Evidence-Based adjuvant treatment of resectable pancreatic adenocarcinoma

Adina Croitoru
Fundeni Clinical Institute
1. Introduction
2. Borderline resectable-Neoadjuvant CHT-RT
3. Adjuvant CHT
4. Adjuvant CHT-RT
5. Timing or completeness of adjuvant CHT
6. Posttreatment surveillance
7. Trials ongoing
8. Our experience
9. Conclusion
Introduction

+ One of the leading causes of cancer related death
  + 5-y survival <5%
  + Potentially curative surgery-alone-5y survival 10%
  + Adjuvant CHT-20-25%
  + CHT-RT-Conflicting evidence
+ The modest survival benefit
  + High prevalence of local recurrence
  + Distant M1 due to residual microscopic disease
The Celebrity Faces of Pancreatic Cancer
So many lost battles!

Luciano Pavarotti
Patrick Swayze
Joan Crawford
Henry Mancini
Pink Floyd Band

Count Basie
Donna Reed
Michael Landon
"Bonanza"
Dizzie Gillespie
Wernher von Braun

Frank Herbert
Marcello Mastroiani
Rene Magritte
Simone Signoret
Steve Jobs
mortality

+ 2000–a disease whose survival has improved little over 45 years

+ 2000–2010, OS increased from 4 mos to 5 mos

+ 2010–2015, OS from 5 mos to 7 mos

PA clinical grouping

1. Metastatic disease
2. Resectable disease
3. Borderline Resectable disease: definition issues
   - Neoadjuvant treatment
     a. CHT
     b. CHT-RT
4. Locally advanced, but clearly not resectable disease
### Pancreatic Cancer by Stage (SEER Database)-2010-2012

<table>
<thead>
<tr>
<th>Stage Classification</th>
<th>% at Diagnosis</th>
<th>Median Survival (mos)</th>
<th>5-Yr Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>9(10-20)*</td>
<td>23(15-19)</td>
<td>24.1(25-35)</td>
</tr>
<tr>
<td>Locally advanced/unresectable</td>
<td>28(35)</td>
<td>6-10</td>
<td>9-10</td>
</tr>
<tr>
<td>Metastatic</td>
<td>53</td>
<td>3-6</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Unknown</td>
<td>11</td>
<td></td>
<td>4.1</td>
</tr>
</tbody>
</table>

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Borderline (BL) resectable

Common Definitions: AHPBA-NCCN-Alliance-MD Andersson

+ Venous involvement of SMV/PV with tumor abutment which may distort lumen
+ Encasement of SMV/PV but not nearby arteries, or short segment venous occlusion from either tumor thrombus or encasement but with suitable vessel proximal and distal to allow safe resection and replacement
+ Gastroduodenal artery encasement up to hepatic artery with either short segment encasement or direct abutment of hepatic artery without extension to celiac axis
+ Tumor abutment of SMA ≤ 180° of vessel wall circumference

# Common Definitions of BLPC

<table>
<thead>
<tr>
<th>Blood Vessel</th>
<th>AHPBA/Consensus&lt;sup&gt;26&lt;/sup&gt;</th>
<th>MD Anderson Cancer Center&lt;sup&gt;24&lt;/sup&gt;</th>
<th>National Comprehensive Cancer Network&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Alliance&lt;sup&gt;25&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV-PV</td>
<td>Abutment, impingement, encasement of the SMV/PV or short segment venous occlusion</td>
<td>Short segment occlusion/reconstructible</td>
<td>Distortion or narrowing of the vessel wall, and/or reconstructible occlusion</td>
<td>Tumor-vessel interface ≥ 180 degrees of the circumference of the vessel wall, and/or reconstructible occlusion</td>
</tr>
<tr>
<td>SMA</td>
<td>Abutment</td>
<td>Abutment</td>
<td>Tumor-vessel interface ≥ 180 degrees of the circumference of the vessel wall</td>
<td>Tumor-vessel interface ≥ 180 degrees of the circumference of the vessel wall</td>
</tr>
<tr>
<td>CA</td>
<td>Uninvolved</td>
<td>Abutment</td>
<td>Tumor-vessel interface ≤ 180 degrees of the circumference of the vessel wall</td>
<td>Tumor-vessel interface ≤ 180 degrees of the circumference of the vessel wall</td>
</tr>
<tr>
<td>HA</td>
<td>Abutment or short segment encasement</td>
<td>Abutment or short segment encasement</td>
<td>Reconstructible short segment interface between tumor and vessel</td>
<td>Reconstructible short segment interface between tumor and vessel</td>
</tr>
</tbody>
</table>

