Treatment strategy in Pancreatic Cancer and Biliary Tract Cancer

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Pancreatic Cancer: Mortality and New Cases

Mortality by Leading Sites* by Sex, United States, 2013 Estimates

Men
- Lung and bronchus: 28%
- Prostate: 10%
- Colon and rectum: 9%
- Pancreas: 6%

Women
- Lung and bronchus: 26%
- Breast: 14%
- Colon and rectum: 9%
- Pancreas: 7%

- The 10th most commonly diagnosed cancer and the 4th leading cause of cancer death
- 44,980 new cases and 38,460 deaths in USA in 2013
- > 80,000 deaths in EU

*Excludes basal and squamous cell skin cancer, and in situ carcinomas except urinary bladder.
PaC, pancreatic cancer.
Table 1. Estimated new cancer cases (thousands), ASRs (per 100,000) and cumulative risks to age 75 (percent) by sex and cancer site worldwide, 2012

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Both sexes</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>ASR</td>
<td>Cum. risk</td>
</tr>
<tr>
<td>Lip, oral cavity</td>
<td>300</td>
<td>2.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>87</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Other pharynx</td>
<td>142</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>456</td>
<td>3.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Stomach</td>
<td>951</td>
<td>6.8</td>
<td>12.1</td>
</tr>
<tr>
<td>Colorectum</td>
<td>1360</td>
<td>9.7</td>
<td>17.2</td>
</tr>
<tr>
<td>Liver</td>
<td>782</td>
<td>5.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>178</td>
<td>1.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Pancreas</td>
<td>338</td>
<td>2.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Larynx</td>
<td>157</td>
<td>1.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Lung</td>
<td>1825</td>
<td>12.9</td>
<td>23.1</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>293</td>
<td>1.6</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 2. Estimated cancer deaths (thousands), ASRs (per 100,000) and cumulative risks to age 75 (percent) by sex and cancer site worldwide, 2012

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Both sexes</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>ASR</td>
<td>Cum. risk</td>
</tr>
<tr>
<td>Lip, oral cavity</td>
<td>145</td>
<td>1.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>51</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Other pharynx</td>
<td>97</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>400</td>
<td>4.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>723</td>
<td>8.8</td>
<td>8.9</td>
</tr>
<tr>
<td>Colorectum</td>
<td>694</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Liver</td>
<td>745</td>
<td>9.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>142</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Pancreas</td>
<td>331</td>
<td>4.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Larynx</td>
<td>83</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Lung</td>
<td>1590</td>
<td>19.4</td>
<td>19.7</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>55</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Pancreatic adenocarcinoma: a very tough disease!

- ~85% of patients are diagnosed with advanced unresectable disease
- ~80% of patients who have resection and adjuvant therapy relapse
- “Cure” rate is only ~5%
- Median survival of patients with metastases without treatment is only about 3 months
Why is pancreatic adenocarcinoma so aggressive?

- No early symptoms
- Very early invasion and metastases
- Chemo-resistant (sanctuary?)
- Debilitating cytokine mediated symptoms
Pancreatic Cancer Survival Rates by Stage

- Majority of patients have inoperable disease at time of diagnosis\(^1\)
- Only 6% of patients (all stages) survive more than 5 years\(^1\)
- Mortality rates from pancreatic cancer in the United States have slowly increased over the past 10 years\(^2\)

PanIN: Pancreatic Intraepithelial Neoplasia
PDAC: Pancreatic Ductal Adenocarcinoma
Multifaceted Biology of Pancreatic Ductal Adenocarcinoma

Cancer pathways:
- Apoptosis
- DNA damage repair
- Cell-cycle control
- RAS
- TGF-β
- Cell adhesion
- Hedgehog
- Integrin
- JNK
- Wnt-β-catenin
- Invasion
- Small GTPases

Selected altered genes:
- CASP10, CAD,
- TP53, ERCC4, BRCA2
- CDK2NA, APC2
- KRAS, MAP2K4
- BMPR2, SMAD4,
- FAT, PCDH9,
- GLI1, GLI3,
- ILK, LAMA1,
- MAP4K3, TNF,
- MYC, TSC2,
- ADAM11, ADAM19, PRSS23,
- PLCB3, RPI

Pancreatic-cancer stem cell pathways:
- Self-renewal
- 1~5% of cell population
- Markers: CD24+, CD44+, EMA, CD133+, ALDH+
- Resistant to chemotherapy and radiotherapy

Cancer stem-cell pathways:
- CXCR4
- Hedgehog
- BMI-1
- Wnt-β-catenin
- EMT
- Notch

Stromal cells:
- Fibroblasts
- Pancreatic stellate cells
- Endothelial cells
- Immune and inflammatory cells
- Adipocytes

Stromal pathways:
- Hedgehog
- Nuclear factor κB
- Cyclooxygenase-2
- TGF-β
- Angiogenesis (VEGF and PDGF)
- HGF/mot
- MMP
- FGF

Extracellular matrix:
- Collagen types I and III
- Laminin
- Fibronectin
- MMP
- TIMP
- SPARC
- CTGF

M Hidalgo, NEJM 2010
Figure 2. Biologic Features of Pancreatic Cancer.

