Neo-adjuvant treatment in resectable pancreatic cancer

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Pancreatic cancer

- The most lethal common cancer, but something happens

- Relative 5-year survival in Sweden
Pancreatic cancer

- Incidence and mortality have decreased in Sweden
- Statistics are not reliable
- Similar in most Western countries
- Incidence (1-)10+/100 000 (age-stand.)
Pancreatic cancer – mainly a disease in the elderly
Pancreatic cancer – more radio-chemoresistant than most other cancers

Ryan et al., NEJM 2014
SMAD-4 loss

- Correlates with risk of distant spread
- Iacobuzio-Donahue et al, JCO 2009
- Boone et al, J Surg Oncol 2014
Risk factors for pancreatic cancer—prevention likely not very effective

<table>
<thead>
<tr>
<th>Variable</th>
<th>Approximate Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>2–3</td>
</tr>
<tr>
<td>Long-standing diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Nonhereditary and chronic pancreatitis</td>
<td>2–6</td>
</tr>
<tr>
<td>Obesity, inactivity, or both</td>
<td>2</td>
</tr>
<tr>
<td>Non-O blood group</td>
<td>1–2</td>
</tr>
<tr>
<td>Genetic syndrome and associated gene or genes — %</td>
<td></td>
</tr>
<tr>
<td>Hereditary pancreatitis (PRSS1, SPINK1)</td>
<td>50</td>
</tr>
<tr>
<td>Familial atypical multiple mole and melanoma syndrome (p16)</td>
<td>10–20</td>
</tr>
<tr>
<td>Hereditary breast and ovarian cancer syndromes (BRCA1, BRCA2, PALB2)</td>
<td>1–2</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome (STK11 [LKB1])</td>
<td>30–40</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer (Lynch syndrome) (MLH1, MSH2, MSH6)</td>
<td>4</td>
</tr>
<tr>
<td>Ataxia–telangiectasia (ATM)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Li–Fraumeni syndrome (P53)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Need for better treatments
Pancreatic cancer

Ductal adenocarcinoma, 80% head, the rest body and tail
Resectability criteria
(no absolute consensus)

• Resectable
  – No extrapancreatic disease
  – No arterial involvement (celiac, SMA, HA)
  – Venous narrowing (SMV, PV, confluence) < 50%

• Borderline resectable
  – Abutment ≤ 180° celiac or SMA
  – Abutment/encasement > 180° short segment HA
  – Venous narrowing >50%
  – Short venous occlusion (possibility to reconstruct)
  – N1 (verified)

• Non-resectable
Pancreatic cancer

- Non-metastatic
  - resectable
  - borderline resectable
  - non-resectable

- Metastatic
Pancreatic cancer

- Non-metastatic
  - resectable 10-15%
  - borderline resectable
  - non-resectable

- Metastatic 50%

*most of these are non-resectable, some 10-20+% borderline
The traditional view
Pancreatic cancer

• Non-metastatic
  – resectable } 10-15%
  – borderline resectable } 5-10%
  – non-resectable LAPC 30%
• Metastatic 50%

A changing view with improvements in surgery. The percentage figures are uncertain and different in populations and hospital series.
Pancreatic cancer

- Non-metastatic
  - resectable
  - borderline resectable
  - non-resectable

- Metastatic

The non-metastatic will soon become metastatic in most patients
Neo-adjuvant treatment in resectable and borderline resectable pancreatic cancer

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Pancreatic cancer

• Is a systemic disease
• The clinical problems are
  – Lack of effective systemic therapies
  – Surgery seldom radical
  – Tolerability to chemoradiotherapy (CRT) not very good
• Can we use the armamentarium we have better, or
• do we have to wait for the biologics?
What is the evidence for neo-adjuvant treatment of resectable/borderline resectable pancreatic cancer?
Borderline resectability –
Multiple meta-analyses of neo-adjuvant therapy

- Neben-Wittich et al., EJCMO 2009
- Gillen et al., PLoS Med 2010
- Assifi et al., Surgery 2011
- Festa et al., JOP 2013
- Sen et al, Clin Oncol 2014
  - 100+ retrospective/phase II trials
  - About 10 relevant prospective studies
  - Overall 60% to surgery, about 80% resected
  - pCR 4%
  - mOS about 2 years
  - Definition dependent (as is the case in phase II studies)

- No RCT
Neo-adjuvant therapy for *resectable* pancreatic cancer

- One randomised negative study
- Is used, several phase II
  - As always positive (safe, promising activity)
- Circumstantial evidence
Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer

Results of the first prospective randomized phase II trial.