Abbreviations: AHPBA, American Hepato-Pancreato-Biliary Association; CA, celiac artery; HA, hepatic artery; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.
3 principle goals of Neoadj Therapy

- Response
  - This may not be RECIST Response
  - Needs to “sterilize margins”
  - Needs to shrink away from the vessels if possible

- Margin free resection
  - All data suggests that margins + resections result in poorer survival outcomes

- Not interfering with surgical outcomes
  - Treatment should not increased morbidity/increased postoperative complications
  - Treatment should not cause fibrosis/scarring that make the operation more difficult
## Recent Large Series of BL PC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of Publication</th>
<th>Study Type</th>
<th>Study Size</th>
<th>BR definition</th>
<th>Neoadjuvant</th>
<th>%resectable</th>
<th>%Negative Margins</th>
<th>Median OS (Mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose et al</td>
<td>2014</td>
<td>Single institution retrospective</td>
<td>64</td>
<td>AHPBA/SSO</td>
<td>Major Multiagent CHT</td>
<td>48</td>
<td>87</td>
<td>23.6</td>
</tr>
<tr>
<td>Chuong et al</td>
<td>2013</td>
<td>Single institution retrospective</td>
<td>57</td>
<td>NCCN</td>
<td>Majority Gem based CHT, SBRT</td>
<td>56.1</td>
<td>96.9</td>
<td>16.4</td>
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<tr>
<td>Takahashi et al</td>
<td>2013</td>
<td>Single institution retrospective</td>
<td>80</td>
<td>other</td>
<td>Gem based CHT-RT</td>
<td>54</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Kat et al</td>
<td>2012</td>
<td>Single institution retrospective</td>
<td>115</td>
<td>AHPBA/SSO</td>
<td>Gem based CHT and CHT-RT or CHT-RT alone</td>
<td>84</td>
<td>95</td>
<td>33</td>
</tr>
<tr>
<td>Chun et al</td>
<td>2010</td>
<td>Single institution retrospective</td>
<td>109</td>
<td>Other Received neoadj ttt</td>
<td>5FU /Gem based CHT-RT</td>
<td>100</td>
<td>59</td>
<td>23</td>
</tr>
</tbody>
</table>

Heestand et al. Approach to Patients with Pancreatic Cancer without detectable Metastases JCO 2014
Combined Analysis shows we can achieve Ro Resection-meta-analysis of 14 phase II trials-536pts

- Suggests that neoadj therapy leads to high Ro resection rate
- These studies had differing definitions of resectable, borderline and unresectable
- Intriguingly, borderline and unresectable pts who had resections had the same survival (22.3mos) as resectable pts (23mos)
  - Does this suggest our definitions of borderline resectable are just bad on these studies?

- Did not differentiate CHT from CHT-RT

Mura Assifi et al Surgery 150:466-73, 2011
Neoadjuvant mFOLFIRINOX in Borderline/Unresectable

- Modified FOLFIRINOX in advanced nonmetastatic pancreatic cancer (N = 43) with goal of downstaging for resection

- Median PFS
  - Resected: 18 mos
  - No resection: 8 mos
  - P < .001

- Conclusion: coupling mFOLFIRINOX with surgery allows high resection rates and PFS benefit

LAP-07: Chemo ± RT in LAPC

Induction chemotherapy (gemcitabine ± erlotinib) (N = 442)

- Secondary analysis: addition of erlotinib to gemcitabine conferred NO benefit
- Chemoradiation associated with lower rates of locoregional progression compared with continued chemotherapy

<table>
<thead>
<tr>
<th>Regimen, Mos</th>
<th>Median OS</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo alone</td>
<td>16.5</td>
<td>8.4</td>
</tr>
<tr>
<td>ChemoRT</td>
<td>15.2</td>
<td>9.9</td>
</tr>
</tbody>
</table>

ESMO-ESDO CLINICAL PRACTICE GUIDELINES

+ For borderline resectable disease, neoadj CHT /CHT-RT is recommended, if Ro RESECTION IS POSSIBLE

+ Not clearly what is the best strategy:
  + More intense regimen w RR!