Pancreatic cancers have a complex microenvironment that might be a target for therapy. TCA denotes tricarboxylic acid.
A small proportion (<10%) are due to inherited germline mutations: BRCA2, p16, ATM, STK11, PRSS1/PRSS2, SPINK1, PALB2, and DNA mismatch repair genes.

## Causes of pancreatic adenocarcinoma

### Table 1. Major non-genetic risk factors [5]a

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative risk</th>
<th>Attributable fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>2</td>
<td>11%–32%</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>1.5</td>
<td>4%–25%</td>
</tr>
<tr>
<td>Non-O-blood group</td>
<td>1.4</td>
<td>13%–19%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.4–2.2</td>
<td>1%–16%</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.2–1.5</td>
<td>3%–16%</td>
</tr>
<tr>
<td>Red meat intake</td>
<td>1.1–1.5</td>
<td>2%–9%</td>
</tr>
<tr>
<td>Heavy alcohol intake</td>
<td>1.1–1.5</td>
<td>9%</td>
</tr>
<tr>
<td>Low fruit and folate intake</td>
<td>0.5–1.0</td>
<td>&lt;12%</td>
</tr>
</tbody>
</table>

aBy permission of Oxford University Press on behalf of The International Epidemiological Association.
Pancreatic tumoural mass

Figure 1. Diagnostic work-up before multidisciplinary decision. CT, computed tomography.
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.

Unresectable
- Distant metastases
- Arterial encasement (celiac trunk, superior mesenteric artery, or hepatic artery)
- Arterial involvement (celiac trunk, superior mesenteric artery, or hepatic artery)
- Venous encasement (portal or superior mesenteric vein)
- Venous involvement (portal or superior mesenteric vein)
- Attached to other organs
- No arterial or venous involvement

Resectable

Portal vein
Hepatic artery
Celiac trunk
Bile duct
Pancreas
Spleen
Pancreatic ducts
Superior mesenteric artery and vein
<table>
<thead>
<tr>
<th>Resectability status</th>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>No arterial tumour contact [coeliac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA)]</td>
<td>No tumour contact with the superior mesenteric vein (SMV), or portal vein (PV) or &lt;180° contact without vein contour irregularity</td>
</tr>
<tr>
<td>Unresectable</td>
<td>• Distant metastases Pancreatic head/uncinate process • Solid tumour contact with SMA &gt;180° • Solid tumour contact with the CA &gt;180° • Solid tumour contact with the first jejunal SMA branch Body and tail • Solid tumour contact with the SMA and CA • Solid tumour contact with the CA and aorta</td>
<td>Pancreatic head/uncinate process • Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)</td>
</tr>
</tbody>
</table>
Pancreatic adenocarcinoma clinical grouping

- Metastatic disease
  - Chemotherapy: modest progress

- Resectable disease

- Borderline resectable disease

- Locally advanced, but clearly not resectable disease
## Metastatic Pancreatic Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Median Survival</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>NCIC 71</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>

* FOLFIRINOX denotes fluorouracil, irinotecan, oxaliplatin, and leucovorin; and NCIC National Cancer Institute of Canada.
Incremental Benefits With New Agents in Frontline

ACCORD trial: Gemcitabine vs FOLFIRINOX

**A  Overall Survival**

Hazard ratio, 0.57 (95% CI, 0.45–0.73)
P<0.001 by stratified log-rank test

**B  Progression-free Survival**

Hazard ratio, 0.47 (95% CI, 0.37–0.59)
P<0.001
MPACT trial: Gemcitabine ± Nabplacitaxel
Overall Survival

Newer options: Liposomal irinotecan in second line in combination with 5FU/LV: NAPOLI Phase III

<table>
<thead>
<tr>
<th></th>
<th>MM-398/5FU/LV</th>
<th>5FU/LV</th>
<th>Hazard ratio, $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>6.1</td>
<td>4.2</td>
<td>0.67, 0.012</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>3.1</td>
<td>1.5</td>
<td>0.56, &lt; 0.001</td>
</tr>
</tbody>
</table>

Single agent MM-398 did not improve over 5FU/LV

Von Hoff D et al, ESMO GI/WCGIC, Barcelona, 2014
Pancreatic adenocarcinoma selection of other new agents

