Pancreatic and Biliary Tract Cancers: What’s New in Treatment?

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Medical Oncology, CancerCare Manitoba
University of Manitoba
Small numbers, big impact

- Upper GI tract cancers are generally rare in our society, but have a disproportionately large impact due to poor prognosis
  - Stomach
  - Liver
  - Bile Ducts
  - Gallbladder
  - Pancreas
  - Small Intestine

Topic of presentation
Canadian Statistics 2010

- RARE: Pancreas Cancer:
  - Incidence: 4000 (2100 ♂, 1950 ♀) – 12th
  - Manitoba: ~ 150 new cases per year

- RARER: Gallbladder Cancer:
  - Incidence: 1 per 100,000 (female: male 2-6:1)
  - Actual Numbers in Canada (2006):
    - Incidence: 407 (128 M, 279 F) (MB 19)
    - Mortality: 292 (102 M, 190 F) (MB 11)

- RAREST: Intra and Extrahepatic Cholangiocarcinomas
  - Incidence: 1-2/100,000 (~3000 cases per year in USA)
  - Not coded/captured separately in Canadian statistics
Nota bene

- This talk will focus on the typical adenocarcinomas associated with the three disease sites
- *I will not be discussing pancreatic endocrine tumors or other rare variants of the already uncommon upper GI tract cancer*
- Focus will be on treatment
- Pancreatic cancer will receive greater emphasis
Pancreatic Carcinoma
Case

- 69 y.o. male, previously well
- Sept 2004 – FP: jaundice, anorexia
  - CT – biliary tract dilatation, no obvious mass; 2 small portal LNs
- Oct 2004 – ERCP – stricture distal CBD
  - Stented
- Nov 2004 – cholangitis, bilirubin 113 – Antibiotics
- 19 Nov 2004 – Whipple’s procedure
Case

Pathology:
- 4.5 cm tumor head of pancreas
- Moderately to poorly differentiated
- 4/5 + peri-pancreatic nodes

Adjuvant chemo – Jan – June 2005
- 5FU/FA as part of clinical trial

March 2006 – epigastric pain

April 2006 – CT: recurrent mass in pancreatic bed, enlarging portal LNs
Case

- 25 April 06 – started on palliative chemo
  - Phase II clinical trial – gemcitabine + oral TKI (targeted at VEGF)
  - After 2 cycles, developed disease progression and *pneumatosis intestinalis*
- July 06 – enrolled in palliative care program
- 5 Sept-06 – died at Riverview

- Time from surgery to recurrence: 16 months
- Time from recurrence to death: 6 months
Pancreatic adenocarcinoma

- Malignant cells within a dense, poorly vascularized stroma ("desmoplastic reaction"):  
  - Poor vascularity  
  - Hard to biopsy

- Genomic analysis of 24 tumors – genetically complex/heterogeneous tumors:  
  - Average of 63 genetic alterations per patient  
  - Grouped in 12 core signaling pathways  
    - Activating mutation Kras2 (90%), inactivation CDKN2A (95%), abnormal TP53 (50-75%), loss of DPC4 (50%)

- ~5% of cells appear to have stem cell characteristics – resistant to chemotherapy and radiotherapy
Burden of Disease

- Vast majority of patients are symptomatic at diagnosis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Head (% of patients)</th>
<th>Body and Tail (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>Jaundice</td>
<td>82</td>
<td>7</td>
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<tr>
<td>Pain</td>
<td>72</td>
<td>87</td>
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<tr>
<td>Anorexia</td>
<td>64</td>
<td>33</td>
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<tr>
<td>Nausea</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>Weakness</td>
<td>35</td>
<td>43</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Signs</th>
<th>Head (% of patients)</th>
<th>Body and Tail (% of patients)</th>
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</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>87</td>
<td>13</td>
</tr>
<tr>
<td>Palpable liver</td>
<td>83</td>
<td>-</td>
</tr>
<tr>
<td>Palpable GB</td>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td>Tender abdomen</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Ascites</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>

