Proximal Bile Duct Cancer: Contemporary Management

William R. Jarnagin, MD, FACS
Biliary Tract Adenocarcinoma

Spectrum of disease

Intrahepatic (IHC)

Gallbladder

Hilar

EH

Distal

GB

CBD

D

PD
Biliary Tract Adenocarcinoma

Incidence

• USA: 8 – 10,000 annual cases
  • GBCA most common
    ➢ At least 1/3 arise from the bile ducts
    ➢ Rising incidence over past several years
      ▪ Intrahepatic cholangiocarcinoma primarily
      ▪ Worldwide
        ❖ HCV, obesity (NAFLD), cirrhosis
      ▪ No change in extrahepatic tumors
  
• Uncommon: < 2% of all cancers

Hilar CC: Anatomical Considerations

- Longitudinal and radial extension

- Rarely confined to the bile duct wall

- Several anatomic features mandate *en bloc* partial hepatectomy (if resectable)
Hilar CC: Anatomical Considerations

- Mucosal/submucosal tumor extension beyond gross tumor (5 – 20 mm)
- Often unilateral extension to 2nd biliary radicles and beyond

Portal vein involvement

- Lobar atrophy and portal vein involvement
  - Often related
  - Common findings: ~50% of patients have one or both
  - Important factors in determining resectability

Hilar CC: Anatomical Considerations
Hilar CC: Anatomical Considerations

- Caudate duct involvement
- Particularly important for tumors arising from the LHD
- Mandates *en bloc* caudate resection
Treatment

• Complete resection is the most effective treatment
  • R0 Resection possible, no metastatic disease
    ➢ Partial hepatectomy required
    ➢ ? Liver transplantation
    ➢ Roles for chemotherapy/radiation therapy are undefined

• Limitations
  • Disease extent
    ➢ Vascular/biliary involvement, atrophy, metastases
  • Underlying liver disease (PSC)

• Five-year overall survival up to 40% after R0 resection
  • Resection is possible in the minority of patients
Hilar Cholangiocarcinoma

MSKCC Results

380 Patients
1991 – 2008

Unresectable at Presentation
85 Patients (22%)
(metastases in 38)

Explored for Cure
295 Patients (78%)

Unresectable
138 Patients (47%)
(metastases in 80)

Resected
157 Patients (53%)

Matsuo et al, Ann Surg, submitted
Patient Evaluation

• Assessment of fitness for major surgery

• Radiographic studies to assess:
  • Biliary tumor extent, vascular involvement, lobar atrophy
  • Distant metastases
  • Cholangiography (MRCP), CT (angiography), duplex US
    ➢ Invasive studies often unnecessary
    ➢ Role for $^{18}$FDG-PET scanning
      ▪ Management decisions changed in ~20%

• Staging laparoscopy
  • Improves resectability by 10 – 20%

Pre-operative Clinical Staging

‘The Blumgart System’

• Three clinical stage groupings based on:
  • Extent of biliary involvement
  • Portal vein involvement
  • Hepatic lobar atrophy

• Patients categorized using data from preoperative imaging

• Correlated with:
  • Resectability
  • Likelihood of metastatic disease
  • Survival
Blumgart Clinical Staging System

T1

T2

T3

Atrophy
# Blumgart Clinical Staging System

**Predictor of resectability and metastatic disease**

<table>
<thead>
<tr>
<th>Preoperative Stage</th>
<th>N</th>
<th>Explored for Cure</th>
<th>Resected*</th>
<th>Metastatic Disease†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>143</td>
<td>85%</td>
<td>64%</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>86%</td>
<td>41%</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>51%</td>
<td>1%</td>
<td>49%</td>
</tr>
</tbody>
</table>

* - p < 0.001  † - p < 0.009
Preoperative evaluation with T-staging system for hilar cholangiocarcinoma

Ru-Fu Chen, Zhi-Hua Li, Jia-Jia Zhou, Jie Wang, Ji-Sheng Chen, Qing Lin, Qi=Bing Tang, Ning-Fu Peng, Zhi-Peng Jiang, Quan-Bo Zhou
GuangZhou 510120, Guangdong Province, China