✓ FIRST LINE:
    ▪ Phase 2 in first line¹;
    ▪ Ongoing phase 3: Maestro trial
  ✓ Pegylated hyaluronidase (PEGPH20)
    ▪ Phase 2 Gem/Nab-paclitaxel +/- PEGH20: benefit in subgroup with high hyaluronan²
  ✓ Ibrutinib
    ▪ Ongoing phase 3: Gem/Nab-paclitaxel +/- ibrutinib

✓ SECOND LINE
  ✓ Ruxolitinib - JAK 1-2 inhibitor:
    ▪ Phase 2: benefit in second line in combination with capecitabine in patients with high CRP³
    ▪ Ongoing phase 3: Janus trials

¹ Borad M et al, JCO 2014
² Hingorani S et al, ASCO 2015
³ Hurwitz H et al, ASCO 2014
Suggested treatment algorithm for metastatic pancreatic cancer

**Poor performance status**
- KPS 50-60%
  - Gemcitabine
  - OR
  - BSC

**Reduced performance status**
- Disease control
  - KPS >60%
  - nab-paclitaxel + gemcitabine
  - OR
  - Gemcitabine ± erlotinib

**Good performance status**
- High pressure for rapid remission
  - KPS 90-100%
  - nab-paclitaxel + gemcitabine
  - OR
  - FOLFIRINOX
Cancer-associated fibroblasts are currently undergoing testing in the adjuvant setting with nab-paclitaxel, whereas the available data on chemoradiotherapy show similar efficacy in patients with resectable pancreatic ductal adenocarcinoma (PDAC). However, gemcitabine treatment with either bolus 5-FU or gemcitabine has not shown significant improvements in overall survival.

Abbreviations: Br, bromodomain; CAR, chimeric antigen receptor; CSC, cancer stem cell; CXCL12, CXC chemokine ligand 12; CXCR4, CXC chemokine receptor 4; PDAC, pancreatic ductal adenocarcinoma; PDGF, platelet-derived growth factor; SPARC, secreted protein acidic and rich in cysteine; VEGF, vascular endothelial growth factor.

In the treatment of PDAC, various targeted therapies are being explored. For instance, Br-IDM (dibromoisophosphoramide mustard) in the hypoxic tumour microenvironment and SMO, Notch, and Wnt/beta-catenin pathway inhibitors are being tested in phase clinical trials. Additionally, CXCR4 plus PD-1 or PD-L1 inhibitors are being investigated alongside CXCL12 (the ligand for CXCR4), which is produced by cancer-associated fibroblasts (CAFs), to enhance T-cell trafficking and promote immune surveillance. The role of tryptophan metabolism in the immune response and the potential of IDO inhibitors, such as INCB-24360, NLG919, and demcizumab, is also being explored.

Treating PDAC involves a complex interplay between tumour cells and the immune system. For instance, Br-IDM, a topoisomerase inhibitor, has shown promising effects in the T-cell compartment. CXCL12, which binds to its receptor in the membrane of T cells, promotes immune surveillance. CAFs, which produce CXCL12, are hypothesized to result in apoptosis or chemorepulsive effects in the T-cell compartment.

PDAC is a systemic disease with a poor prognosis, and improving outcomes requires a comprehensive approach. The expanding range of targets for therapy highlights the need for multifaceted strategies to overcome immune evasion by tumour cells and create a more immunosuppressive environment in PDAC. Novel cytotoxics such as nab-paclitaxel, TH-302, and MM-398 (a liposomal formulation of irinotecan) are being tested to target pancreatic cancer cells, CSCs, and the immunosuppressive stroma.

Targeted cellular compartments plotted in this figure include Growth factors (HGF, PDGF, VEGF), SMO, Notch, and Wnt/beta-catenin pathway inhibitors, CAFs, and the immunosuppressive stroma. Novel cytotoxics such as nab-paclitaxel, TH-302, and MM-398 are being tested in the treatment of PDAC. The hypothesis that PDAC is a systemic disease is supported by the fact that 5-year survival rates for patients with resectable pancreatic cancer are less than 20%.

Significant improvements in surgical technique in the past decade have resulted in decreased perioperative morbidity and mortality after pancreatic cancer resection. Referral of patients to large volume centres is important, as not only surgeon experience, but also medical and nursing expertise have been shown to be key factors that influence the risk of death following surgery.