+ Multidisciplinary approach is paramount in assessing resectability
  + Surgeon, radiologist, oncologist, gastroenterologist and radiotherapist

1. Seufferlein T ... Van Cutsem Ann oncol 2012;25(2):II1-II4
2. Seufferlein T ... Ph Rougier Ann oncol 2014;25(2):II1-II4
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Prognostic features of PA resected

- N+
- Poorly differentiated histology
- Perineural invasion
- Lymphovascular invasion
- Elevated CA19-9
- Incomplete resection-margin: R0, R1, R2
<table>
<thead>
<tr>
<th>Year published</th>
<th>Author</th>
<th>Arm (n)</th>
<th>Median survival (mo)</th>
<th>2-yr survival</th>
<th>5-yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Stocken</td>
<td>CT (348) No CT (338)</td>
<td>19 (16.4-21.1) 13.5 (12.2-15.8)</td>
<td>38% 28%</td>
<td>19% 12%</td>
</tr>
<tr>
<td>2007</td>
<td>Hoeck: resection margins</td>
<td>CT (482) No CT (469)</td>
<td>3 mo (0.3-5.7) survival benefit with CT vs no CT (p=0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Butturini</td>
<td>CT (236) No CT (222) CT (109) No CT (114)</td>
<td>Ro resections 20.8 (17.7-23.2) 13.8 (12.2-16.4) R1 resections 15 (11.7-18.1) 13.2 (10.5-17.6)</td>
<td>42% (35%-48%) 27% (21%-33%) 29% (20%-38%) 31% (22%-40%)</td>
<td>22% (17%-28%) 10% (5%-14%) 14% (7%-21%) 17% (10%-24%)</td>
</tr>
<tr>
<td>2013</td>
<td>Liao</td>
<td>Flurouracil (876) Observation (670) Gemcitabine (774) Observation (670) Gemcitabine (774) Flurouracil (876)</td>
<td>Hazard ratio for death (95%CI) 0.62 (0.42-0.88) 0.68 (0.44-1.07) 1.1 (0.78-1.66)</td>
<td></td>
<td></td>
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</table>
**Adjuvant Chemotherapy With Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer: The CONKO-001 Randomized Trial:**
The JAMA Network

Kaplan-Meier Estimates of Disease-Free and Overall Survival:

A. Median DFS 13.4 months (95% CI, 11.6-15.3 months) in the gemcitabine group compared with 6.7 months (95% CI, 6.0-7.5 months) in the observation group (HR 0.55 [95% CI, 0.44-0.69]).

B. Median OS 22.8 months (95% CI, 18.5-27.2 months) in the gemcitabine group compared with 20.2 months (95% CI, 17.7-22.8 months) in the observation group (HR 0.76 [95% CI, 0.61-0.95]). Vertical lines on curves indicate patients censored on the date of their last follow-up.

Statistically significant improvement in 5 and 10 y OS rates vs observation-5y OS 10.3% 10y OS 4.5% improvement

1-1 w adjuvant Gem for 6 mos leads to 24% improvement in OS vs Observation.
Adjuvant Chemotherapy With Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer: The CONKO-001 Randomized Trial: The JAMA Network

Disease-Free and Overall Survival Size of data markers indicates the amount of statistical information in the respective subgroup.

ESPAC-3

- the largest ever adj therapy
- 1088p in 159 centers in 17 countries
  - after undergoing complete macroscopic resection for ductal adenocarcinoma of the pancreas
- 551p w 5FU+LV/537p with gem
- Follow-up for 2y
Figure 2. Survival Results by Randomized Treatment

Neoptolemos, J. P. et al. JAMA 2010;304:1073-1081
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<th>Median survival(mo)</th>
<th>2-y survival</th>
<th>5-y survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Stocken</td>
<td>CRT No CRT</td>
<td>15.8(13.9-18.1)</td>
<td>30%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15.2(13.1-18.2)</td>
<td>34%</td>
<td>17%</td>
</tr>
<tr>
<td>2008</td>
<td>Butturini</td>
<td>CRT(188) No CRT(183) CRT(53) No CRT (53)</td>
<td>Ro Resections 15.9 (14-18.5) 15.8(13.4-20.1)</td>
<td>30%(23%-36%) 38%(31%-45%)</td>
<td>10% (5%-15%) 20%(13%-26%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R1 Resections 14.7(11.5-20.5) 11.2 (9.4-16.7)</td>
<td>30%(17%-42%) 19% (8%-31%)</td>
<td>18% (7%-29%) 8% (0%-16%)</td>
</tr>
<tr>
<td>2013</td>
<td>Liao</td>
<td>CHT-RT (169) Observation CHT-RT + 5-FU (323) 5-FU (876) CHT-RT + 5-FU (323) CHT-RT (169) CHT-RT + gem</td>
<td>HR for death (95%CI) 0.91 (0.55-1.46)</td>
<td>0.87 (0.27-2.69)</td>
<td>0.59 (0.19-1.74)</td>
</tr>
</tbody>
</table>