### Stage Distribution

**Table 1. Staging of Pancreatic Cancer.***

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Grade</th>
<th>Nodal Status</th>
<th>Distant Metastases</th>
<th>Median Survival (mo)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>24.1</td>
<td>5298  (4.4)</td>
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<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>20.6</td>
<td>6662  (5.4)</td>
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<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>15.4</td>
<td>12,332 (10.1)</td>
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<tr>
<td>IIB</td>
<td>T1, T2, or T3</td>
<td>N1</td>
<td>M0</td>
<td>12.7</td>
<td>14,398 (11.8)</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>N0 or N1</td>
<td>M0</td>
<td>10.6</td>
<td>15,831 (13.0)</td>
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<tr>
<td>IV</td>
<td>T1, T2, T3, or T4</td>
<td>N0 or N1</td>
<td>M1</td>
<td>4.5</td>
<td>67,192 (55.2)</td>
</tr>
</tbody>
</table>

* N denotes regional lymph nodes, M distant metastases, and T primary tumor.

† Data are from Bilimoria et al.45

- 121,713 patients from National Cancer Data Base (1992-1998)
- Head 76.4%, Body 11.1%, Tail 6.4%
- 18,743 (15.4%) underwent resection

Bilimoria et al Cancer 2007
At Presentation

- Percent possibly resectable – 20%
- Percent found to be unresectable intraoperatively – 20-40%
- Percent advanced - >80%
Life Expectancy Figures

- Overall: 19% 1-year, 4% 5-years
- Resectable: ~20-30% 5-years
- Locally advanced: median ~ 10 months
- Metastatic: median < 6 months
Treatment of advanced pancreatic cancer
Definition: Advanced Disease

- Locally advanced unresectable
  - No overt evidence of metastases
- Metastatic disease
  - Most commonly to liver, lungs
Chemotherapy for Advanced Pancreas Cancer

- No useful chemotherapy drugs identified until mid-90s
- Burris et al, JCO 1997; 15: 2403
  - 126 patients with symptomatic pancreas cancer – weekly gemcitabine versus weekly bolus 5-FU
  - Main endpoint – clinical benefit response
  - Secondary endpoints – OS, PFS, ORR
Results

- ORR: Gemcitabine – 5.4%, 5FU – 0%
- CBR:
  - composite measure of pain, PS and weight improvement in at least one for ≥ 4 weeks
  - Gemcitabine – 15 patients – 23.8%
  - 5FU – 3 patients – 4.8%
  - Median time to CBR – 7 weeks for gemcitabine, 3 weeks for 5FU, mean duration 18 weeks versus 13 weeks

P=0.002
Survival

Doublets – Gemcitabine versus...

<table>
<thead>
<tr>
<th>Gemcitabine +</th>
<th>N</th>
<th>Median Survival (months)</th>
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<tbody>
<tr>
<td>5FU</td>
<td>349</td>
<td>6.7</td>
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<tr>
<td>Infusional 5FU</td>
<td>330</td>
<td>6.3</td>
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<tr>
<td>BAY 12-9566</td>
<td>239</td>
<td>5.5</td>
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<tr>
<td>Infusional 5FU</td>
<td>377</td>
<td>3.74</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>688</td>
<td>6.5</td>
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<tr>
<td>Cisplatin</td>
<td>99</td>
<td>38% 1-yr</td>
</tr>
<tr>
<td>Oxaliplatin (+ FDR G)</td>
<td></td>
<td>6.6</td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td></td>
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<tr>
<td>Exatecan</td>
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<tr>
<td>Pemetrexed</td>
<td></td>
<td></td>
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<tr>
<td>Marimastat</td>
<td></td>
<td></td>
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<tr>
<td>Tipifarnib</td>
<td></td>
<td></td>
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<tr>
<td>PEFG</td>
<td></td>
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</tr>
</tbody>
</table>

Meta-analyses: combination chemo (gemcitabine + platinum or capecitabine) improves survival modestly but at significant risk of increased toxicity.
NCIC PA.3
Gem +/- Erlotinib

- Pancreas tumors often overexpress EGFR; worse prognosis
- Canadian-led RCT
- 569 subjects
  - Locally advanced or metastatic
  - ECOG PS 0-2

Moore et al. JCO 2007
• Despite these results, not generally adopted: expensive, toxic, minimal benefit
• In light of CRC Kras data, wrong target (90% Kras mutated)
OFF – CONKO-003

- Second-line RCT
- All progressed on Gem
- 168 subjects
  - 77 OFF
  - 91 FF
- Reasonably tolerable