In this regard, referral of patients to large volume centres is important, as not only surgeon experience, but also medical and nursing expertise have been shown to be key factors that influence the risk of death following surgery.
Pancreatic adenocarcinoma clinical grouping

- Metastatic disease

- **Resectable disease:**
  - resection plus adjuvant treatment

- Borderline resectable disease

- Locally advanced, but clearly not resectable disease
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Survival</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG⁵⁸</td>
<td>43</td>
<td>Observation, Fluorouracil plus radiotherapy</td>
<td>10% at 2 yr, 20% at 2 yr</td>
<td>0.007</td>
</tr>
<tr>
<td>EORTC⁵⁹</td>
<td>218</td>
<td>Observation, Fluorouracil plus radiotherapy</td>
<td>26% at 2 yr, 34% at 2 yr</td>
<td>0.10</td>
</tr>
<tr>
<td>ESPAC-1⁶⁰</td>
<td>289</td>
<td>Observation, Chemoradiotherapy</td>
<td>16.9 mo (median), 13.9 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorouracil, Chemoradiotherapy plus fluorouracil</td>
<td>21.6 mo, 19.9 mo</td>
<td></td>
</tr>
<tr>
<td>CONKO-01⁵¹</td>
<td>368</td>
<td>Observation, Gemcitabine</td>
<td>10.4% at 5 yr, 20.7% at 5 yr</td>
<td>0.01</td>
</tr>
<tr>
<td>ESPAC 3⁶²</td>
<td>1088</td>
<td>Fluorouracil, Gemcitabine</td>
<td>23.0 mo (median), 23.6 mo</td>
<td>0.39</td>
</tr>
<tr>
<td>RTOG 9704⁵³</td>
<td>451</td>
<td>Fluorouracil plus radiotherapy, Gemcitabine plus radiotherapy</td>
<td>22% at 5 yr, 18% at 5 yr</td>
<td>0.12</td>
</tr>
<tr>
<td>JASPAC-01⁵⁴</td>
<td>378</td>
<td>S-1 (oral fluoropyrimidine), Gemcitabine</td>
<td>70% at 2 yr, 53% at 2 yr</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* CONKO-01 denotes Charité Onkologie 01, EORTC European Organization for Research and Treatment of Cancer, ESPAC European Study Group for Pancreatic Cancer, GITSG Gastrointestinal Tumor Study Group, JASPAC-01 Japan Adjuvant Study Group of Pancreatic Cancer, and RTOG 9704 Radiation Therapy Oncology Group 9704.

† The estimated 5-year survival rate was 10% among patients who received chemoradiotherapy and 20% among patients who did not receive chemoradiotherapy (P=0.05). The 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy (P=0.009).
Adjuvant Gemcitabine After Complete Tumor Resection

Treatment with adjuvant gemcitabine for 6 months leads to 24% improvement in OS over observation

- 5-year OS: 10.3% improvement (20.7% vs 10.4%)\(^a\)
- 10-year OS: 4.5% improvement (12.2% vs 7.7%)\(^b\)

95% CI for gemcitabine and observation, respectively
\(^a\)(95% CI: 14.7\%-26.6\%) vs (95% CI, 5.9\%-15.0\%)
\(^b\)(95% CI: 7.3\%-17.2\%) vs (95% CI: 3.6\%-11.8\%)

APACT: Adjuvant Pancreatic Adenocarcinoma Clinical Trial

Nab-paclitaxel and Gemcitabine vs Gemcitabine Alone as Adjuvant Therapy for Patients With Resected Pancreatic Cancer

- Primary endpoint: Disease Free Survival (DFS)
- Secondary endpoints: OS, safety and tolerability
- Exploratory endpoints: molecular profiling of tumours, QoL

Pancreatic adenocarcinoma clinical grouping

- Metastatic disease
- Resectable disease

- Borderline resectable disease: definition issues
  - Neoadjuvant treatment
    - Chemotherapy
    - Chemoradiotherapy

- Locally advanced, but clearly not resectable disease
3 Principle Goals of Neoadjuvant Therapy

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

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

- **Not interfering with surgical outcome**
  - Treatment should not cause increased morbidity/increased post-operative complications
  - Treatment should not cause fibrosis/scarring that make the operation more difficult
Combined Analysis of Published Data Shows Low Response Rates

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 330)</td>
<td>1.8%</td>
<td>18.8%</td>
<td>59.2%</td>
<td>18.9%</td>
</tr>
<tr>
<td>Resectable (n = 196)</td>
<td>0.8%</td>
<td>9.5%</td>
<td>73.9%</td>
<td>17%</td>
</tr>
<tr>
<td>Borderline/unresectable (n = 134)</td>
<td>4%</td>
<td>31.8%</td>
<td>40.9%</td>
<td>21.8%</td>
</tr>
</tbody>
</table>

54.2% of all patients underwent resection
65.8% of resectable patients underwent resection
80.6% of these were R0
31.6% of borderline/unresectable patients underwent resection
62.2% of these were R0
All patients received chemo, 85% had chemohxrt

Mura Assifi et al Surgery 150:466-73, 2011
Combined Analysis Shows We Can Achieve RO Resection

- Suggests that neoadjuvant therapy leads to high R0 resection rate
  - These studies had differing definitions of resectable, borderline and unresectable
  - Intriguingly, borderline and unresectable patients who had resection had the same survival (22.3 months) as resectable patients (23 months)
    - Does this suggest our definitions of borderline resectable are just bad in these studies?
  - Did not differentiate chemo from chemoradiation

Does chemoradiation have a higher response rate than chemo alone?