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>Resected*</th>
<th>Metastatic Disease†</th>
<th>Survival (3-year)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>74%</td>
<td>39%</td>
<td>34%</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>60%</td>
<td>53%</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>7%</td>
<td>70%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* - p < 0.05 † - p < 0.03 § - p < 0.001
Goals of Resection

R0 resection, leaving behind a well-perfused liver remnant with adequate biliary drainage

- Remove bile duct
- Remove involved liver
- Selective caudate resection
- Portal lymphadenectomy
- Remove/reconstruct areas of portal vein invasion
- Biliary reconstruction
### Hepatic Resection and Margin Status

<table>
<thead>
<tr>
<th>Author</th>
<th>Complete Gross Resection (n)</th>
<th>Partial Hepatectomy (%)</th>
<th>(-) Margin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsao (’00)</td>
<td>25</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>Cameron (’90)</td>
<td>39</td>
<td>20</td>
<td>15</td>
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<tr>
<td>Gerhards (’00)</td>
<td>112</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Hadjis (’90)</td>
<td>27</td>
<td>60</td>
<td>56</td>
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<tr>
<td>Klempnauer (’97)</td>
<td>147</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Neuhaus (’00)</td>
<td>95</td>
<td>85</td>
<td>61</td>
</tr>
<tr>
<td>Jarnagin (’05)</td>
<td>106</td>
<td>87</td>
<td>82</td>
</tr>
<tr>
<td>Kawasaki (’05)</td>
<td>79</td>
<td>96</td>
<td>68</td>
</tr>
<tr>
<td>Nimura (’90)</td>
<td>55</td>
<td>98</td>
<td>83</td>
</tr>
</tbody>
</table>
Survival after Resection

DSS stratified by resection margin status

- Median follow-up 30 months for resected patients
- Survival: R1 >> R2 > no resection
## Variables Associated with Survival after Resection

<table>
<thead>
<tr>
<th></th>
<th>p (univariate)</th>
<th>p (multivariate)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 Resection</td>
<td>0.0003</td>
<td>0.007</td>
<td>2.0</td>
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<tr>
<td>Liver Resection</td>
<td>0.021</td>
<td>0.005</td>
<td>2.2</td>
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<tr>
<td>Well-Differentiated</td>
<td>0.0001</td>
<td>0.0001</td>
<td>2.6</td>
</tr>
<tr>
<td>Node (-)</td>
<td>0.0007</td>
<td>0.64</td>
<td>1.15</td>
</tr>
</tbody>
</table>
Survival Stratified by Lymph Node Count

- Inadequate lymphadenectomy risks understaging
- N0 status requires resection/examination of minimum number of lymph nodes

Ito K et al. Ann Surg 2010;251:675
## Survival after Resection

<table>
<thead>
<tr>
<th>Author</th>
<th>Resections</th>
<th>Survival (5-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakeeb et al 1996</td>
<td>109</td>
<td>11</td>
</tr>
<tr>
<td>Klempnauer et al 1997</td>
<td>151</td>
<td>28</td>
</tr>
<tr>
<td>Miyazaki et al 1998</td>
<td>76</td>
<td>26</td>
</tr>
<tr>
<td>Neuhaus et al 1999</td>
<td>80</td>
<td>22</td>
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<tr>
<td>Kosuge et al 1999</td>
<td>65</td>
<td>33</td>
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<tr>
<td>Gerhards et al 2000</td>
<td>75</td>
<td>42</td>
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<tr>
<td>Kawarada et al 2002</td>
<td>65</td>
<td>26</td>
</tr>
<tr>
<td>Rea et al 2004</td>
<td>46</td>
<td>26</td>
</tr>
<tr>
<td>Nashio et al 2005</td>
<td>301</td>
<td>22</td>
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<tr>
<td>Hemming et al 2005</td>
<td>53</td>
<td>35</td>
</tr>
<tr>
<td>Jarnagin et al 2005</td>
<td>106</td>
<td>40</td>
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<tr>
<td>Unno et al 2009</td>
<td>125</td>
<td>35</td>
</tr>
<tr>
<td>Igami et al 2009</td>
<td>298</td>
<td>42</td>
</tr>
</tbody>
</table>

