Treatment strategy in Pancreatic Cancer and Biliary Tract Cancer

ESMO Africa
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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
- Incidence numbers and numbers of deaths are almost identical
Evolution in Pancreatic Ductal adenocarcinoma & Role of Stroma in the Development

Figure 2. Biologic Features of Pancreatic Cancer.
Pancreatic cancers have a complex microenvironment that might be a target for therapy. TCA denotes tricarboxylic acid.
Pancreatic adenocarcinoma: treatment strategy clinical grouping

- **Metastatic disease**
  - Chemotherapy: modest progress

- **Resectable disease**

- **Borderline resectable disease**

- **Locally advanced, but clearly not resectable disease**
Treatment of Pancreatic Cancer

Key Milestones

- Median survival remains under 1 year in advanced stage
- In early stage, 5-year survival rate is only about 20-25%

But despite improvements:
- Median survival remains under 1 year in advanced stage
- In early stage, 5-year survival rate is only about 20-25%
Treatment of Metastatic Pancreatic Cancer is Palliative

Benefits
- Prolong survival
- Improve clinical symptoms
- Improve quality of life

Toxicity
Incremental Benefits With New Agents in Frontline

Gemcitabine + nab-paclitaxel and FOLIRINOX in metastatic pancreatic adenocarcinoma

**Very fit:**
Pressure for rapid regression

**Fit:**
But reduced PS

**Unfit:**
poor PS

Potential second line after GEM + Nab-paclitaxel
Naliri + 5FU/LV
FOLFIRINOX

Potential second line after FOLFIRINOX:
GEM based
**NAPOLI-1 Results**

**OS**

- **A**
  - Nanoliposomal irinotecan plus fluorouracil and folinic acid
  - Fluorouracil and folinic acid
  - Kaplan-Meier curve showing overall survival.
  - HR 0.67 (95% CI 0.49 - 0.92)
  - p = 0.012 (unstratified log-rank)

- **Number at risk**
  - Nanoliposomal irinotecan plus fluorouracil and folinic acid: 117
  - Fluorouracil and folinic acid: 119

**PFS**

- **C**
  - Nanoliposomal irinotecan plus fluorouracil and folinic acid
  - Fluorouracil and folinic acid
  - Kaplan-Meier curve showing progression-free survival.
  - HR 0.56 (95% CI 0.41 - 0.75)
  - p = 0.0003 (unstratified log-rank)

- **Number at risk**
  - Nanoliposomal irinotecan plus fluorouracil and folinic acid: 117
  - Fluorouracil and folinic acid: 119

- **B**
  - Nanoliposomal irinotecan monotherapy
  - Fluorouracil and folinic acid
  - Kaplan-Meier curve showing overall survival.
  - HR 0.99 (95% CI 0.77 - 1.28)
  - p = 0.94 (unstratified log-rank)

- **Number at risk**
  - Nanoliposomal irinotecan monotherapy: 151
  - Fluorouracil and folinic acid: 149

- **D**
  - Nanoliposomal irinotecan monotherapy
  - Fluorouracil and folinic acid
  - Kaplan-Meier curve showing progression-free survival.
  - HR 0.81 (95% CI 0.63 - 1.04)
  - p = 0.1 (unstratified log-rank)

- **Number at risk**
  - Nanoliposomal irinotecan monotherapy: 151
  - Fluorouracil and folinic acid: 149

*Wang-Gillam et al, Lancet 2016*
Future developments?

- **Targeting the stroma:**
  - PEGylated-rHuPH20 (PEGPH20): hyaluronic acid
  - Hedgehog inhibitors

- **Targeting stem cells:**
  - napabucasin

- **Exploiting DNA repair defects:**
  - PARP inhibitors in gBRCA mutants

- **Immunotherapy:**
  - MSI tumors: anti-PD(L) AB

- **Targeting abnormal metabolism:**
  - CPI-613: selectively blocks PDH and KGDH triggering cell death that is highly selective to tumor Cells

- **Bruton kinase inhibitors:**
  - ibrutinib

- **Targeting CDK4/6:**
  - abemaciclib, ribociclib

- **Mesothelin-based Immunotherapy**

- **Asparaginase loaded RBC**

- ..

