Risk Factors and Patterns of Recurrent Biliary Cancer after Surgical Resection

Sung-Sik Han
National Cancer Center
Biliary Cancer

- Biliary Cancer
  - Intrahepatic cholangiocarcinoma
  - GB cancer
  - Extrahepatic cholangiocarcinoma
    - Hilar cholangiocarcinoma
    - Mid/Distal CBD cancer
주요 암종 발생분율: 남녀전체, 2011
총 발생자수 218,017명

- 간, 7.6
- 유방, 7.3
- 전립선, 4.1
- 흉장, 2.3
- 담낭 및 기타담도, 2.3
- 비호지킨 림프종, 2.0
- 갑상선, 18.6
- 위, 14.5
- 대장, 12.9
- 폐, 10.0
(단위: %)
주요 암종 5년 생존율 추이: 남녀전체

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<td>46.6</td>
<td>50.8</td>
<td>59.9</td>
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* 중감: '93-'95년 대비 '07-'11년 암발생자의 생존율 차이
Recurrence rate

• 5-year **Survival** after surgical resection
  – Hilar Cholangioca 30-40%
  – Distal bile duct ca 20-50%

• **Recurrence** rate
  – 50%-70%
  – 80% develop within 3yrs
  – Median time to recurrence 20mo
Recurrence Patterns

- Why do we need to understand the recurrence pattern?
  - To select adjuvant therapy
    - RT for loco-regional recurrence
    - Chemotherapy for distant metastasis
Loco-regional recurrence

• Porta hepatis
  – Resection margin
  – Biliary-enteric anastomosis site

• From
  – Microscopic residual disease
  – Disease in lymphatics
Distant metastasis

- Hematogenous spread

- To
  - Intrahepatic metastasis
  - Peritoneal seeding
  - Para-aortic LN
  - Extraabdominal metastasis
# Patterns of Initial Disease Recurrence after Resection of Gallbladder Carcinoma and Hilar Cholangiocarcinoma

*Cancer* 2003;98:1689–700

<table>
<thead>
<tr>
<th></th>
<th>GB ca (n=97)</th>
<th>Klatskin tumor (n=76)</th>
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<tr>
<td>Median time to recurrence</td>
<td>11</td>
<td>20</td>
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<tr>
<td>Recurrence rate, overall</td>
<td>66%</td>
<td>68%</td>
</tr>
<tr>
<td>Isolated loco-regional recur</td>
<td>15%</td>
<td><strong>59%</strong></td>
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<tr>
<td>Distant mets</td>
<td>85%</td>
<td><strong>41%</strong></td>
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<tr>
<td>1-year recurrence rate</td>
<td>62</td>
<td>30</td>
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<tr>
<td>2-year recurrence rate</td>
<td>88</td>
<td>56</td>
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Loco-regional > Distant
Recurrence Patterns

Patterns of Initial Disease Recurrence after Resection of Biliary Tract Cancer

Se Jin Jung\textsuperscript{a}  Sang Myung Woo\textsuperscript{a}  Hyung Ki Park\textsuperscript{a}  Woo Jin Lee\textsuperscript{a}  Mi Ah Han\textsuperscript{b,c}  Sung-Sik Han\textsuperscript{a}  Seong Hoon Kim\textsuperscript{a}  Sang-Jae Park\textsuperscript{a}  Tae Hyun Kim\textsuperscript{a}  Young Hwan Koh\textsuperscript{a}  Eun Kyung Hong\textsuperscript{a}

\textsuperscript{a}Center for Liver Cancer, \textsuperscript{b}National Cancer Control Institute, National Cancer Center, Goyang, and \\
\textsuperscript{c}Department of Preventive Medicine, College of Medicine, Chosun University, Gwangju, Republic of Korea

Time to recurrence

13mo
Recurrence Patterns

Patterns of Initial Disease Recurrence after Resection of Biliary Tract Cancer

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Table 5. Pattern of recurrence according to primary tumor origin; patients (n) with recurrence

<table>
<thead>
<tr>
<th>Pattern of recurrence</th>
<th>Total</th>
<th>GBC</th>
<th>IHC</th>
<th>EHC</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Patients with recurrence</td>
<td>135/224 (60.3%)</td>
<td>24/61 (39.3%)</td>
<td>53/71 (74.6%)</td>
<td>58/92 (63.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Locoregional pattern</td>
<td>39/135 (28.8%)</td>
<td>7/24 (29.2%)</td>
<td>7/53 (13.2%)</td>
<td>25/58 (43.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Local only</td>
<td>27 (20.0)</td>
<td>3 (12.5)</td>
<td>3 (5.6)</td>
<td>21 (36.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Regional only</td>
<td>8 (5.9)</td>
<td>2 (8.3)</td>
<td>3 (5.6)</td>
<td>3 (5.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Local + regional</td>
<td>4 (3.0)</td>
<td>2 (8.3)</td>
<td>1 (1.9)</td>
<td>1 (1.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Distant pattern</td>
<td>96/135 (71.1%)</td>
<td>17/24 (70.8%)</td>
<td>46/53 (86.8%)</td>
<td>33/58 (56.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Distant only</td>
<td>47 (34.8)</td>
<td>5 (20.8)</td>
<td>28 (52.8)</td>
<td>14 (24.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Locoregional + distant</td>
<td>49 (36.3)</td>
<td>12 (50.0)</td>
<td>18 (34.0)</td>
<td>19 (32.8)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