5 year survival: Up to 40% after resection

0 without resection
## The Price: Morbidity and Mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Resections</th>
<th>Morbidity</th>
<th>Mortality</th>
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</thead>
<tbody>
<tr>
<td>Nakeeb et al 1996</td>
<td>109</td>
<td>47</td>
<td>4</td>
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<tr>
<td>Klempnauer et al 1997</td>
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<td>Miyazaki et al 1998</td>
<td>76</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>Neuhaus et al 1999</td>
<td>80</td>
<td>55</td>
<td>8</td>
</tr>
<tr>
<td>Kosuge et al 1999</td>
<td>65</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>Gazzaniga et al 2000</td>
<td>75</td>
<td>85</td>
<td>10</td>
</tr>
<tr>
<td>Launois et al 2000</td>
<td>131</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Lee et al 2000</td>
<td>128</td>
<td>64</td>
<td>10</td>
</tr>
<tr>
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<td>112</td>
<td>63</td>
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<td>9</td>
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<td>50</td>
<td>7.5</td>
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<td>125</td>
<td>49</td>
<td>8</td>
</tr>
<tr>
<td>Igami et al 2009</td>
<td>298</td>
<td>43</td>
<td>2</td>
</tr>
</tbody>
</table>

**Morbidity:** 33 – 76%

**Mortality:** 2 – 17%
Resection: Morbidity and Mortality

- Extended hepatic resections for small tumors
  - Major sacrifice of functional parenchyma
  - Concomitant biliary and vascular reconstructions
  - Jaundiced liver
    - Impaired post-operative liver regeneration

- Infections
  - (+) Bile cultures ↑ infective complications
  - Correlated closely with preoperative biliary stents

Resection: Morbidity and Mortality

Improving results

Preoperative Biliary Drainage

Preoperative Portal Vein Embolization
Resection: Morbidity and Mortality

Improving results

One Hundred Two Consecutive Hepatobiliary Resections for Perihilar Cholangiocarcinoma With Zero Mortality

Tsuyoshi Sano, MD, Kazuaki Shimada, MD, Yoshihiro Sakamoto, MD, Junji Yamamoto, MD, Susumu Yasazaki, MD, and Tomoo Kusuge, MD

• Extensive use of preoperative biliary drainage and PVE
  • Resectability = 82%
  • Morbidity = 50%
  • Mortality (in hospital) = 0%
  • 5-year survival = 44%
Resection: Morbidity and Mortality

Impact of preoperative drainage and FLR volume

Kennedy et al. HPB (Oxford) 2009; 11(5):445-51
Liver Transplantation for Hilar Cholangiocarcinoma

• Advantages:
  • Constraints that limit resection are less critical
    ➢ Biliary tumor extent
    ➢ Atrophy
    ➢ Underlying hepatic parenchymal disease (PSC)
  • R0 resection easier to achieve

• Limitations:
  • Regional nodal disease (~40-50% of patients)
  • Graft availability
Liver Transplantation

Not a new concept

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Recurrence (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer CG et al 2000</td>
<td>207</td>
<td>51</td>
<td>28% (5 yr)</td>
</tr>
<tr>
<td>Robles R et al 2004</td>
<td>36</td>
<td>53</td>
<td>30% (3 yr)</td>
</tr>
<tr>
<td>Alessiani M et al 1995</td>
<td>20</td>
<td>57</td>
<td>20% (3 yr)</td>
</tr>
</tbody>
</table>

• Benefit in selected patients
• Overall poor results: contraindication to transplantation
Liver Transplantation

Mayo Clinic experience

• Eligibility criteria:
  • Unresectable disease
  ➢ (+) cytology OR ‘malignant’ stricture with Ca 19-9 > 100
  • Stage I or II disease - confined to periductal tissue, node (-)
  • PSC with resectable disease
  • Candidate for liver transplantation

• Exclusion criteria:
  • Metastatic disease (regional nodal or distant)
  • Prior attempt at resection
  • Prior treatment with radiation therapy or chemotherapy

De Vreede et al Liver Transplantation 2000;6:309
Liver Transplantation

Mayo Clinic protocol

External Beam Irradiation
(4500 cGy – 150 cGy BID)
Bolus 5-FU (500 mg/m²/day x 3)

Transcatheter Irradiation (¹⁹²Ir ~ 2-3000 cGy)
5-FU (225 mg/m²/day)