Jones et al-Adjuvant therapy in Pancreatic Cancer WJG, 2014
ESPAC-1 Study CHT-RT Adjuvant: the first adequately powered randomized trial: Adj CHT vs adj CHT-RT

Median Survival
No chemoradiotherapy: 17.9 months
Chemoradiotherapy: 15.9 months

HR: 1.28 (95% CI: 0.99-0.66); \( P = .05 \)

Adj CHT–RT: lower median survival vs no CHT–RT

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Timing

+ metastasis is an **early event** in the development of PC

+ removal of a primary tumor may accelerate growth of microM1, potentially causing the release of growth factors that may stimulate microM1 at distant sites.

+ delay in starting treatment
  + drug-resistant micrometastases
  + an increase in angiogenesis in the vascular bed surrounding metastases

+ preclinical observations in cancer would support the concept of early initiation of adjuvant chemotherapy.
Kaplan-Meier plot of the effect of overall survival of the time between surgery and the start of treatment for patients who receive all planned therapies (six cycles) and those who did not (< six cycles), after excluding any patients who died within 8 w of surgery.

Juan W. Valle et al. JCO 2014;32:504-512
Timing or completeness of 6 cycles??

- completion of all six cycles of adjuvant CHT was an independent favorable prognostic variable
- no survival disadvantage from delaying the start of treatment for up to 12 weeks after surgery
- no survival advantage for starting early treatment, within 8 weeks of surgery

Juan W. Valle et al. JCO 2014;32:504-512
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Posttreatment surveillance

The majority of recurrences after potentially curative treatment of pancreatic exocrine cancer occur within 2 years
- locoregional
- distant sites, most often liver, lung, and peritoneal cavity

The primary goal of surveillance: prolong survival

Early identification of recurrent or metastatic disease in asymptomatic patients improves long-term survival is limited(!?!?)
- early introduction of palliative CHT or RT
  - to slow disease progression
- an aggressive regimen such as FOLFIRINOX
  - improve survival
NCCN(2015) recommendations

- a history and PE
- CA 19-9 determinations
- CT scan
  - Every 3mos for the first 2y after curative resections
  - Annually for the next 3y after curative resections
- Low level of evidence
- Uniform consensus
ESMO recommendations 2012 vs 2015

**2012**
- individualized to minimize emotional stress and economic burden
- CT scan of the abd and pelvis every 6mos
- CA 19-9 levels every 3 mos for 2years if CA19-9 levels were elevated preoperatively

**2015**
- There is no evidence that regular follow-up after initial therapy with curative intent is useful
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## Current phase III trials investigating adj CHT

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Co-ordinating country</th>
<th>First enrolment</th>
<th>Target sample size (n)</th>
<th>Adjuvant treatment arms</th>
<th>Primary outcome</th>
<th>Secondary outcomes (clinical only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom (ESPAC 4)</td>
<td>2008</td>
<td>1396</td>
<td>(I) Gem (II) Gem plus capecitabine</td>
<td>OS</td>
<td>Toxicity Quality of life OS at 2 and 5 y DFS at 5 y</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>2008</td>
<td>436</td>
<td>(I) Gem (II) Gem plus erlotinib</td>
<td>DFS</td>
<td>OS Toxicity</td>
<td></td>
</tr>
<tr>
<td>United States (RTOG 0848)</td>
<td>2009</td>
<td>950</td>
<td>(I) Gem (II) Gem plus erlotinib If DFS at end of treatment (I) or (II), further randomisation to: (III) A further course of (I) or (II) as previously received plus Capecitabine CRT (IV) A further course of (I) or (II) as previously received plus 5-FU CRT</td>
<td>OS</td>
<td>DFS Toxicity Correlation between baseline fatigue and survival</td>
<td></td>
</tr>
<tr>
<td>NCT01072981</td>
<td>United States</td>
<td>2010</td>
<td>722</td>
<td>Gem +/- 5-FU CRT +/- HyperAcute®-Pancreas (algenpantucel-L) immunotherapy</td>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>NCT01526135</td>
<td>France/Canada (ACCORD 24)</td>
<td>2012</td>
<td>490</td>
<td>(I) Gem (II) mFolfirinox</td>
<td>DFS at 3 y</td>
<td>OS at 3 yr</td>
</tr>
<tr>
<td>NCT01074742</td>
<td>Germany</td>
<td>2012</td>
<td>336</td>
<td>(I) Gem (II) Gem plus cisplatin plus regional hyperthermia</td>
<td>DFS</td>
<td>OS</td>
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<tr>
<td>NCT01964430</td>
<td>United States (APACT)</td>
<td>Not yet active</td>
<td>-</td>
<td>(I) Gem (II) Gemcitabine plus nab-paclitaxel</td>
<td>DFS/OS</td>
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</table>