Strahlenther Onkol
DOI: 10.1007/s00066-014-0737-7

Henriette Golcher · Thomas B. Brunner · Helmut Witzigmann · Lukas Marti · Wolf-Otto Bechstein · Christiane Bruns · Henry Jungnickel · Stefan Schreiber · Gerhard G. Grabenbauer · Thomas Meyer · Susanne Merkel · Rainer Fietkau · Werner Hohenberger

- N = 73, 66 evaluable
- Terminated because of slow accrual
- Safe, but no diff in OS/DFS, R0-resection rate, postop complications
- Planned in 1999
One example of a "favourable" outcome
In a phase II study
From MD Anderson
Stages I/II included

UICC stage
Ia  T1N0, <2 cm,
Ib  T2N0, >2cm, within pancreas
IIa T3N0, outside, no large vessels
IIb T3N1, "-"
III  T4Nany, large vessels
IV   TNanyM1
Neo-adjuvant therapy
for resectable/borderline pancreatic cancer

• Is this routine therapy?
  – If so, what therapy?

• Worth to initiate a RCT?
  – If so, what to test? and
  – What control group?
Here comes my answers to the questions and a summary
Neo-adjuvant therapy
for resectable/borderline pancreatic cancer

• Routine therapy?
  – Resectable No
  – Borderline Yes
  – (Non-resectable) Start as/treat as if M1

• Worth to initiate a RCT?
  – Resectable Yes, against surgery alone
  – Borderline Yes, to find optimum schedules
Neo-adjuvant therapy
for resectable/borderline pancreatic cancer

• What to explore in a RCT?

• Systemic chemotherapy followed by chemoradiation and then surgery

• Why do I believe this?
Neo-adjuvant therapy for resectable/borderline pancreatic cancer

- What to explore in a RCT?

- Systemic chemotherapy followed by chemoradiation and then surgery

- Why do I believe this?

- An adjuvant trial with this design is ongoing
RTOG 0848
actively recruiting again testing ± CRT adjuvant
(with QA of the RT)

FIRST RANDOMIZATION

STRATIFY
- Nodal Status:
  1: involved
  2: uninvolved
- CA19-9 result:
  1: < 90
  2: > 90 – 180
- Surgical margin:
  1: positive (R1)
  2: negative (R0)

RANDOMIZE
- Arm 1:
  Gemcitabine x 5 cycles
- Arm 2:
  Gemcitabine + Erlotinib x 5 cycles

Evaluate to Confirm No Progression

SECOND RANDOMIZATION
For Non-Progressing Patients

STRATIFY
1. Arm 1: gemcitabine
2. Arm 2: gemcitabine + erlotinib

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

Is based upon RTOG 9704, no diff CRT with gem or 5-FU, diff according to RT quality (Regine Ann Surg Oncol 2011; Abrams Red J 2012)
Why neo-adjuvant CT followed by CRT?

- Most pancreas cancers are systemic
- Most pancreas cancer resections are R1
- Nodal metastases are very frequent
- Local recurrences are frequent (although many also have systemic disease)
Two patient series:
2002-2004 "standard" German pathology
2005-2006 "careful" German pathology

R1-resections
2002-2004 14% (n=178)
2005-2006 76% (n=111)
Most often medially and posteriorly

Survival not significantly influenced (by better pathology)

86% node-positive
Node positivity in pancreatic cancer

- 80-90% (M Büchlers group and others)
- Usually find 20+ nodes

- Most often involved nodes

- Means that nodes must be covered if CRT
Patterns of Recurrence After Curative Resection of Pancreatic Cancer, Based on Autopsy Findings

Shoichi Hishinuma, M.D., Yoshiro Ogata, M.D., Moriaki Tomikawa, M.D.,
Iwao Ozawa, M.D., Kaoru Hirabayashi, M.D., Seiji Igarashi, M.D.