(n=92)

Relatively higher loco-regional recurrence than GB ca or IHC
But, overall recurrence : Distant > loco-regional
Recurrence Patterns

Disease recurrence patterns after R0 resection of hilar cholangiocarcinoma

A. Kobayashi, S. Miwa, T. Nakata and S. Miyagawa

(n=79)

(British J Surg 2010; 97: 56–64)
Recurrence Patterns

The Survival Outcome and Prognostic Factors for Middle and Distal Bile Duct Cancer Following Surgical Resection

SAE BYEOL CHOI, MD, 1 SEUNG WOO PARK, MD, PhD, 2 KYUNG SIK KIM, MD, 1 JIN SUB CHEOI, MD, 1 AND WOO JUNG LEE, MD 1

- Recurrence rate 58.5%
- Median disease-free survival time 23.9mo

(J Surg Oncol 2009;99:335–342)

<table>
<thead>
<tr>
<th>Pattern of recurrence</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local</strong></td>
<td></td>
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<tr>
<td>Total</td>
<td>35</td>
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<tr>
<td>SMA, celiac axis, aortocaval area</td>
<td>16</td>
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<tr>
<td>Porta hepatic, hepatoduodenal ligament</td>
<td>4</td>
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<tr>
<td>Pancreatic head</td>
<td>2</td>
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<tr>
<td>Anastomosis site</td>
<td>9</td>
</tr>
<tr>
<td>Intrahepatic bile duct</td>
<td>3</td>
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<tr>
<td>Periureteral recurrence</td>
<td>1</td>
</tr>
<tr>
<td><strong>Distant</strong></td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>26</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>7</td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
</tr>
<tr>
<td>Pleura</td>
<td>1</td>
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<tr>
<td>Nodal</td>
<td>12</td>
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Recurrence Patterns

• Distant > Loco-regional
• Loco-regional is relatively higher than GB ca or IHC
• Distant sites
  – Liver > Peritoneum, para-aortic LN…
Interpretation of Previous Reports

- Small sample size d/t rarity
- Different modality and regimen of adjuvant therapy
- R0 resection rate
- S1 resection for Klatskin tumor?
PTBD Tract Recurrence

- Not negligible rate of recurrence
- Survival is poorer than those without recurrence

<table>
<thead>
<tr>
<th></th>
<th>Takahashi</th>
<th>Hwang</th>
<th>Kang</th>
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<tbody>
<tr>
<td>Incidence (%)</td>
<td>5.2</td>
<td>1.7</td>
<td>2.6</td>
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<tr>
<td>Time to recurrence (mo)</td>
<td>14.4</td>
<td>13.5</td>
<td>10.9</td>
</tr>
<tr>
<td>Median survival (mo)</td>
<td>23</td>
<td>25</td>
<td>17.5</td>
</tr>
</tbody>
</table>

References:
- (Br J Surg 2010)
- (World J Surg 2012)
- (World J Surg 2013)
Risk Factors

• T-Stage
• LN metastasis
• Surgical margin (+)
• Adjuvant Therapy (-)
• Poor tumor differentiation
• Elevated CA19-9
Risk Factors for Loco-regional Recurrence

• Loco-regional recurrences are from
  – Microscopic residual disease
  – Disease in lymphatics

• Risk factors
  – Surgical margin(+)
  – Perineural invasion
Surgical Margin

For R1 patients

→Adjuvant RT/ CCRT is strongly recommended

(J Hepatobiliary Pancreat Sci 2010 17:166–173)
Risk Factors of Distant Mets

• LN involvement
• Lymphatic invasion
• CA19-9 > 37 U/ml
Adjuvant therapy after resection

- Radiation therapy? Chemotherapy?
- In general
  - RM (+) → RT
  - LN (+) → Chemo

Results
Twenty studies involving 6,712 patients were analyzed. There was a nonsignificant improvement in overall survival with any AT compared with surgery alone (pooled OR, 0.74; $P = .06$). There was no difference between gallbladder and bile duct tumors ($P = .68$). The association was significant when the two registry analyses were excluded. Those receiving CT or CRT derived statistically greater benefit than RT alone (OR, 0.39, 0.61, and 0.98, respectively; $P = .02$). The greatest benefit for AT was in those with LN-positive disease (OR, 0.49; $P = .004$) and R1 disease (OR, 0.36; $P = .002$).

1. Non-significant improvement in overall survival with any AT

2. CT or CRT derived statistically greater benefit than RT alone

3. The greatest benefit for AT was in those with LN-positive disease and R1 disease
Summary & Conclusion

• Recurrence patterns
  – Distal > Loco-regional
  – Loco-regional is relatively higher than GB ca. and IHC

• Risk Factors
  – T, N stage
  – Surgical margin (+)
  – Adjuvant therapy (-)