Exploratory Laparotomy

5-FU (500mg/m²/day)

Transplantation

De Vreede et al Liver Transplantation 2000;6:309
Liver Transplantation

**Initial results**

918 Patients with Cholangiocarcinoma
1993 - 1998

25 Patients Evaluated for Treatment (2.7%)

- 6 Metastatic Disease
- 19 Chemoradiation

- 11 Transplantation (1.2%)
  - 5-year RFS 91%

- 1 Death (sepsis)
  - 7 Metastatic Disease

De Vreede et al Liver Transplantation 2000;6:309
Liver Transplantation

Updated results

71 Patients Enrolled
Chemoradiation
1993 - 2004

5 Deaths (7%)
(4 sepsis, 1 PE)

4 Disease Progression

62 Patients Explored

38 Transplantation (54%)

3 Postoperative Deaths (8%)

14 Advanced Disease

10 Listed

# Liver Transplantation

## Updated results: Survival

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Transplanted (n = 38)</th>
<th>Resected (n = 26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence Rate</td>
<td>13%</td>
<td>27%</td>
<td>NR</td>
</tr>
<tr>
<td>Time to Recurrence</td>
<td>40 months</td>
<td>21 months</td>
<td>NR</td>
</tr>
<tr>
<td>5-Year Survival</td>
<td>82%</td>
<td>21%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Liver Transplantation with Neoadjuvant Chemoradiation is More Effective than Resection for Hilar Cholangiocarcinoma*

---

David J. Rea, MD,* Julie K. Heimbach, MD,† Charles B. Rosen, MD,† Michael G. Haddock, MD,‡ Steven R. Alberts, MD,§ Walter K. Kremers, PhD,† Gregory J. Gores, MD,§ and David M. Nagorney, MD*

*Annals of Surgery • Volume 242, Number 3, September 2005*
## Liver Transplantation

### Updated results: Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transplanted (n = 38)</th>
<th>Resection (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>48 years</td>
<td>63 years</td>
</tr>
<tr>
<td>1° Sclerosing Cholangitis</td>
<td>58%</td>
<td>8%</td>
</tr>
<tr>
<td>Stage I or II (%)</td>
<td>100%</td>
<td>NR</td>
</tr>
<tr>
<td>Node (+)</td>
<td>0</td>
<td>31%</td>
</tr>
<tr>
<td>Histologic Diagnosis of Cancer</td>
<td>58%</td>
<td>96%</td>
</tr>
<tr>
<td>(+) Margin</td>
<td>23%</td>
<td>12%</td>
</tr>
</tbody>
</table>
## Liver Transplantation

### Updated results: Survival

<table>
<thead>
<tr>
<th></th>
<th>Transplant Protocol (n = 71)</th>
<th>Explored for Resection (n = 34)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Operability’</td>
<td>54%</td>
<td>48%</td>
<td>NR</td>
</tr>
<tr>
<td>Treatment Related Mortality</td>
<td>11%</td>
<td>12%</td>
<td>NR</td>
</tr>
<tr>
<td>5-Yr Survival</td>
<td>58%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Summary

• Resection remains the most effective therapy
  • Requires en bloc partial hepatectomy
  • Possible in the minority of patients
  • Effective non-operative therapy needed

• Considerable morbidity with resection
  • Improvements have been made
  • Role for selective biliary drainage/PVE

• Transplantation plays a small role
  • Very carefully selected patients
    ➢ Limited disease
    ➢ Underlying parenchymal disease (ie, PSC)
Cholangiocarcinoma: Etiology & Pathogenesis

Risk factors for cholangiocarcinoma

- Established:
  - PSC
  - Congenital biliary cysts
  - Hepatolithiasis
  - Biliary parasitic disease

- More recently appreciated:
  - HCV
  - Obesity
    - NAFLD
    - Diabetes mellitus
  - Non-alcoholic cirrhosis

- No clear increase
- All increasing

- Demographic changes favor rising incidence of IHC over HCCA

Intrahepatic Cholangiocarcinoma (IHC)

Rising incidence and mortality

- Incidence of extrahepatic bile duct cancer static/declining

Patel. Hepatology 2001;33:1353