- Local recurrences are common (literature says 20-60%)
- In an autopsy series, local tumour growth was seen more often than known,
- as were systemic growth

Fig. 2. Histological findings for an autopsy specimen (patient 4) having local recurrence that could not be detected by CT. Cancer cells are scattered in the dense fibrous stroma. (H & E staining; original magnification, ×280)

J Gastrointest Surg 2006
Why CT and CRT before surgery?

- Most pancreas cancers are systemic
  - Often quite rapidly (10-30% within 2-4 months)
  - Start with CT (the best, without platinum if followed by RT?) to detect those that rapidly disseminate/do not respond
  - 4 months of gem-nab-paclitaxel (or gem-cap or FOLFIRINOX?)
  - Evaluation after 2 and 4 months
  - If no progression, give CRT
Metastatic pancreatic cancer – selected trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Median Survival (mo)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burris et al.⁷⁰</td>
<td>126</td>
<td>Fluorouracil Gemcitabine</td>
<td>4.4/5.6</td>
<td>0.002</td>
</tr>
<tr>
<td>NCIC⁷¹</td>
<td>569</td>
<td>Gemcitabine Gemcitabine plus erlotinib</td>
<td>5.9/6.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Ueno et al.⁷²</td>
<td>834</td>
<td>Gemcitabine S-1</td>
<td>8.8/9.7</td>
<td>&lt;0.001 for non-inferiority</td>
</tr>
<tr>
<td>Conroy et al.⁷³</td>
<td>342</td>
<td>Gemcitabine FOLFIRINOX</td>
<td>6.8/11.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Von Hoff et al.⁷⁴</td>
<td>861</td>
<td>Gemcitabine Gemcitabine plus nab-paclitaxel</td>
<td>6.7/8.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Why CT followed by CRT?

- Most pancreas cancers are systemic
- Most pancreas cancer resections are R1
  - CRT locally more effective than CT
- Nodal metastases are frequent
- Local recurrences are frequent
  - GTV + elective nodal irradiation
  - 54-56 Gy with gem or cap, nodes 50.4 Gy
  - Use the best available technique (IMRT-variant, SIB, protons?)
  - Stratify for SMAD-4 (or select??)
Why CRT? –
in spite of all negative experience from RCTs?

• In the adjuvant situation
  – Several trials and meta-analyses
• Not a hit in LAPC
  – LAP-07
• Virtually no data in resectable/borderline outside phase II
Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis

Wei-Chih Liao, Kuo-Liong Chien, Yu-Lin Lin, Ming-Shiang Wu, Jaw-Town Lin, Hsiu-Po Wang, Yu-Kang Tu

Illustrates the present knowledge base
Number of comparisons

Figure 2: Network of the comparisons for the Bayesian network meta-analysis

Liao et al Lancet Oncol 2013
Effects of adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Trial</th>
<th>Hazard ratio (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoptolenos, 2001</td>
<td>ESPAC-1</td>
<td>0.44 (0.29-0.65)*</td>
<td>23.84</td>
</tr>
<tr>
<td>Neoptolenos, 2004</td>
<td>ESPAC-1</td>
<td>0.70 (0.49-1.02)*</td>
<td>24.99</td>
</tr>
<tr>
<td>Neoptolenos, 2009</td>
<td>ESPAC-1+</td>
<td>0.58 (0.42-0.80)</td>
<td>28.15</td>
</tr>
<tr>
<td>Neoptolenos, 2009</td>
<td>ESPAC-3 v1</td>
<td>0.89 (0.59-1.34)</td>
<td>23.03</td>
</tr>
<tr>
<td>Subtotal (I²=55.6%, p=0.080)</td>
<td></td>
<td>0.62 (0.48-0.83)</td>
<td>100.00</td>
</tr>
<tr>
<td>Network meta-analysis</td>
<td></td>
<td>0.62 (0.42-0.88)</td>
<td></td>
</tr>
<tr>
<td>Oettle, 2007</td>
<td>CONKO-001</td>
<td>0.79 (0.63-1.01)*</td>
<td>74.52</td>
</tr>
<tr>
<td>Ueno, 2009</td>
<td>JSAP-02</td>
<td>0.77 (0.52-1.15)</td>
<td>25.48</td>
</tr>
<tr>
<td>Subtotal (I²=0.0%, p=0.90)</td>
<td></td>
<td>0.79 (0.64-0.97)</td>
<td>100.00</td>
</tr>
<tr>
<td>Network meta-analysis</td>
<td></td>
<td>0.68 (0.44-1.07)</td>
<td></td>
</tr>
<tr>
<td>Neoptolenos, 2010</td>
<td>ESPAC-3 v2</td>
<td>0.90 (0.38-2.104)</td>
<td></td>
</tr>
<tr>
<td>Network meta-analysis</td>
<td></td>
<td>1.10 (0.70-1.86)</td>
<td></td>
</tr>
</tbody>
</table>
Effects of CRT