Pancreatic adenocarcinoma

treatment strategy

clinical grouping

- Metastatic disease

- **Resectable disease**: resection in experienced teams/high volume
  - resection plus adjuvant treatment
  - Evolution towards trials with neo-adjuvant treatment

- Borderline resectable disease

- Locally advanced, but clearly not resectable disease
Anatomy of pancreatic cancer

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.
Table 2. Adjuvant Therapy for Pancreatic Cancer.*

<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>GITSG</td>
<td>43</td>
<td>Observation</td>
<td>10% at 2 yr, 20% at 2 yr</td>
<td>0.007</td>
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<tr>
<td></td>
<td></td>
<td>Fluorouracil plus radiotherapy</td>
<td></td>
<td></td>
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<tr>
<td>EORTC</td>
<td>218</td>
<td>Observation</td>
<td>26% at 2 yr, 34% at 2 yr</td>
<td>0.10</td>
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<tr>
<td></td>
<td></td>
<td>Fluorouracil plus radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPAC-1</td>
<td>289</td>
<td>Observation, Chemoradiotherapy</td>
<td>16.9 mo (median)†, 13.9 mo</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Chemoradiotherapy plus fluorouracil</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Fluorouracil Chemoradiotherapy</td>
<td>21.6 mo, 19.9 mo</td>
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<tr>
<td></td>
<td></td>
<td>plus fluorouracil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONKO-01</td>
<td>368</td>
<td>Observation, Gemcitabine</td>
<td>10.4% at 5 yr, 20.7% at 5 yr</td>
<td>0.01</td>
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<tr>
<td>ESPAC 3</td>
<td>1088</td>
<td>Fluorouracil, Gemcitabine</td>
<td>23.0 mo (median), 23.6 mo</td>
<td>0.39</td>
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<tr>
<td>RTOG 9704</td>
<td>451</td>
<td>Fluorouracil plus radiotherapy</td>
<td>22% at 5 yr, 18% at 5 yr</td>
<td>0.12</td>
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<tr>
<td></td>
<td></td>
<td>Gemcitabine plus radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JASPAC-01</td>
<td>378</td>
<td>S-1 (oral fluoropyrimidine),</td>
<td>70% at 2 yr, 53% at 2 yr</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td></td>
<td></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

Statistically significant improvement in 5 and 10 year OS rates vs 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%)

PRODIGE 24/CCTG PA.6

Disease-Free Survival

stratified HR=0.58 [95%CI: 0.46-0.73], p<0.0001

No DFS events: 314
Median DFS:
- 21.6 mths [95%CI: 17.7-27.6] with mFolfoxirinox
- 12.8 mths [95%CI: 11.7-15.2] with Gemcitabine

3-year DFS:
- 39.7% [95%CI: 32.8-46.6] with mFolfoxirinox
- 21.4% [95%CI: 15.8-27.5] with Gemcitabine

Primary endpoint

Presented By Thierry Conroy at 2018 ASCO Annual Meeting
PRODIGE 24/CCTG PA.6

**Overall Survival**
- Median overall survival:
  - 54.4 months [95%CI: 41.8-NR] with mFolfirinox
  - 35.0 months [95%CI: 28.7-43.9] with Gemcitabine

**Specific Survival**
- Disease Specific Survival is the time delay between the date of randomization and the patient's death due to the treated cancer or a treatment-related complication.
- 3-year specific survival:
  - No OS events=180
  - 66.2% (mFolfirinox) vs 51.2% (Gem)

**3-year overall survival:**
- No OS events=192
- 63.4% (mFolfirinox) vs 48.6% (Gem)
Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05)

Study objective

- To assess the efficacy and safety of neoadjuvant chemotherapy compared with upfront surgery in patients with resectable pancreatic ductal adenocarcinoma

Key patient inclusion criteria

- Pancreatic ductal adenocarcinoma
- Treatment naïve
- R0/R1 resectable
- ECOG PS 0–1 (n=364)

Neoadjuvant chemotherapy (gemcitabine + S-1)* + surgery + adjuvant (S-1)† (n=182)

Stratification

- CA19-9
- Institutions

Surgery + adjuvant (S-1)† (n=180)

Primary endpoint

- OS

Secondary endpoints

- Resection rate, RFS, safety

*Gemcitabine 1 g/m² D1, 8 + oral S-1 40 mg/m² bid D1–14 for 2 cycles; †S-1 for 6 months in patients with curative resection and fully recovered within 10 weeks of surgery

Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05)

Key results

Neoadjuvant chemotherapy:
36.7 months (95%CI 28.7, 43.3)
Upfront surgery:
26.7 months (95%CI 21.0, 31.3)

HR 0.72 (95%CI 0.55, 0.94);
log-rank test p=0.015

2-year OS: 63.7% vs. 52.5%

Adjuvant treatment in PDAC

- Optimal surgery in experienced team and high volume centers

- Adjuvant treatment is still the standard, although neo-adjuvant treatment has a good rationale and is being explored