Riess et al. ASCO 2007
First Line FOLFIRINOX

- RCT – FOLFIRINOX v Gemcitabine
- Measurable metastatic disease, PS 0,1
- N = 342 (171 in each arm)
  - Only 35% pancreatic head
- FOLFIRINOX more effective, more toxic
  - T. Conroy et al. ASCO 2010

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX</th>
<th>Gem</th>
</tr>
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<tbody>
<tr>
<td>Gr 3,4 neutropenia</td>
<td>45.7%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Grade 3,4 FNE</td>
<td>5.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>G-CSF use</td>
<td>42.5%</td>
<td>5.3%</td>
</tr>
<tr>
<td>PR</td>
<td>31%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>70.2%</td>
<td>50.9%</td>
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</table>
Progression-Free Survival

Median PFS Folfirinox: 6.4 mo.  Median PFS Gemcitabine: 3.3 mo

HR = 0.47 : 95% CI [0.37-0.59]

p < 0.0001

Number at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Gemcitabine</th>
<th>Folfirinox</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>171</td>
<td>171</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>121</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>85</td>
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<td>9</td>
<td>8</td>
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<td>12</td>
<td>5</td>
<td>17</td>
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<td>15</td>
<td>2</td>
<td>7</td>
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<tr>
<td>18</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
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<td>30</td>
<td>0</td>
<td>0</td>
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<tr>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>36</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median PFS Folfirinox: 6.4 mo.
Median PFS Gemcitabine: 3.3 mo
Overall Survival

Median OS Folfirinox: 11.1 mo.  Median OS Gemcitabine: 6.8 mo

Stratified Log-rank test, p<0.0001
HR=0.57 : 95%CI [0.45-0.73]

Number at risk
Gemcitabine 171 134 89 48 28 14 7 6 3 3 2 2 2
Folfirinox 171 146 116 81 62 34 20 13 9 5 3 2 2

Months

Median OS Folfirinox: 11.1 mo.
Median OS Gemcitabine: 6.8 mo
Future targets

As of 2008

- “molecular targeting”
- Potential targets:
  - EGFR
  - Her 2/neu
  - VEGF/VEGF-R
  - Ras/Raf/MEK/ERK
  - PI3K/AKT
  - mTOR
  - NF-κB
- Potential agents: MoAbs, TKIs

As of 2011?

- Targetting the stem-cell?
- Potential targets:
  - Notch
  - Hedgehog
  - Wingless in drosophila (Wnt) – βcatenin
- Developmental pathways
- Clinical trial currently open at CCMB with hedgehog inhibitor
Locally advanced unresectable disease – the Role of Radiotherapy

- Setting the American standard - GITSG

N=194

60 Gy*  
N = 25

60 Gy* + Bolus 5FU x 2 yr  
N = 86

40 Gy* + Bolus 5FU x 2 yr  
N = 83

* Split course – 2 weeks on, 2 weeks off

MS (weeks)

22.9  
40.3  
42.2

Moertel Cancer 1981; 48: 1705
Role of Radiotherapy in LA Disease

- Does radiotherapy really contribute?
- One old study has looked at chemo vs chemo+RT
  - N=91
  - 5FU vs 40 Gy + 5FU
  - MS 8.2 mo. vs 8.3 mo.

- Cochrane review, other meta-analyses:
  - Chemo alone, Chemo-XRT, BSC all acceptable for LA unresectable disease
    - Yip. Cochrane Database of Systematic Reviews 2006
Small contemporary RCT

- 119 subjects, non-metastatic LAPC
- “Induction” CHRT v Gem
  - 60 Gy + 5FU/cisplatin
- Maintenance Gem
- Induction schedule more toxic, less effective
  Chauffert Ann Oncol 2008

- Trials now in design: induction chemo – followed by CHRT in those benefitting
Role of adjuvant therapy
Adjuvant chemotherapy

- Concept is to decrease risk of recurrence
- Eliminate micrometastases
Prognosis post pancreatectomy

- SEER data: N=396, all over 65
- Median survival 17.6 mo.
- 3-year survival 34.3%