- Very little evidence of this (even for older chemo regimens, mainly gemcitabine monotherapy)
- Even in the combined analysis, the definitions of response varied over the years
- Primary pancreatic cancers
  - Appear less responsive than metastases
  - Are difficult to measure even with high quality scans
## Treatment For Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Stage</th>
<th>Study Design</th>
<th>N</th>
<th>ORR, %</th>
<th>Resection rate, %</th>
<th>R0 resections, %</th>
<th>1-year PFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOLFIRINOX</strong>¹</td>
<td>BL or unresectable</td>
<td>Retrospective</td>
<td>18</td>
<td>---</td>
<td>39</td>
<td>28</td>
<td>83</td>
</tr>
<tr>
<td><strong>FOLFIRINOX</strong>²</td>
<td>laPC</td>
<td>Retrospective</td>
<td>16</td>
<td>50</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>FOLFIRINOX</strong>³</td>
<td>laPC or BL</td>
<td>Registry</td>
<td>23</td>
<td>34</td>
<td>---</td>
<td>---</td>
<td>75</td>
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<tr>
<td><strong>FOLFIRINOX</strong>⁴</td>
<td>laPC or BL</td>
<td>Retrospective</td>
<td>43</td>
<td>---</td>
<td>54</td>
<td>42</td>
<td>---</td>
</tr>
<tr>
<td><strong>FOLFIRINOX</strong>⁵</td>
<td>BL or unresectable</td>
<td>Phase II</td>
<td>32</td>
<td>37</td>
<td>41</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>FOLFIRINOX</strong>⁶</td>
<td>laPC</td>
<td>Phase II b</td>
<td>8</td>
<td>63</td>
<td>37</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Nab-paclitaxel + gemcitabine⁷</td>
<td>BL or resectable</td>
<td>Phase II</td>
<td>16</td>
<td>31c</td>
<td>56d</td>
<td>89e</td>
<td>---</td>
</tr>
</tbody>
</table>

¹Sequencial regimen including FOLFIRINOX and nab-paclitaxel plus gemcitabine
²1 complete pathological response and 4 near complete responses (few (<5%) residual tumor)
³At the time of the analysis
⁴Of patients who had been operated on at the time of the analysis

**BL**: borderline
**laPC**: locally advanced pancreatic cancer

ESMO–ESDO Clinical Practice Guidelines

- For borderline resectable disease, neoadjuvant chemotherapy or CRT is recommended, if R0 resection is possible²
  - Not clear what is the best strategy:
    - More intense regimen with high RR!
    - In fit patients: FOLFIRINOX?

- Multidisciplinary approach is paramount in assessing resectability²
  - Surgeon, radiologist, oncologist, gastroenterologist and radiotherapist

Pancreatic adenocarcinoma clinical grouping

- Metastatic disease
- Resectable disease
- Borderline resectable disease
- Locally advanced, but clearly not resectable disease
Frontline CRT versus chemotherapy in LAPC

Contradictory results
Induction CT followed by CRT in LAPC

CRT after 3 months of induction chemotherapy

Huguet F et al, J Clin Oncol 2007

Promising strategy
LAP07 study

1 month = Gemcitabine (1000 mg/m²)/wkX3

Erlotinib: 100 mg/d with gem 150 mg/d as single agent

Secondary surgery allowed at any time

Hammel P et al, JCO, ASCO 2013
LAP 007: 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

Hammel P et al, JCO, ASCO 2013
LAP-007: Progression Free Survival

Chemotherapy: n=136 n.events=125 median time=8.4
Chemoradiotherapy: n=133 n.events=122 median time=9.9
Log-rank p=0.055
HR - 95%CI: 0.78 [0.61-1.01]

Hammel P et al, JCO, ASCO 2013
LAP07 Conclusions

- LAP07 prospectively confirmed the value of frontline chemotherapy in LAPC patients

- Overall survival in CRT arm is not superior to chemotherapy arm in LAPC patients with tumor controlled after 4 months of chemotherapy

- However, trend for PFS in favor of CRT

- In the CRT arm, patients had a significantly less local tumor progression and a longer period without chemotherapy