Heestand et al. Approach to Patients with Pancreatic Cancer without detectable Metastases JCO. 2014
# Current phase II/III trials investigating neoadj CHT

<table>
<thead>
<tr>
<th>Trial acronym</th>
<th>Trial No/Study Group</th>
<th>Treatment Arm</th>
<th>No of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph II of preop FOLFIRINOX vs Gem/Nab-paclitaxel in rectable PC</td>
<td>Massachusetts General hospital</td>
<td>4mos of neoadj Gem/Nab then proton beam RT vs 4 mos of neoadj FOLFIRINOX, then proton beam RT</td>
<td>112</td>
</tr>
<tr>
<td>Neoadj plus adj or only adj Gem/Nab-paclitaxel for resectable PC</td>
<td>NEONAX</td>
<td>2mos of neoadj Gem/Nab, then 4mos of adj Gem/Nab vs 6mos of adj Gem/Nab</td>
<td>166</td>
</tr>
<tr>
<td>Randomized Ph II/III study w adj Gem vs Neoadj/adj FOLFIRINOX in resectable PC</td>
<td>NEPAFOX</td>
<td>6mos of adj Gem vs 3mos of neoadj FOLFIRINOX then 3 mos of adj FOLFIRINOX</td>
<td>126</td>
</tr>
</tbody>
</table>

Heestand et al - Approach to Patients with Pancreatic Cancer without detectable Metastases JCO .2014
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Our experience: 2010-2014

- 49pts
  - 27B/22F
  - mean age: 59y (37-82y)
- Whipple procedure-36pts
- Splenocorporeopancreatectomy-13pts
- Median follow-up-24.9mo
- Gem 1g/m2 d1,8,15 w 28w for 6mo
Patients

**Stage:**
- IA - 1 p
- IB - 10 p
- IIA - 12 p
- IIB - 19 p
- III - 7 p

**Hp exam:**
- 46ADK
- 1cystADK
- 1 adeno squamous
- 1 carcinoma w giant cells (osteoblastic lyke)
Progression of the disease

- 14 pts w M1
  - LM1
  - Lung M1
  - Abd LNs
  - Peritoneal M1
  - LM1+abd LN

- 9 pts w local recidive
  - abd LNs
  - LM1
  - Lung M1

- 5 pts w M1+LR
  - abd LNs
  - LM1
  - Lung M1
Results: TTP

- 29 p completed 6mos
- 12 p <6mos
  - 1p-renal insufficiency
  - 11p-progressive disease-with M1/local recidive
- 4 p –adj CHT ongoing
- 27 p had M1/LR

<table>
<thead>
<tr>
<th>Mean(a)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate</td>
<td>Std. Error</td>
</tr>
</tbody>
</table>
Results: OS

- 28pts alive
- 21pts died

<table>
<thead>
<tr>
<th>Mean(a)</th>
<th>Std. Error</th>
<th>95% Confidence Interval</th>
<th>Median</th>
<th>Std. Error</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate</td>
<td>Std. Error</td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td>Estimate</td>
<td>Std. Error</td>
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<tr>
<td>35.601</td>
<td>3.879</td>
<td>27.998</td>
<td>43.204</td>
<td>29.852</td>
<td>4.611</td>
</tr>
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Conclusion

- a substantial challenge for surgeons and oncologists alike
- surgical resection remains the foundation for any patient with resectable disease
- adjuvant CHT improves both OS & PFS
  - now irrefutable evidence
- several phase III trials are currently in progress aiming to challenge gemcitabine as the gold standard adjuvant drug
- adjuvant CHT-RT
  - not be recommended as standard therapy