Heavily influenced by ESPAC-1 with its permissive 2x2 design
ESPAC -1, negative for CRT, positive for CT adjuvant

 CRT tended worse

 CT better

(Neoptolemos et al, Lancet 2001;358:1576-85)
### Meta-Analysis of Adjuvant Treatment: Chemoradiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>CRT/Patients</th>
<th>CRT Events</th>
<th>Hazard Ratio &amp; CI</th>
<th>Reduction (%) &amp; SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC</td>
<td>44/63 (68.8%)</td>
<td>48/57 (84.2%)</td>
<td>-8.1 22.5</td>
<td>30% sd 18</td>
</tr>
<tr>
<td>ESPAC1-2x2</td>
<td>125/145 (86.2%)</td>
<td>112/144 (77.8%)</td>
<td>14.8 58.1</td>
<td>-28% sd 15</td>
</tr>
<tr>
<td>ESPAC1-plus</td>
<td>27/33 (61.8%)</td>
<td>29/36 (60.6%)</td>
<td>1.1 13.6</td>
<td>-8% sd 20</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>196/241 (81.3%)</strong></td>
<td><strong>189/237 (79.7%)</strong></td>
<td>7.7 94.3</td>
<td><strong>-9% sd 11</strong> (2p=.43)</td>
</tr>
<tr>
<td>Heterogeneity between 3 groups ( \chi^2 = 6.1; p=.05 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>CRT/Patients</th>
<th>CRT Events</th>
<th>Hazard Ratio &amp; CI</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG*</td>
<td>15/21 (74.2%)</td>
<td>19/22 (86.4%)</td>
<td>-5.3 8.5</td>
<td>46% sd 26</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>211/262 (80.5%)</strong></td>
<td><strong>208/259 (80.3%)</strong></td>
<td>2.5 102.8</td>
<td><strong>-2% sd 10</strong> (2p=.81)</td>
</tr>
<tr>
<td>Heterogeneity between 4 groups ( \chi^2 = 10.0; p=.02 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ID not available

**Stocken et al, Br J Cancer 2005; 92:1372-81**
Adjuvant CRT does not work

Why not?
Pancreas cancer is a systemic disease
No QC of the RT in ESPAC-1 (dominating the evidence)
Low RT-dose, split course (shouldn´t work with present knowledge, historical interest)
Basically we don´t know if CRT works adjuvant, a trial ongoing (RTOG 0848)
Adjuvant Radiotherapy and Lymph Node Dissection in Pancreatic Cancer Treated With Surgery and Chemotherapy

Eric A. Mellon, MD, PhD\textsuperscript{1}; Gregory M. Springett, MD, PhD\textsuperscript{2}; Sarah E. Hoffer, MD\textsuperscript{1}; Pamela Hodul, MD\textsuperscript{3}; Mokenge P. Malafa, MD\textsuperscript{2}; Kenneth L. Meredith, MD\textsuperscript{2}; William J. Fulp, MPH\textsuperscript{3}; Xiuhua Zhao, MPH\textsuperscript{3};
and Ravi Shridhar, MD, PhD\textsuperscript{1}

Retrospective SEER data 2004-2006, \( n = 2966 \)
Modest but sign. better OS in N1 for those receiving PORT

Cancer 2014
Retrospective SEER, better gain if better surgery?