Hammel P et al, JCO, ASCO 2013
Pancreatic adenocarcinoma
clinical grouping

- Metastatic disease
- Resectable disease
- Borderline resectable disease
- Locally advanced, but clearly not resectable disease
Biliary Tract Cancer

- Adenocarcinomas (95%) +/- mucin, 3% of all GI cancers
- Overall prognosis is poor (5-year survival 5-15%)¹,²
- <35% of patients present with resectable disease and relapse rates are high

UK
- Cholangiocarcinoma
  - 1600 cases ³
- Gallbladder cancer
  - 650 cases ³

USA ⁴
- Gallbladder 10,900
- IH-CCA: 5000-6000

Cholangiocarcinoma
High quality – expert surgery is crucial
Importance of Margin and LN status

Johns Hopkins
- 564 patients (1973-2004)
- Multivariable analysis
  - Negative margins (p<0.001)
  - Tumour differentiation (p<0.001)
  - Negative nodal status (p<0.001)

For R0-resected patients
- Lymph node status (p<0.001) predicted survival
- Tumour diameter, histology or differentiation did not

Adjuvant therapy: limited data available

Asian Phase III study

Curative resection (n=508) 1986-1992

Stage II-IV (Japan)
- Pancreas (n=173)
- Bile duct (n=139)
- Gallbladder (n=140)
- Ampullary (n=56)

1º end-point | Survival

MF* chemotherapy

Observation

Results

No benefit
- Pancreas
- BTC
- Ampullary

Improved DFS and OS
- Ca gallbladder

In patients with Ca Gallbladder
- Improved 5Y-DFS (20.3% vs. 11.6%, p=0.0210) per-protocol analysis
- Improved 5YS (26.0% vs. 14.4%, p=0.0367) per-protocol analysis
- Effect lost with ITT analysis (imbalance of ineligible (stage 1) patients

Takada et al, Cancer 2002
# Registry studies | Lessons

## Surveillance, Epidemiology, and End Results Program
Turning Cancer Data Into Discovery

<table>
<thead>
<tr>
<th>SEER</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-hepatic cholangiocarcinoma</td>
<td>No improvement in survival observed from RT</td>
<td>Vern-Gross <em>JROBP</em> 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-hepatic cholangiocarcinoma</td>
<td>Improved survival observed from RT</td>
<td>Shinohara <em>IJROBP</em> 2008</td>
</tr>
<tr>
<td></td>
<td>• Median OS 11 vs. 6 months p=0.014</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• HR (adjusted) 0.82; 95% CI, 0.70–0.96</td>
<td></td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Improved survival observed from RT</td>
<td>Mojica <em>J Surg Onc</em> 2007</td>
</tr>
<tr>
<td></td>
<td>• Median OS 14-15 vs. 8 months (p&lt;0.0001)</td>
<td>Wang <em>JCO</em> 2008</td>
</tr>
<tr>
<td></td>
<td>• Greatest benefit in T2+/N+ disease</td>
<td><em>Wang JCO</em> 2011</td>
</tr>
<tr>
<td></td>
<td>• Updated 2011* chemo-RT better than chemo alone</td>
<td></td>
</tr>
</tbody>
</table>

SEER studies have many limitations; there is no information available on many factors;

Courtesy: Juan Valle
Forest plot of studies for extra-hepatic cholangiocarcinoma

Pooled HR for overall survival using a random effects model

Not randomized! Not prospective! RT to patients with adverse features! Adverse Events!

"Consider adjuvant radiotherapy for patients with involved margins"

Bonet Beltrán et al, Cancer Treat Rev 2012
## Adjuvant Therapy in the Treatment of Biliary Tract Cancer: A Systematic Review and Meta-Analysis

Anne M. Horgan, Eitan Amir, Thomas Walter, and Jennifer J. Knox

<table>
<thead>
<tr>
<th>Overall population</th>
<th>No benefit for adjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>If registry data is excluded</td>
<td>Benefit for adjuvant therapy</td>
</tr>
<tr>
<td>Greatest benefit for chemotherapy or chemo-radiotherapy</td>
<td></td>
</tr>
</tbody>
</table>

**Overall population**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo:</td>
<td>0.39 (0.23-0.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>CRT:</td>
<td>0.61 (0.38-0.99)</td>
<td>0.049</td>
</tr>
<tr>
<td>RT:</td>
<td>0.98 (0.67-1.43)</td>
<td>0.90</td>
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**If registry data is excluded**

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<td>0.90</td>
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</table>