- Adjuvant treatment: Fit patients
  - West: FOLFIRINOX for 6 months in very fit patients
  - Gemcitabine (± capecitabine) for 6 months

- Japan: S1

- Other regimens are being explored: gem/nab-paclitaxel
Pancreatic adenocarcinoma clinical grouping

- Metastatic disease
- Resectable disease

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

- Locally advanced, but clearly not resectable disease
Continuum between technically resectable and unresectable disease

**RESECTABLE**
- tumor

- No distant metastasis
- No tumor contact with CA, SMA or CHA
- No tumor contact with SMV or PV or contact ≤ 180°

**BORDERLINE**
- resectable tumor

- No distant metastasis
- Solid tumor contact with SMV/PV >180°
- Solid tumor contact with CHA or with SMA or CA ≤ 180°

**Locally Advanced**
- UNRESECTABLE tumor

- Distant metastasis
- Unreconstructible SMV/PV involvement or occlusion
- Solid tumor contact of >180° with the SMA or CA

National Comprehensive Cancer Network 2016 www.nccn.org
Currently available induction strategies

Staging: Borderline Resectable Pancreatic Cancer

1. Chemoradiation → Surgery

2. Combination chemotherapy → Surgery → Adjuvant chemotherapy
   - restaging

3. Combination chemotherapy → Chemoradiation → Surgery
   - restaging
   - restaging
## 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>
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</thead>
<tbody>
<tr>
<td>FOLFIRINOX¹</td>
<td>BL or unresectable</td>
<td>Retrospective</td>
<td>18</td>
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<td>39</td>
<td>28</td>
<td>83</td>
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<tr>
<td>FOLFIRINOX²</td>
<td>laPC</td>
<td>Retrospective</td>
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<td>FOLFIRINOX³</td>
<td>laPC or BL</td>
<td>Registry</td>
<td>23</td>
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<td>75</td>
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<td>FOLFIRINOX⁴</td>
<td>laPC or BL</td>
<td>Retrospective</td>
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<td>54</td>
<td>42</td>
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<tr>
<td>FOLFIRINOX⁵</td>
<td>BL or unresectable</td>
<td>Phase II</td>
<td>32</td>
<td>37</td>
<td>41</td>
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<tr>
<td>FOLFIRINOX⁶</td>
<td>laPC</td>
<td>Phase IIᵇ</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>

ᵇSequential regimen including FOLFIRINOX and nab-paclitaxel plus gemcitabine  
c¹complete pathological response and ４near complete responses (few (<5%) residual tumor)  
dAt the time of the analysis  eOf patients who had been operated on at the time of the analysis

Dutch PREOPANC Trial: resectable & borderline resectable PDAC

**Trial design**

- **Surgery**
- **Gem:** gemcitabine 1000 mg/m² day 1,8,15, one week rest
- **Gem’** gemcitabine 1000 mg/m² day 1,8, one week rest
- **RT:** 36 Gy in 15 fractions of 2.4 Gy

**Statistics:** stratification: resectability/institution
Primary endpoint: Overall survival (ITT)
Expected trial duration: 36 months + 12 months FUP
Hypothesis: improvement median survival from 11 to 17 months

80% power assuming 10% dropouts; 244 patients / 176 events
Dutch PREOPANC Trial

Disease-Free Survival

Overall DFS (ITT)

- DFS: 7.9 vs 9.9 Months, HR 0.71; p=0.023

Distant Metastasis Free Interval

- HR 0.71; p = 0.013

Locoregional Recurrence Free Interval

- HR 0.55; p = 0.002

Presented By Geertjan Van Tienhoven at 2018 ASCO Annual Meeting
Dutch PREOPANC Trial

Overall Survival Analyses

Intention to Treat
- Exploratory laparotomy
- Radiochemotherapy followed by exploratory laparotomy
- $p$-value stratified logrank test: 0.0742

Post Resection
- Exploratory laparotomy
- Radiochemotherapy followed by exploratory laparotomy
- $p$-value stratified logrank test: 3e-04

Median: 13.7 vs 17.1 Mos. HR 0.74; $p=0.074$
Median Survival 16.8 vs 29.9 Months, $p = 0.001$
Does neoadjuvant chemoradiation therapy benefit patients with resectable or borderline resectable disease?

- Trial design cannot definitively define that neoadjuvant CRT better than direct surgical resection.

- The results of this trial in aggregate with other recently published prospective trials demonstrate that the benefit of radiation therapy is in the neoadjuvant setting.

- Neoadjuvant CRT based therapy is associated with higher R0 resection rate.

