Treatment of locally advanced and borderline resectable pancreatic cancer: Does radiation have a role?

Andrew H. Ko, MD
Associate Professor, Division of Hematology/Oncology
UCSF Comprehensive Cancer Center

PATIENTS WITH LOCALLY ADVANCED TUMORS SHOULD BE TREATED SEPARATELY FROM THOSE WITH METASTATIC DISEASE!

- Different prognosis
- Different biology?
- Different treatment paradigms?

NCCN DEFINITIONS OF LOCALLY ADVANCED UNRESECTABLE PANCREATIC CANCER

- SMA encasement > 180°
- Unreconstructible SMV/portal vein occlusion
- Any celiac abutment (head) or celiac encasement > 180° (body/tail)
- Aortic invasion or encasement
- Lymph node metastases beyond field of resection

LOCALLY ADVANCED PANCREATIC CANCER: UNRESOLVED QUESTIONS

**WHAT WE KNOW**
- ChemoRT is superior to RT alone (GITSG 1981)
- Outcomes are different from those with metastatic disease – should be studied in separate clinical trials, or stratified within a given study (multiple phase III trials; Philip, J Clin Oncol 2009;27:5660–9)

**WHAT WE STILL DON’T KNOW**
- Is radiation absolutely necessary?
- If so, when should it be given?
- Most studies to date have examined initial chemoRT, with very mixed results
- There may be a better rationale for delaying radiation until later
- How often are ‘borderline’ unresectable patients successfully converted to being able to undergo successful surgery?

THE SEQUENCING OF CHEMOTHERAPY AND RADIATION: DOES IT MAKE A DIFFERENCE?

Start with radiation?  Start with chemotherapy?

- Importance of obtaining optimal local control
- Better symptom palliation (pain, bowel obstruction)
- Better likelihood of cytoreduction to downstage a patient for potential surgery

- Greatest imperative is to eradicate micrometastatic disease
- Select out patients who develop metastases during initial chemotherapy (~25–30%), avoid morbidities assoc. with RT

EARLY TRIALS OF LOCALLY ADVANCED PANCREATIC CANCER

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Results</th>
<th>Take home message?</th>
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</thead>
<tbody>
<tr>
<td>GITSG 1981</td>
<td>194</td>
<td>- RT alone (6000 cGy): median surv = 23 weeks</td>
<td>ChemoRT is superior to RT alone</td>
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<tr>
<td></td>
<td></td>
<td>- RT (4000 cGy) + bolus 5-FU: median surv = 42 weeks</td>
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<tr>
<td></td>
<td></td>
<td>- RT (6000 cGy) + bolus 5-FU: median surv = 40 weeks</td>
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<tr>
<td>GITSG 1988</td>
<td>43</td>
<td>- 5-FU/RT (4000 cGy) followed by SMF: median surv = 42 weeks</td>
<td>ChemoRT followed by chemo is superior to chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 5-FU alone (streptozocin/MMC/5-FU): median surv = 32 weeks</td>
<td></td>
</tr>
<tr>
<td>ECOG 1985</td>
<td>91</td>
<td>- 5-FU/RT (4000 cGy) followed by 5-FU: median survival = 8.3 mos</td>
<td>ChemoRT followed by chemo is equivalent to chemotherapy</td>
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<tr>
<td></td>
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<td>- 5-FU alone: median surv = 8.2 mos</td>
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COMPARISON OF MODERN RANDOMIZED STUDIES IN LOCALLY ADVANCED PDAC

**FFCD/SFRO**
- Locally advanced disease (n=119)
  - ChemoRT (6 weeks)
  - Concurrent cisplatin/5-FU
  - Chemotherapy (gemcitabine)
  - Continue gemcitabine

**ECOG 4201**
- Locally advanced disease (n=74)
  - ChemoRT (6 weeks)
  - Concurrent gemcitabine (600 mg/m2 weekly)
  - Gemcitabine (6 weeks)
  - Gemcitabine x 5 cycles

**COMPARING FFCD-SFRO vs. ECOG 4201**

<table>
<thead>
<tr>
<th>FFCD-SFRO</th>
<th>ECOG</th>
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<tbody>
<tr>
<td><strong>Induction regimen</strong></td>
<td>Cisplatin/5-FU + 6000 cGy RT (6 weeks)</td>
</tr>
<tr>
<td><strong>Maintenance chemotherapy</strong></td>
<td>Gemcitabine until progression</td>
</tr>
<tr>
<td><strong>Median OS compared to chemo alone</strong></td>
<td>8.6 vs. 13.9 months, in favor of chemo alone</td>
</tr>
<tr>
<td><strong>1-year survival</strong></td>
<td>32% vs. 53%</td>
</tr>
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- Did ECOG study use a more effective radiosensitizing regimen?
- Was the induction regimen prescribed by FFCD/SFRO overly intensive → delayed administration and total amount of subsequent systemic therapy?
- Further exploration of *delayed* chemoradiation is required.