**Table 4. MULTIVARIATE ANALYSIS**

<table>
<thead>
<tr>
<th>Independent Prognostic Factor</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adjuvant therapy</td>
<td>1.73</td>
<td>1.31–2.30</td>
<td>.0002</td>
</tr>
<tr>
<td>Diameter &gt; 2 cm</td>
<td>1.57</td>
<td>1.10–2.26</td>
<td>.004</td>
</tr>
<tr>
<td>Positive lymph nodes</td>
<td>1.36</td>
<td>1.05–1.75</td>
<td>.009</td>
</tr>
<tr>
<td>Not well differentiated</td>
<td>1.67</td>
<td>1.12–2.50</td>
<td>.01</td>
</tr>
<tr>
<td>Nonteaching hospital</td>
<td>1.44</td>
<td>1.10–1.88</td>
<td>.01</td>
</tr>
<tr>
<td>Low SES</td>
<td>1.33</td>
<td>1.04–1.70</td>
<td>.02</td>
</tr>
</tbody>
</table>

**Figure 1.** Overall survival (Kaplan-Meier) for study population of 396 patients who underwent curative surgical resection for nonmeiastatic pancreatic adenocarcinoma.

GITSG Study

- Defined therapy south of the border

Randomization

**Curative Intent Surgery**

- **No further Rx**
  - **N=22**

- 40 Gy/20# (split course) + 5FU 500 mg/m² q7d for up to 2 yrs
  - **N=21**

**Median Survival**

- 11 months
- 20 months
- P=0.03

Kalser et al. Arch Surg 1985; 120: 889
ESPAC-1

- 2x2 factorial design study
- N=289 (541 enrolled initially)
  - 69 – observation
  - 73 – chemoRT
  - 75 – chemo
  - 72 – chemo + chemoRT
- Comparison reported:
  - No chemoRT (144) vs chemoRT (145)
  - No chemo (142) vs chemo (147)

<table>
<thead>
<tr>
<th></th>
<th>Obs.</th>
<th>CRT</th>
<th>C</th>
<th>C+CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS (mo.)</td>
<td>16.9</td>
<td>13.9</td>
<td><strong>21.6</strong></td>
<td>19.9</td>
</tr>
</tbody>
</table>

Neoptelemos NEJM 2004; 350:12
CONKO-001 Study Design

Resected pancreatic cancer
368 patients (7/98 to 12/04)

Stratification: R; T; N

Gemcitabine
for 6 months

Observation
for 6 months

Follow up every 8 weeks

Primary Endpoint: DFS

368 pts to detect improved DFS of 6 months, a 0.05 and power 90%.
CONKO-001
<table>
<thead>
<tr>
<th>Table 3. Disease-Free and Overall Survival by Intent-to-Treat Analysis in the Total Population and in Patient Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Patients</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>R0</td>
</tr>
<tr>
<td>R1</td>
</tr>
<tr>
<td>N-</td>
</tr>
<tr>
<td>N+</td>
</tr>
<tr>
<td>T1-2</td>
</tr>
<tr>
<td>T3-4</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*Log-rank test.
RTOG 9704

- Large American Intergroup study
- N=538
  - 380 had pancreatic head tumors

Regine et al. JAMA 2008
Figure 2. Overall Survival Among All Eligible Patients

**CHEMOTHERAPY WITH FLUOROURACIL VS GEMCITABINE PLUS CHEMORADIATION**

- **All Patients**
  - Log-rank $P = 0.34$

- **Patients With Pancreatic Head Tumors**
  - Log-rank $P = 0.09$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at Risk</th>
<th>Years From Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoradiation + gemcitabine</td>
<td>221</td>
<td>230 160 87 55 35 21</td>
</tr>
<tr>
<td>Chemoradiation + fluorouracil</td>
<td>230</td>
<td>201 139 68 49 30 18</td>
</tr>
</tbody>
</table>

RTOG 9704
Upcoming

- Recently completed accrual – 5FU/FA versus gemcitabine
- Unanswered question: what does XRT contribute?
  - US Intergroup Study – adjuvant chemotherapy x 6 months; if no progression randomize to CHRT or not
- Neoadjuvant – pre-surgical treatment
  - No RCTs yet
  - MDACC – 86 subjects – gem + 30Gy/10#
    - Median survival 34.7 months; 2 pCR
RTOG 0848

**Nodal Status:**
1: involved
2: uninvolved

**CA19-9 result:**
1: \( \leq 90 \)
2: \( > 90 - 180 \)

**Surgical margins:**
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**

If no progression, then:

First Randomization Treatment Arm:
1. Arm 1 gemcitabine vs.
2. Arm 2 gemcitabine + erlotinib