- What is the impact of Resectable vs Borderline Resectable disease as well as R1 resection on outcome?

- Will the use of modern combination chemotherapy increase the magnitude of the effect associated with neoadjuvant/perioperative CRT-based therapy.
  - Alliance Trial – Total Neoadjuvant FOLFIRINOX vs FOLFIRINOX plus SBRT
  - SWOG 1505 – Perioperative FOLFIRINOX vs Gemcitabine + nab-Paclitaxel
  - AGICC – Perioperative Gemcitabine + nab-Paclitaxel plus SBRT
Borderline resectable/unresectable pancreatic cancer

- Prospective data support the use of induction chemotherapy and/or chemoradiation before resection, but convincing data from randomized studies are still lacking.

- The treatment of BRPC remains a multidisciplinary challenge and staging/restaging results must be regularly discussed in multidisciplinary team meetings in high volume centers.

- Decline in CA 19.9 may help the assessment of response.

- The optimal strategy for induction therapy for patients with BRPC has not been established. FOLFIRINOX seems to be the most promising approach.

- The best management for these patients occurs in a clinical trial.

Pancreatic adenocarcinoma treatment strategy clinical grouping

- Metastatic disease
- Resectable disease
- Borderline resectable disease
- Locally advanced, but clearly not resectable disease
LAP07 study in locally advanced PDAC

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, JAMA 2016
LAP 07 study

Overall Survival and Progression-Free Survival, According to the First Randomization (primary endpoint)

Gem: 13.6 mo (95% CI, 12.3-15.3)
Gem/Erlotinib: 11.9 mo (95% CI, 10.4-13.5)

Hammel P et al, JAMA 2016

Overall Survival and Progression-Free Survival, According to the Second Randomization

Gem: 16.5 mo (95% CI, 14.5-18.5)
Gem/Erlotinib: 15.2 mo (95% CI, 13.9-17.3)
Pancreatic adenocarcinoma

Treatment strategy

Clinical grouping

- Metastatic disease
- Resectable disease
- Borderline resectable disease
- Locally advanced, but clearly not resectable disease
Biliary Tract Cancers are Heterogeneous

- 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
- IntraHepatic Cholangiocarcinoma vs. ExtraHepatic Cholangiocarcinoma vs Gallbladder cancer

<table>
<thead>
<tr>
<th>IHCCA</th>
<th>Specific Targetable GAs</th>
<th>Prevalence</th>
<th>Targeted Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR2 Fusions</td>
<td>10% to 20%</td>
<td>BQ128, Ponalizumab, IN502676,403, PAN8171, TAG-120, FGFR antibodies and FGFR trap molecules</td>
<td></td>
</tr>
<tr>
<td>IDH1/2</td>
<td>22% to 28%</td>
<td>AG-120, AG-881</td>
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</tr>
<tr>
<td>BAP1</td>
<td>15% to 25%</td>
<td>Histone Deacetylase (HDAC) inhibitors like vorinostat and panobinostat</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>EHCCA</th>
<th>Specific Targetable GAs</th>
<th>Prevalence</th>
<th>Targeted Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2/neu (mutation)</td>
<td>11% to 20%</td>
<td>Tyrosine Kinase inhibitors like olaparib, neratinib, and tasquinimod</td>
<td></td>
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<tr>
<td>PRKACA and PKRACA2</td>
<td>9%</td>
<td>Protein Kinase A inhibitors under development</td>
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<tr>
<td>ARID1A</td>
<td>5% to 12%</td>
<td>Histone Deacetylase (HDAC) inhibitors like vorinostat and panobinostat</td>
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</table>

<table>
<thead>
<tr>
<th>GBC</th>
<th>Specific Targetable GAs</th>
<th>Prevalence</th>
<th>Targeted Therapies</th>
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</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>4% to 13%</td>
<td>Erlotinib, Gefitinib</td>
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<tr>
<td>NEU2 (amplification)</td>
<td>10% to 15%</td>
<td>Trastuzumab, Lapatinib, Pertuzumab, T-DM1</td>
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<tr>
<td>ERBB3</td>
<td>0% to 12%</td>
<td>Sertibrutinib (Ma-121), Pertuzumab, Trastuzumab, T-DM1</td>
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<tr>
<td>PTEN</td>
<td>0% to 4%</td>
<td>mTOR inhibitors like Everolimus, AKT inhibitor like MK2206, PI3K inhibitors like BKM120, BYL719 and SF1126</td>
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<tr>
<td>PKDCA</td>
<td>6% to 13%</td>
<td>mTOR inhibitors like Everolimus, AKT inhibitor like MK2206, PI3K inhibitors like BKM120, BYL719 and SF1126</td>
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</tbody>
</table>
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 until recently