**Greatest benefit for chemotherapy or chemo-radiotherapy**

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<th>Treatment</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td>CRT:</td>
<td>0.61 (0.38-0.99)</td>
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</tr>
<tr>
<td>RT:</td>
<td>0.98 (0.67-1.43)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Horgan A et al, JCO 2012
Adjuvant therapy of Biliary Tract Cancer
Current status

- Radical surgery remains the mainstay of cure for patients with BTC
- No clear recommendations regarding adjuvant chemotherapy or radiotherapy
  - High risk fit patients may benefit from CT; positive resection margins: consider CRT
- Many limitations in interpreting studies to date
Chemotherapy for advanced BTC
Better than Best Supportive Care (BSC) alone

<table>
<thead>
<tr>
<th>Study</th>
<th>OS (months)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glimelius</strong> <em>Ann Oncol</em> 1996</td>
<td>BSC 2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU/etoposide/LV v BSC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas (n=53) + BTC (n=37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved QoL</td>
<td>FELV 6</td>
<td></td>
</tr>
<tr>
<td>Improved survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sharma</strong> <em>J Clin Oncol</em> 2010</td>
<td>BSC 4.5</td>
<td>0.039</td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGemOx* v 5FU/FA v BSC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallbladder cancer only (n=81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved PFS</td>
<td>5FU 4.6</td>
<td></td>
</tr>
<tr>
<td>Improved survival</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Gem 900 mg/m² + oxali 80 mg/m² D1, 8 q21d mGemOx 9.5
Chemotherapy for advanced BTC
A number of active agents and combinations

• 5FU
• S1
• UFT
• Capecitabine

Phase II studies
RR 10 - 36%
TTP 3.7 - 9.0 mo
Survival 5 - 14 mo

Phase II studies of Gemcitabine
RR 17 - 64%
TTP 3.5 – 8.5 mo
Survival 6 – 15.4 mo

Phase II studies of Platinum
RR 17 - 64%
TTP 3.5 – 8.5 mo
Survival 6 – 15.4 mo

Phase II studies of Fluoropyrimidine
RR 10 - 46%
TTP 4.0 - 7.0 mo
Survival 5 - 18 mo

Modified from Juan Valle
Randomized phase III studies
gemcitabine ± cisplatin

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>No. at Risk</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC-02</td>
<td>Valle <em>NEJM</em> 2010</td>
<td>206, 204</td>
<td>5.0, 8.0</td>
<td>8.1, 11.7</td>
</tr>
<tr>
<td>BT-22</td>
<td>Okusaka <em>BJC</em> 2010</td>
<td>204, 204</td>
<td>3.7, 5.8</td>
<td>7.7, 11.2</td>
</tr>
</tbody>
</table>
## Combination chemotherapy | Better outcomes

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Phase</th>
<th>N</th>
<th>Categories</th>
<th>Response (%)</th>
<th>Outcome (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem/Cis vs. Gem</td>
<td>3</td>
<td>410</td>
<td>Gem</td>
<td>0.7</td>
<td>14.8</td>
<td>Valle NEJM 2010</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Gem/Cis</td>
<td>0.6</td>
<td>25.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>83</td>
<td>Gem</td>
<td>0</td>
<td>11.9</td>
<td>Okusaka BJC 2010</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Gem/Cis</td>
<td>0</td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td>Gem+S1 / S1</td>
<td>2</td>
<td>101</td>
<td>S1</td>
<td>NR</td>
<td>17.4</td>
<td>Morizane Cancer Sc 2013</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Gem+S1</td>
<td>NR</td>
<td>36.4</td>
<td></td>
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<tr>
<td>5-FU vs.5-FU/FA/Cis</td>
<td>2</td>
<td>58</td>
<td>5-FU</td>
<td>0</td>
<td>7</td>
<td>Ducreux Eur J Cancer 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-FU/FA/ Cis</td>
<td>4</td>
<td>15</td>
<td></td>
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<tr>
<td>FELV vs. ECF</td>
<td>3</td>
<td>54</td>
<td>FELV</td>
<td>0</td>
<td>15</td>
<td>Rao BJC 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ECF</td>
<td>3.8</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>MMC/Gem vs. MMC/Cape</td>
<td>2</td>
<td>51</td>
<td>MMC/Gem</td>
<td>0</td>
<td>20</td>
<td>Kornek Ann Oncol 2004</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>MMC/Cape</td>
<td>0</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

**Key message:**
Combination chemotherapy (doublet) is associated with improved PFS & OS

Table adapted from Geynishman *Disc Medicine* 2012
## Role of radiotherapy | Recent experience