**Second Randomization**
For Non-Progressing Patients

**Arm 3:**
1 cycle of chemotherapy

**Arm 4:**
1 cycle of chemotherapy followed by XRT with either capecitabine or 5-FU
Progress?

- Gemcitabine remains the standard first-line chemotherapy.
- OFF has some second-line activity.
- FOLFIRINOX appears to be an advance, but at a cost (toxicity).
- Gemcitabine is the preferred adjuvant drug.
- Role of radiotherapy remains unclear.
- Reasons for lack of response are becoming more apparent – can we adequately target?
Biliary Tract Cancers
Terminology

- Traditionally:
  - Biliary Tract Cancers - gallbladder + extrahepatic bile duct and ampulla of vater
  - Liver Cancers - liver and intrahepatic bile duct

- More recently:
  - Cholangiocarcinoma - extra and intrahepatic bile ducts
Gallbladder Carcinoma

- Rare cancer in the Western world
- Incidence ~ 1/100,000 per year
- Most frequently diagnosed in 6-7th decades of life
- Female: male - 2-6:1
- When diagnosed under age 40, female: male ratio is 20:1
Canadian Statistics

- For 2006:
  - New cases: 407 (128 M, 279 F)
  - Deaths: 292 (102 M, 190 F)
<table>
<thead>
<tr>
<th>Subsite</th>
<th>Gender</th>
<th>Female</th>
<th>Male</th>
<th>FM</th>
<th>Female</th>
<th>Male</th>
<th>FM</th>
<th>Female</th>
<th>Male</th>
<th>FM</th>
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<tbody>
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<td>Gallbladder</td>
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<tr>
<td>NORTHERN EUROPE</td>
<td>Female</td>
<td>1.6</td>
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<td>1.5</td>
<td>0.4</td>
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<td></td>
<td>Male</td>
<td>1.5</td>
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<td>1.5</td>
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<td>0.8</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td></td>
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<td>2.3</td>
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<td>0.8</td>
<td>0.8</td>
<td>-</td>
<td>0.7</td>
<td>0.7</td>
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<tr>
<td>SOUTHERN AND CENTRAL EUROPE</td>
<td>Female</td>
<td>0.8</td>
<td>0.3</td>
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<td>1.7</td>
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<td>0.5</td>
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<tr>
<td></td>
<td>Male</td>
<td>0.7</td>
<td>0.5</td>
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<td>1.7</td>
<td>0.5</td>
<td>0.7</td>
<td>0.3</td>
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<tr>
<td></td>
<td>FM</td>
<td>1.5</td>
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<td>0.8</td>
<td>-</td>
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Figure 4. Age-standardized incidence rates per 100,000 (world standard population) and female-to-male ratio for biliary tract cancer by subsite and gender: gall-bladder cancer, extrahepatic bile duct cancer, ampulla of Vater, and 'subsite not specified' in selected areas of the world, 1998–2002.
Populations at increased risk

- Chilean women - number one cause of cancer mortality
- Northeastern Europeans, Israelis, Southwestern American natives, and Mexican Americans (likely all have a higher incidence of cholelithiasis), Maoris
- Low rates seen in Middle and Far East, UK, USA
Epidemiology

- Chronic GB inflammation is felt to act as a promoter (hence the ↑ risk in women).

- In >75% of cases, cholelithiasis is present (larger stones → ↑ risk).

- Other risk factors: anomalous p-b duct junction, IBD, chronic typhoid infection (*Salmonella typhi*), *H. pylori*, rubber industry chemicals, petroleum industry, textile industry.
Clinical presentation

- Usually presents late
- Symptoms often resemble those of chronic cholecystitis
  - RUQ pain - ± worse with fatty meal
  - RUQ tenderness
- N/V, anorexia
- Jaundice - clinically evident in ~ 45%
- > 10% weight loss - ~ 50%
Stage at presentation

- Only 10% confined to GB wall
- Direct invasion into adjacent structures occurs in up to 75% of cases:
  - Liver - ~75% (< 12% of these have no other sites of involvement)
- Nodes are involved in up to 70%
Resection

- Most patients are not candidates for curative surgery
- Likelihood of curative resection (all comers)
  - 10-30%
- Extended resection includes 3-5 cm wedge excision of liver around GB fossa, and extensive LND ± en bloc resection of extrahepatic bile duct
  - 0-21% mortality
  - up to 5-46% major morbidity
Laparascopic cholecystectomy (LC)