**Curative resection (n=508)**
1986-1992

<table>
<thead>
<tr>
<th>Stage II-IV (Japan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pancreas (n=173)</td>
</tr>
<tr>
<td>• Bile duct (n=139)</td>
</tr>
<tr>
<td>• Gallbladder (n=140)</td>
</tr>
<tr>
<td>• Ampullary (n=56)</td>
</tr>
</tbody>
</table>

**1st end-point | Survival**

**Asian Phase III study**

- **MF* chemotherapy**
- **Observation**

*MMC 6mg/m² IV peri-operatively then
5-FU 310mg/m² IV infusion D1-5 (W1&3) then
5-FU 100mg/m²/d PO W5 till disease recurrence

**Results**

- No benefit
  - Pancreas
  - BTC
  - Ampullary
- **Improved DFS and OS**
  - Ca gallbladder

In patients with **Gallbladder Cancer**

- Improved 5Y-DFS (20.3% vs. 11.6%, p=0.0210) per-protocol analysis
- Improved 5Y-S (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
The BILCAP randomized study
Adjuvant capecitabine for biliary tract cancer:

Study objective
To determine whether capecitabine improves OS compared with observation following radical surgery in cholangiocarcinoma or gallbladder cancer

Key patient inclusion criteria
- Completely resected cholangiocarcinoma or gallbladder cancer (including liver and pancreatic resection, as appropriate)
- Adequate biliary drainage
- ECOG PS ≤2 (n=447)

Primary endpoints
- OS

SECONDARY ENDPOINTS
- RFS, TTP, toxicity, QoL

*Primary analysis after a minimum 2-year follow-up

The BILCAP randomized study
Adjuvant capecitabine for biliary tract cancer:

### OS (ITT population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, months (95%CI)</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>51.1 (34.6, 59.1)</td>
<td>0.81 (0.63, 1.04)</td>
</tr>
<tr>
<td>Observation</td>
<td>36.4 (29.7, 44.5)</td>
<td></td>
</tr>
</tbody>
</table>

#### Sensitivity analyses

Adjusting for further prognostic factors (nodal status, disease grade, gender)

HR 0.70
(95%CI 0.55, 0.91); p=0.007

>80% patients followed-up for 36 months

The BILCAP randomized study
Adjuvant capecitabine for biliary tract cancer:

RFS (ITT population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, months (95%CI)</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>24.6 (18.9, 36.7)</td>
<td>0.76 (0.58, 0.99)</td>
</tr>
<tr>
<td>Observation</td>
<td>17.6 (12.8, 27.6)</td>
<td>p=0.039</td>
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</tbody>
</table>

No. at risk
- Observation 224
- Capecitabine 223

Time since randomisation, months
- Observation: 126, 92, 67, 52, 37

Optimal Radical surgery in experienced high volume centers remains the mainstay of cure for patients with BTC.

No clear recommendations regarding adjuvant chemotherapy or radiotherapy until recently.

- High risk fit patients may benefit from CT; positive resection margins: consider CRT.

2017: Large prospective randomized study suggests benefit of adjuvant chemotherapy (BILCAP).
Chemotherapy for advanced BTC
A number of active agents and combinations

- 5FU
- S1
- UFT
- Capecitabine

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

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

Platinum
- Cisplatin
- Carboplatin
- Oxaliplatin

Fluoropyrimidine
- 5FU
- S1
- UFT
- Capecitabine

RR 10 - 36%
TTP 3.7 - 9.0 mo
Survival 5 - 14 mo
Randomized phase III studies

gemcitabine ± cisplatin

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Gem</th>
<th>CisGem</th>
<th>Gem</th>
<th>CisGem</th>
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<tr>
<td>ABC-02</td>
<td>Valle <em>NEJM</em> 2010</td>
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<td>BT-22</td>
<td>Okusaka <em>BJC</em> 2010</td>
<td>3.7</td>
<td>5.8</td>
<td>7.7</td>
<td>11.2</td>
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</tbody>
</table>
Surgery is the only option for curative treatment: expert centers! New data suggest benefit of adjuvant chemotherapy

Chemotherapy is associated with modest benefit in advanced disease
- Standard option in fit patients in 2019: gemcitabine/cisplatin
- Future molecular analysis: FGR, IDH, BRAF, HER2, MSI, NTRAK fusions….

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

Health Sciences Campus

Hospital
Research
Teaching

Eric.VanCutsem@uzleuven.be
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