**INDUCTION CHEMOTHERAPY SELECTS OUT PATIENTS WHO ARE NOT APPROPRIATE CANDIDATES FOR CHEMORADIATION**

<table>
<thead>
<tr>
<th>LAD PDAC STUDIES WHERE INDUCTION CHEMOTHERAPY WAS GIVEN</th>
<th>n</th>
<th>Induction regimen</th>
<th>% NOT going on to receive chemoRT 2o to disease progression/toxicity/other</th>
</tr>
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<tbody>
<tr>
<td>Ko (UCSF)</td>
<td>25</td>
<td>Gem/cisplatin</td>
<td>32%</td>
</tr>
<tr>
<td>Crane (MD Anderson)</td>
<td>69</td>
<td>GemOx + cetuximab</td>
<td>13%</td>
</tr>
<tr>
<td>Moureau-Zabotto (GERCOR)</td>
<td>59</td>
<td>GemOx</td>
<td>15%</td>
</tr>
<tr>
<td>Kim (Korea)</td>
<td>37</td>
<td>Gem/cisplatin</td>
<td>19%</td>
</tr>
<tr>
<td>Mukherjee (SCALOP)</td>
<td>114</td>
<td>Gem/capecitabine</td>
<td>35%</td>
</tr>
<tr>
<td>Huguet (GERCOR, retrospective)</td>
<td>181</td>
<td>Gem-based</td>
<td>29%</td>
</tr>
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**RETROSPECTIVE ANALYSIS OF LOCALLY ADVANCED DISEASE IN GERCOR STUDIES**

- 181 patients with LA pancreatic adenocarcinoma
- Evaluation after 3 months of initial chemotherapy
- 53 patients (29.3%) with disease progression
- 128 patients (70.3%) without disease progression
- 72 patients treated with CRT (group A)
- 56 patients treated with CT alone (group B)


- Median PFS: 10.8 vs. 7.4 mos (p=0.005)
- Median OS: 15.0 vs. 11.7 mos (p=0.0009)
**International phase III LAP-07 study**
(Hammel, *J Clin Oncol* 2013 (suppl; abstr LBA 4003))

**FIRST RANDOMIZATION**
- Induction chemotherapy
  - Gemcitabine x 4 months
  - Gemcitabine plus erlotinib x 4 months

**SECOND RANDOMIZATION**
- Stop until progression
  - RT (5400 cGy) + capecitabine
  - Gemcitabine plus erlotinib x 2 months
  - RT (5400 cGy) + capecitabine

**Primary question:** Does chemoradiation after induction chemotherapy improve overall survival? (looking for HR 0.75 → increase from 9 to 12 mos)

**Secondary question:** Does adding erlotinib to gemcitabine help?

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**LAP-07 RESULTS**
- Original n=722 → interim analysis after 442 patients allowed enough events to reach futility boundary
- Results:
  - 442 enrolled, received induction chemotherapy (gemcitabine +/- erlotinib)
  - 269 randomized
  - 136 chemo alone
  - 133 chemoRT

**After 4 months:**
- MEDIAN OS 16.4 mos
- MEDIAN PFS 11.8 mos
- 173 dropped out (mainly due to progressive dz)

**Secondary analysis:** addition of erlotinib to gemcitabine conferred NO benefit (gem alone, 13.6 months; gem/erlotinib: 11.9 months)

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**IMPLICATIONS/UNRESOLVED ISSUES OF STUDY**
- Do we conclude on this basis that radiation should not be routinely given to patients with locally advanced pancreatic cancer?
  - Do more effective systemic therapies, such as FOLFIRINOX, and gemcitabine/Abraxane, attenuate any survival benefit that radiation might offer?
  - Conversely, does the superior and more durable systemic disease control expected with FOLFIRINOX attach even greater importance to achieving local control with RT?
  - Does radiation impact local recurrence rate? What about QoL?
  - Do we have any biomarkers that can guide us on patterns of recurrence? (SMAD4)

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**RTOG 1201: Proposed study design**
- Locally advanced PDAC
  - Stratify: SMAD4 Status
  - Gemcitabine/nab-paclitaxel x 3 months
- 3D-CRT + cape 50.4 Gy
- IMRT + cape 63 Gy
- Continue gemcitabine/nab-paclitaxel
SMAD4 (DPC4) AS A PREDICTIVE BIOMARKER
Results of Hopkins rapid-autopsy series

<table>
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<tr>
<th># of metastases</th>
<th>Locally destructive/oligometastatic</th>
<th>Extensive metastatic</th>
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<tbody>
<tr>
<td>0</td>
<td>22% (2/9)</td>
<td>35% (7/20)</td>
</tr>
<tr>
<td>1-10</td>
<td>45% (5/11)</td>
<td>72% (33/46)</td>
</tr>
<tr>
<td>11-99</td>
<td>71% (14/24)</td>
<td></td>
</tr>
<tr>
<td>100s-1,000s</td>
<td>73% (16/22)</td>
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Could DPC4 expression be used to guide treatment decisions re: radiation?