- Since advent of LC incidence of peritoneal metastases has risen
- GB carcinoma is diagnosed in 1-2% of patients undergoing “routine” LC
- 70,000 LC done yearly in US - so ~1400 patients at risk of inadvertent dissemination of disease
- convert to open procedure if possible or terminate without biopsy
- 17% of patients with unsuspected GB cancer undergoing LC develop port site recurrence within 180 days
Contemporary surgical outcomes (MSKCC) – 5-year survival

- Stage I – 85-100%
- Stage II – 83%
- Stage III – 63%

- In general – when more aggressive surgery is the norm, median survival for whole population increases from 9 to 17 months, and 5-year survival from 7% to 35%
Adjuvant therapy

- In ~ 50% post-resection local recurrence is the first (and often only) site of failure
- Could adjuvant radiotherapy ± chemotherapy reduce this LR rate?
- One small prospective randomized trial available - improved 5-yr survival with 5FU + MM-C
- Some authorities suggest post-op XRT is worth trying since it causes little toxicity...
  - Essentially no data
Japanese Adjuvant Study

- 508 patients randomized from 1988-1992 post resection of “pancreatic-biliary carcinoma”; 5 year follow-up

- surgery alone vs

  - MMC 6 mg/m² day of surgery
  - 5FU 310 mg/m² iv days 1-5 weeks 1 and 3 post-op
  - 5FU 150 mg po daily x 1 yr starting week 5 post-op
Japanese Adjuvant Study

<table>
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<th>Site</th>
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<th>5-year survival (%)</th>
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<td>Surgery</td>
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<td>Bile Duct</td>
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<td>23.9</td>
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<td>GB</td>
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<td>Ampulla</td>
<td>48</td>
<td>19.3</td>
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<tr>
<td>Pancreas</td>
<td>158</td>
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Only 436/508 patients reported on
Toxicity - “not serious”

ASCO Proc 1999; Abst. 1049
Palliative therapy

- Median survival for unresectable disease is 2-4 months
- Goal of palliation is to relieve pain, jaundice and bowel obstruction
- Palliative surgery may be helpful in some
- Role of radiotherapy is limited
- How about chemotherapy?
Modern Chemotherapy

- Patients with GB and Cholangiocarcinomas often lumped together

- Recent RCT in unresectable GB cancer looked at FUFA (Mayo) versus mGEMOX versus BSC
  - Single centre
  - 81 subjects (28, 26, 27 by arm)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>BSC (n = 27)</th>
<th>FUFA (n = 28)</th>
<th>mGEMOX (n = 26)</th>
<th>P</th>
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<td>8</td>
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<td>38</td>
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<tr>
<td>PD</td>
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<tr>
<td><strong>Survival</strong></td>
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<tr>
<td>Median OS, months</td>
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<td>.039†</td>
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<tr>
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<tr>
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<td>2</td>
<td>7.7 .31</td>
</tr>
</tbody>
</table>

Abbreviations: BSC, best supportive care; FUFA, fluorouracil and folinic acid; mGEMOX, modified gemcitabine and oxaliplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; PFS, progression-free survival.

*Fisher’s exact test comparing response rates for all three groups.
†Log-rank test comparing all the three groups.
Fig 2. Overall survival for three groups in months. GE, modified gemcitabine and oxaliplatin; FUFA, fluorouracil and folinic acid; BSC, best supportive care.
Cholangiocarcinoma

- ~ 3000-4000 cases per year in USA
- 1-2/100,000 population per year
- peak incidence is 6 - 7th decade of life
- slight male preponderance
Classification

- Can arise anywhere within biliary tree
- Intrahepatic - ~10%
- Perihilar - ~50%
  - From cystic duct-common duct junction to confluence of hepatic ducts
  - "Klatskin tumours"
- Distal - ~20% (make up 5-10% of "periampullary tumors")
- Multifocal/diffuse - < 10%
Clinical Presentation

- Intrahepatic:
  - abdominal/back pain, malaise & weight loss
  - jaundice in ~ 1/3
  - usually large tumors at diagnosis
  - 30% have peritoneal or liver mets at presentation (may not be appreciated until laparotomy)
  - often mistaken for HCC or metastatic disease
Clinical Presentation - 2