<table>
<thead>
<tr>
<th>No. of LNs Resected&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of N1 Patients</th>
<th>HR: PORT vs No PORT</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥8</td>
<td>1653</td>
<td>0.866</td>
<td>0.769-0.976</td>
<td>.018</td>
</tr>
<tr>
<td>≥10</td>
<td>1450</td>
<td>0.864</td>
<td>0.761-0.982</td>
<td>.025</td>
</tr>
<tr>
<td>≥12</td>
<td>1225</td>
<td>0.855</td>
<td>0.744-0.982</td>
<td>.027</td>
</tr>
<tr>
<td>≥15</td>
<td>940</td>
<td>0.805</td>
<td>0.687-0.945</td>
<td>.008</td>
</tr>
<tr>
<td>≥20</td>
<td>514</td>
<td>0.790</td>
<td>0.635-0.983</td>
<td>.035</td>
</tr>
<tr>
<td>≥25</td>
<td>259</td>
<td>0.765</td>
<td>0.560-1.046</td>
<td>.094</td>
</tr>
<tr>
<td>≥30</td>
<td>128</td>
<td>0.562</td>
<td>0.362-0.872</td>
<td>.010</td>
</tr>
</tbody>
</table>

Postoperative CRT will likely not have a major influence on OS
LAP 07
Gercor-FFCD, international groups
Locally Advanced Pancreatic adenocarcinoma
PI Pascal Hammel, Clichy, France

Bengt Glimelius, co-ordinator Sweden
**Design of LAP07 study**

- **EVALUATION : non progressive**
- **R1**
- **EVALUATION : non progressive**
- **R2**
- **Cape**
- Erlotinib 1000 mg/m²/wk x 3
- Erlotinib 100 mg/d
- Erlotinib 150 mg/d as single agent (maintenance)
- **RT**
- Radiation therapy 54 Gy (5 x 1.8 Gy/d) with concurrent Capecitabine 1600 mg/m²/d
- **Until progression**

erlotinib did not add efficacy in LAPC
Assessed for eligibility (n= 449)

1st Randomization
Intent-to-treat principle (n= 442)

Excluded (n= 7)

Gemcitabine (n= 223)

Gemcitabine + erlotinib (n= 219)

2nd Randomization
Intent-to-treat principle (n= 269)

Excluded (n= 173)
111 progressive disease
15 toxicity
11 delay
11 patients' will
16 investigator decision
6 intercurrent disease
3 surgery

Chemotherapy (n= 136)

Chemoradiotherapy (n= 133)

Hammel P et al. ASCO 2013
LAP-07, overall survival

Overall Survival Probability

Chemotherapy: n=136  n.events=112  median time=16.5
Chemoradiotherapy: n=133  n.events=109  median time=15.2
Log-rank p=0.829
HR - 95%CI: 1.03 [0.79-1.34]

N at risk
Chemotherapy  136  136  133  117  94  70  55  39  24  14  12  8  4  4  4
Chemoradiotherapy  133  133  131  113  87  66  45  34  26  18  12  9  9  8  6
LAP-07, PFS

Progression Free Survival Probability vs Time since the first randomization (months)

Chemotherapy: n=136  n.events=125  median time=8.1
Chemoradiotherapy: n=133  n.events=122  median time=9.9
Log-rank p=0.055
HR - 95%CI: 0.78 [0.61-1.01]

N at risk
Chemotherapy 136  136  113  61  35  21  7  3  1  1  1  1  1  1
Chemoradiotherapy 133  133  117  76  45  30  21  11  8  7  4  4  4  4
Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study


France, Belgium, Australia, New Zealand, Sweden

ASCO 2014
Site of first progression

**R2 patients:**
- 236/269 patients (88%) with tumor progression
- 93 with local progression only (39%)
- 122 with metastatic (± local) progression (52%)
- 21 unknown (9%)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Local</th>
<th>Metastatic</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy (n=125)</td>
<td>46%</td>
<td>44%</td>
<td>10%</td>
</tr>
<tr>
<td>Chemoradiation (n=111)</td>
<td>32%</td>
<td>60%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*p=0.035*
LAP-07, time to new txt

Survival free treatment Probability

Time since the last LAP protocol treatment (months)

Log-rank p=0.017

N at risk
- Chemotherapy: 136, 75, 37, 27, 17, 10, 6, 6, 2
- Chemoradiotherapy: 133, 89, 80, 37, 24, 11, 8, 6, 5
Time without treatment

- 24 patients (19%) in the CT arm and 30 patients (27%) in the CRT arm did not receive a second line of treatment ($p=0.1$)

- **In patients who received a second line of chemotherapy:**

Median time before reintroduction of chemotherapy

<table>
<thead>
<tr>
<th>Chemotherapy (n= 101)</th>
<th>Chemoradiation (n= 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2 months (0.3-22)</td>
<td>5.2 months (0.2-25.7)</td>
</tr>
</tbody>
</table>

$p=0.045$
Radiation for LAPC –
Danish experience, Bjerregaard et al Red J 2012

• Retrospective, n=178, stage IIab+III, all had CRT (50Gy+UFT), some preCRT gem
• 40% T3N0, 40% T3N1, 20% T4Nany
• 13% (n=23) could be resected, which?
• Performance, preCRT gem and resection prognostic
• Stage not very important (T4 tendency)
Messages from retrospective/prospective phase II studies?