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th>Design</th>
<th>N=</th>
<th>Tumour size</th>
<th>Treatment</th>
<th>Dose Gy Med (range)</th>
<th>Fx</th>
<th>1 year OS</th>
<th>1 year LC</th>
<th>Grade ≥ toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Josef J Clin Oncol/2005</td>
<td>Michigan, US</td>
<td>Phase 2</td>
<td>46</td>
<td>2-2000 mL</td>
<td>3D CRT, hyper-fractionated</td>
<td>61 (40-90)</td>
<td>1.5Gy/ fx bid</td>
<td>Median 13.3 months</td>
<td>70% at 16 mo follow up</td>
<td>40%</td>
</tr>
<tr>
<td>Goodman Int J Radiat 2010</td>
<td>Stanford, US</td>
<td>Phase 1</td>
<td>5</td>
<td>&lt; 5 cm</td>
<td>SBRT Cyberknife</td>
<td>18-30</td>
<td>1</td>
<td>71%</td>
<td>23% 1 year local failure</td>
<td>0%</td>
</tr>
<tr>
<td>Tse J Clin Onc 2008</td>
<td>Toronto, Canada</td>
<td>Phase 1</td>
<td>10</td>
<td>10-465 mL</td>
<td>SBRT</td>
<td>33 (28-48)</td>
<td>6</td>
<td>58%</td>
<td>65%</td>
<td>20%</td>
</tr>
<tr>
<td>Ibarra Acta Oncol 2012</td>
<td>Multi</td>
<td>Poooled analysis</td>
<td>11</td>
<td>31-819 mL</td>
<td>SBRT</td>
<td>30 (22-50)</td>
<td>1-10</td>
<td>45%</td>
<td>50%</td>
<td>7% RILD only</td>
</tr>
<tr>
<td>Barney Radiat Oncol 2012</td>
<td>Minnesota, US</td>
<td>Retrospective</td>
<td>10</td>
<td>16-412 mL PTV</td>
<td>IMRT or 3D-CRT</td>
<td>55 (45-60)</td>
<td>3-5</td>
<td>73%</td>
<td>100%</td>
<td>20%</td>
</tr>
<tr>
<td>Dewas Radiat Oncol 2012</td>
<td>Lille, France</td>
<td>Retrospective</td>
<td>6</td>
<td>0.5-11 cm</td>
<td>SBRT Cyberknife</td>
<td>39-45</td>
<td>3-4</td>
<td>100%</td>
<td>100%</td>
<td>NS</td>
</tr>
<tr>
<td>Goyal HPB Surg 2010</td>
<td>Ohio, US</td>
<td>Retrospective</td>
<td>3</td>
<td>80-818 mL</td>
<td>SBRT Cyberknife</td>
<td>24-45</td>
<td>1-3</td>
<td>0%</td>
<td>67%</td>
<td>0%</td>
</tr>
<tr>
<td>Blomgren Acta Oncol 1995</td>
<td>Stockholm, Sweden</td>
<td>Retrospective</td>
<td>1</td>
<td>67 mL</td>
<td>SBRT</td>
<td>63</td>
<td>3</td>
<td>Median 14 months</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abbreviations** | 3D-CRT, three-dimensional conformal radiation therapy; Fx, fractions; IMRT, intensity-modulated radiation therapy; RILD, radiation-induced liver disease; SBRT, stereotactic body radiation therapy; TVT, tumour vascular thrombosis.
SIRT | In intra-hepatic cholangiocarcinoma

Systematic review
12 studies (7 prospective, 5 retrospective), 298 patients (prior chemo 54%, surgery 33%)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>End-point</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>Co-primary</td>
<td>11 studies</td>
</tr>
<tr>
<td>Response rate</td>
<td>Co-primary</td>
<td>6 studies</td>
</tr>
<tr>
<td>Conversion to resectability</td>
<td>Secondary</td>
<td>3 studies</td>
</tr>
</tbody>
</table>

Adverse events
- Fatigue
- Abdominal pain
- Fever
- Nausea
- Deranged liver function tests
- Treatment-related death (n=1)

Others
- 1 gastroduodenal ulcer
- 2 pleural effusions
- 7 ascites
- 1 duodenal ulcer
- 1 Pulmonary embolism
- 4 ascites
- 2 pleural effusion
- 2 acute radiation hepatitis
- 1 chronic radiation hepatitis

Al-Adra Eur J Surg Oncol 2015
Conclusions: Advanced Biliary Tract Cancer

- Chemotherapy is associated with modest benefit – more effective treatments are needed
  - Standard option in fit patients in 2015: gemcitabine/cisplatin

- Radiotherapy (including radio-embolisation) may be considered in selected patients – no phase III data

- Patients with inoperable disease responding to any treatment should be re-discussed at the tumour board

- The role and modality of adjuvant therapy needs to be defined more clearly

- The use of targeted therapy remains investigational in 2016