- Perhilar:
  - deep painless jaundice (pruritus may precede)
  - abnormal liver enzymes
  - fever doesn’t usually ensue until biliary manipulation

- Distal:
  - jaundice in > 90%
  - abdominal pain, weight loss, fever
Outcome

- Unresectable disease - 6-12 month survival
- Death usually from liver failure or biliary sepsis
- Distal disease - ~ 40% can be resected with curative intent
- Proximal or hilar - ~ 30% can be resected with curative intent
Resection of distal disease

- Pancreaticoduodenectomy in the 1990s:
  - operative mortality < 5%
  - median survival 22-33 months
  - 3-yr survival - 16-46%
  - 5-yr survival - 14-40%

- Predictors of survival:
  - margins, nodal metastases and tumor differentiation

Better than pancreas cancer
Resection of perihilar disease

- Biliary resection ± major liver resection ± major vascular and biliary reconstruction

Results in the 1990s

- Operative mortality: 5-10%
- Median survival: ~ 24 months (range 16-60)
- 3-yr survival: 21-55% (ave 35%)
- 5-yr survival: 11-56% (ave 27%)
Resection of proximal disease

- Partial hepatectomy is possible in ~30%
- Small series available:
  - median survival: 12-59 months
Orthotopic Liver Transplantation

- Has been tried in patients with intrahepatic (proximal) and perihilar cholangiocarcinoma
- Recent large series (207 patients) - 51% recurred & 5-yr survival was 23%
  - Most authorities do not recommend OLT
The Mayo approach

- Highly selected patients
- Pre-op EBRT + internal transcatheter radiation
- CI chemotherapy
- Pre-transplantation exploratory laparotomy

\[\Rightarrow\]

OLT

- Results “good” (but not published)
Role of radiotherapy

“Curative Intent”:
- Neoadjuvant radiation or chemoradiation (usually with 5FU ± MMC or other)
- Adjuvant radiation or chemoradiation
- Adjuvant EBRT and intraluminal brachy
- Many US centres give adjuvant XRT/5FU for M+ or N+
- There are no RCT to guide such treatment
- There are no compelling data to support
Role of Radiotherapy

“Palliative Intent”

- XRT for unresectable but limited disease
- EBRT or endoluminal brachytherapy
- No good data to support
Role of Chemotherapy - Adjuvant

- Radiosensitizer in adjuvant or neoadjuvant setting - role not proven
- Only one randomized trial available
  - Japanese adjuvant trial of 5FU + MM-C - no improvement in 5 year survival (118 patients)
  - ASCO 1999
Role of Chemotherapy - Palliative

- Knox Protocol – GemCap Phase II
- LA or metastatic adenocarcinoma of intra or extrahepatic cholangiocarcinoma or GB cancer
- 45 subjects – 47% GB, 89% M1
- ORR 31%, + 42% SD
- Median OS 14 months (7.3-nr)
- Well tolerated

Knox JCO 2005
Fig 1. Overall survival (OS). Kaplan-Meier survival estimates with 95% confidence intervals. Median follow-up is 11 months (range, 1.1 to 34 months).
ABC-02 Trial

- Phase II extended into Phase III
- 86 + 324 subjects
  - GB 36%, BD 58%, Ampulla 5%
  - LA 24%, Metastatic 76%
- Gemcitabine + cisplatin (1000/m^2 + 25/m^2 days 1, 8 q21d) versus gemcitabine (1000/m^2 1,8,15 q28d)
- Up to 24 weeks of therapy

Valle NEJM 2010
- Not much difference in toxicity between two arms
- Bit more neutropenia with gem-cis, and slightly more thrombo-embolic events
- Overall – each had about 70% of subjects with some Grade 3/4 toxicity
### Figure 3. Hazard Ratio, According to Trial and Prespecified Baseline Factors.

ABC denotes Advanced Biliary Cancer, and ECOG Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning. The red line indicates the hazard ratio for death (0.64) in the intention-to-treat population.

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<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
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<td>01</td>
<td>86</td>
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<td>02</td>
<td>324</td>
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Palliative Maneuvers

- Interventional
  - Bypass surgery
  - External biliary drain
  - Stenting
  - Photodynamic therapy of biliary tract
Gallbladder and Bile Ducts

- Chemotherapy can make a bit of a difference in advanced disease
- Very little objective data about other therapies
- Rare, hard to study...
Go Canucks Go!