- MD Anderson, CRT for resectable, stage I/II
- Odense, CRT for non-resectable, stage II/III (80% stage II)
- Overlapping stages – what to believe?
Radiation for LAPC

- Not very effective as given
- Has palliative effects
- Not worse than chemotherapy
- The large trials not done (as usual for RT)
- Could be done better
  - both better trials and
  - with better techniques/QA and QC
  - worthwhile explore in new trials (many ongoing)
    - but seldom part of routine (except for palliation)
MDT conclusion LAPC
(for the radiation oncologist)

- Can this tumour be resected if
  - No mets, no progression after CT/CRT?
    - Explore the patient if not
  - No mets, sufficient regression seen?
    - Potential exploration if
  - Never?
    - Treat as M1 for palliation, CRT not routine (but may have a role in the best LAPC-patients)
Prognostic subgroups LAP-07
Vernerey et al, unpublished

3 subgroups based on
age
pain
albumin
size
CA 19-9

OS benefit from CRT in group 1
(very few in group 3 made it to R2)

There may be a subgroup who gains from consolidation CRT
Radiation modifies the clinical course of LAPC.  Why not better?

LgII mets frequent
For cure, large volumes needed
Standard dose to about 50 Gy with fluoropyrimidine/gemcitabine insufficient for macroscopic tumour (most solid cancers)
The CRT given in the past ”ineffective”
And toxic, specially for elderly
Better techniques are available

**VMAT/IMRT** is just one step vs 3D-CRT,
e.g. Yovino et al, Red J 2011

**IMPT** would likely do it even better,
e.g. Hong et al, Red J 2011

**SBRT** also possible (but doesn´t cover the nodes)
e.g. Chuong et al Red J 2013
What to irradiate?

• Several recent attempts to define targets
  – RTOG
  – German group
  – John Hopkins

• based on consensus (RTOG) or lymph node mapping/analysis of recurrence patterns
RTOG consensus
Goodman et al, Red J 2012
Based upon careful anatomical description of 175 surgical resections
Limit 3-5% risk of involvement
With description how to delineate
Mapping Patterns of Local Recurrence After Pancreaticoduodenectomy for Pancreatic Adenocarcinoma: A New Approach to Adjuvant Radiation Field Design

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Fig. 1. Local recurrence map. (A) Anterior-posterior and (B) lateral views of local recurrence plots in relation to the celiac artery (yellow) and superior mesenteric artery (blue) after pancreaticoduodenectomy for patients receiving no adjuvant therapy (red), chemotherapy alone (orange), and chemoradiation (green).
Comparison with RTOG consensus

Indicates that smaller targets are possible if 80–90% of local recurrences are covered. Anyhow, more than GTV should be included if the aim is cure.

Fig. 4. A standard Radiation Therapy Oncology Group 0848 clinical target volume (orange) and planning target volume (red) are shown simultaneously with the proposed PTV80-final (blue) and PTV90-final (green) of this study on an anterior-posterior digitally reconstructed radiograph (A) and on axial (B), sagittal (C), and coronal (D) computed tomographic sections of 1 simulated patient as an example of where areas could potentially be reduced to minimize the toxicity of adjuvant treatment. PTV80-final = planning target volume containing 80% of mapped recurrences with avoidance of proximal organs at risk; PTV90-final = planning target volume containing 90% of mapped recurrences with avoidance of proximal organs at risk.
Neo-adjuvant therapy for resectable/borderline pancreatic cancer - conclusions

- Will improve outcome
- Should contain both the best chemotherapy we know
- Should also contain the best radiotherapy we know of
- Likely in that order
- Need a randomised trial in upfront resectable
- Optimize details in the borderline
- If adjuvant chemotherapy then improves OS must be retested