CRT (50.4Gy) CT</td>
<td>34</td>
<td>Gem</td>
<td>12%</td>
<td>11 mo</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>Gem</td>
<td>30%</td>
<td>9.2 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.017</td>
<td></td>
<td>p=0.017</td>
</tr>
</tbody>
</table>
GERCOR- Retrospective

- Analysis 181 pts LAPC
- Phase II/III trials
- Chemo 1\textsuperscript{st} then CRT or chemo
- PFS/OS comparison of CT vs. CRT
  - PFS: CRT 10.8 mo vs chemo 7.4mo
  - OS: CRT 15 mo vs chemo 11.7mo

Huguet et al JCO 2007;25:326
Design of LAP07 study

Random 1

EVALUATION: non progressive

Random 2

EVALUATION: non progressive

Cape

RT

EVALUATION

EVALUATION

EVALUATION

Until Progression

1 month = Gemcitabine 1000 mg/m²/wk x 3

Erlotinib with gem : 100 mg/d

150 mg/d as single agent (maintenance)

Cape

Capecitabine 1600 mg/m²/d plus radiation therapy 54 Gy (5 x 1.8 Gy/d)

Secondary surgery allowed at any time

ASCO 2013
Overall survival by Random 2 status

ASCO 2014:

- In pts with no progression after 4 months of chemo
- CRT less tumor progression
  - 34% CRT
  - 65% Chemo
  - p<0.0001
- Longer time without treatment
  - 159 days CRT
  - 96 days Chemo

HR – 95%CI = 1.03 - [0.79; 1.34]
SCALOP

Randomize

74 pts
Unresectable
pancreas
12 weeks gem/Cap
WHO 0-1

Primary endpoint: 9 mo PFS

Gemcitabine/RT
N=38

Capecitabine/RT
N=36

RT: 50.4Gy
No ENI

Mukherjee et al Lancet Oncology 2013;14:317
SCALOP

- More toxicity in Gem/RT arm
  - Non-hematologic: 26% vs. 12%
  - Hematologic: 18% vs. 0%
Metastatic Disease
ECOG (2005-2009)

340 pts
Metastatic pancreas
ECOG 0 or 1

Randomize

Gemcitabine
N=171

FOLFIRINOX
N=171

Primary endpoint: OS

Conroy et al. NEJM 2011;364:1817
ECOG (2005-2009)

A Overall Survival

Hazard ratio, 0.57 (95% CI, 0.45–0.73)

P<0.001 by stratified log-rank test

No. at Risk

Gemcitabine  171 134  89 48 28 14  7  6  3  2  2  2  2  1
FOLFIRINOX  171 146 116 81 62 34 20 13  9  5  3  2  2  2  2

Conroy et al NEJM 2011;364:1817
nab-Paclitaxel (2009-2012)

861 pts
Metastatic pancreas
KPS≥70

RANDOMIZE

Gemcitabine
N=430

nab-paclitaxel/Gem
N=431

Primary endpoint: OS

Von Hoff et al NEJM 2013;369:1691
nab-Paclitaxel (2009-2012)

Von Hoff et al NEJM 2013;369:1691
Future Directions: RTOG 1201

STEP 1 REGISTRATION

Central SMAD4 TESTING
Mandatory submission of a cell block or core biopsy
NOTE: Tumor tissue must be received and central review completed before STEP 2 randomization can occur

STEP 2 REGISTRATION

Stratify: CA19-9 (< 1 vs. ≥ 1 to ≤ 90 vs. > 90); SMAD4 (intact vs. loss. vs. undetermined)

RANDOMIZE

Arm 1
Gemcitabine x 12 weeks

Arm 2
Gemcitabine x 12 weeks

Arm 3
FOLFIRINOX x 12 weeks

Arm 1
63.0 Gy in 28 fractions (IMRT), capecitabine

Arm 2
50.4 Gy in 28 fractions (3D-CRT), capecitabine

Arm 3
50.4 Gy in 28 fractions (3D-CRT), capecitabine
Emerging Radiation Technologies
IMRT

- Useful in reducing dose to normal tissues
- Dose escalation
- Incorporation of systemic therapy/novel agents
IMRT: Early Clinical Experience

- University of Chicago
- 25 patients pancreas and biliary tumors
- Most received concurrent 5-FU
- RT dose: 45-59.4 Gy
- IMRT reduced mean dose to liver, kidneys, stomach and small bowel
- 80% ≤ Grade 2 upper GI acute toxicity
- Local control not compromised with use of IMRT
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>RT Dose</th>
<th>RT field</th>
<th>Chemo</th>
<th>Grade 3+ acute</th>
<th>Grade 3+ late</th>
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</thead>
<tbody>
<tr>
<td>Passoni et al</td>
<td>25</td>
<td>LAPC 58Gy (SIB/hypo)</td>
<td>GTV</td>
<td>cap</td>
<td>4%</td>
<td>13%</td>
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<tr>
<td>Combs et al</td>
<td>57</td>
<td>LAPC 54Gy</td>
<td>ENI</td>
<td>Gem</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pipias et al</td>
<td>37</td>
<td>Localized/LAPC 54Gy</td>
<td>ENI</td>
<td>Cetuximab/gem</td>
<td>43% hospitalized</td>
<td>-</td>
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<tr>
<td>Ben-Josef et al*</td>
<td>50</td>
<td>LAPC 60Gy (dose escalation)</td>
<td>GTV</td>
<td>Gem</td>
<td>24%</td>
<td></td>
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<tr>
<td>Yovino et al</td>
<td>71</td>
<td>Resected 50.4Gy</td>
<td>Post-op</td>
<td>5-FU/gem</td>
<td>8% (N/V)</td>
<td>7% (SBO/fistula)</td>
</tr>
<tr>
<td>Abelson et al</td>
<td>47</td>
<td>29 adj 18 definitive 50.4Gy/54Gy</td>
<td>ENI</td>
<td>5-FU</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Patel et al</td>
<td>17</td>
<td>BPC 50Gy</td>
<td>No ENI</td>
<td>5-FU</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yovino et al</td>
<td>46</td>
<td>Resected/LAPC 50.4/59.4Gy</td>
<td>ENI</td>
<td>5-FU</td>
<td>2% diarrhea 2% anorexia</td>
<td>4% (SBO)</td>
</tr>
</tbody>
</table>
SBRT: Early Experience

• Stanford University
• 77 pts unresectable pancreas cancer
• 25Gy single fraction
• 96% received gemcitabine based chemo
• 1 yr freedom from local progression- 84%
• 9% Grade 3+ acute toxicity
• 1 yr Grade 2+ late toxicity: 25%

Chang et al Cancer 2009;115:665
SBRT-Prospective

• Multi-institutional Phase II
• 49 pts LAPC
• Gemcitabine -> SBRT (6.6Gy x 5 fractions)
• Median OS 16.7 mo
• Median local progression free survival: 13.8 mo
• Acute: 3+ toxicity: 1 pt duodenal ulcer
• Late grade 3+ toxicity: 6% (fistula/GI bleed)
Pancreas Conclusions

• Resectable/Localized
  – Adjuvant CRT (U.S)
  – Adjuvant CT (Europe)
  – Neoadjuvant Therapy

• Borderline Resectable
  – Neoadjuvant CRT
  – Neoadjuvant Chemo

• Unresectable/locally Advanced
  – Chemo 1st then consideration of CRT