Stage classification % at diagnosis 5-year survival

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<tr>
<th>Stage classification</th>
<th>% at diagnosis</th>
<th>5-year survival</th>
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<tbody>
<tr>
<td>Localized</td>
<td>8</td>
<td>20%</td>
</tr>
<tr>
<td>BORDERLINE RESECTABLE</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Locally advanced/ unresectable</td>
<td>31</td>
<td>8%</td>
</tr>
<tr>
<td>Metastatic</td>
<td>61</td>
<td>2%</td>
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DISTINGUISHING BETWEEN LOCALLY ADVANCED vs. BORDERLINE RESECTABLE PANCREATIC CANCER

<table>
<thead>
<tr>
<th>VESSEL</th>
<th>Tumor involvement</th>
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<tbody>
<tr>
<td>Superior mesenteric vein – portal vein</td>
<td>Abutment, encasement, occlusion</td>
</tr>
<tr>
<td>Superior mesenteric artery</td>
<td>Abutment</td>
</tr>
<tr>
<td>Common hepatic artery</td>
<td>Abutment</td>
</tr>
<tr>
<td>Celiac trunk</td>
<td>No abutment or encasement</td>
</tr>
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AHPBA/SSAT/SSO DEFINITION OF “BORDERLINE RESECTABILITY”

Chance of R0 resection can be predicted on basis of relationship between the tumor and mesenteric vasculature.
Borderline resectable disease

FOLFIRINOX 4 cycles + 2 - 6 weeks break

Resect + 6 – 8 weeks break

Resect

50.4Gy EBRT + CAPE + 4 – 10 weeks break

50.4Gy EBRT + CAPE + 4 – 10 weeks break

Surgery

Resect

GEM

FOLLOW

Alliance A021101: TREATMENT SCHEMA

N = 20 (primarily feasibility study)

Is radiation necessary to successfully downstage?

Efficacy Results of Contemporary Chemotherapy Regimens

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<thead>
<tr>
<th></th>
<th>FOLFIRINOX</th>
<th>Gemcitabine</th>
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<tbody>
<tr>
<td>ORR</td>
<td>31.6%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>6.4 months</td>
<td>3.3 months</td>
</tr>
<tr>
<td>Median survival</td>
<td>11.1 months</td>
<td>6.7 months</td>
</tr>
<tr>
<td>1 year survival</td>
<td>48.4%</td>
<td>20.6%</td>
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Stereotactic Body Radiotherapy (e.g. Cyberknife)

- Alternative to conventionally fractionated XRT?
- More intensified treatment in a single (25 Gy) or small # of fractions (5-6.5 Gy x 5)
- Greater convenience
- Treat tumor + small margin only; limited nodal coverage
- Sharper dose fall-off gradients to normal tissue
- Early studies raised concern re: late/chronic toxicity, e.g. ulceration/mucositis of stomach and duodenum

PHASE II MULTI-INSTITUTIONAL STUDY OF SBRT
FOR UNRESECTABLE PANCREATIC CANCER

(Gemcitabine, up to 1 Cycle allowed)*

1 week break

SBRT 6.6 Gy x 5
Mon-Fri

1 week break

Gemcitabine
(3 wks on, 1 wk off)
Until toxicity or progression

Primary endpoint: Late GI Toxicity > 4 months
Secondary: Local Progression Free Survival, QoL

N = 49

Trial opened at Stanford, Johns Hopkins, Memorial Sloan Kettering.
Courtesy of J. Herman (Johns Hopkins)

Objective tumor response rates (by RECIST) up to 6 months:
• 17% PR
• 69% SD
Local control at 1 year = 83%

Late GI toxicities
• Grade 2: 2.1%
• Enteritis
• Grade ≥3: 8.5%
  • Fistula (1), ulcer (3)

TAKE-HOME MESSAGES
• Locally advanced PDAC has different prognosis and treatment paradigms vs. metastatic disease; should therefore be considered separately and develop clinical trials unique to this stage
• Role of chemoRT remains controversial!
  • Up-front chemoRT has produced mixed results
  • Growing interest in delayed chemoRT, although recent LAP-07 trial raises questions re: relative importance of RT
• Secondary questions include:
  • Selection of radiosensitizing agents
  • Radiation techniques and dosing
  • Predictive biomarkers (e.g. DPC4)
• Borderline resectable disease has very specific radiographic criteria, and may itself even separated out from locally advanced
  • Again, role of neoadjuvant RT in this context has yet to be defined