Current Treatment Strategies for Hilar and Intrahepatic Cholangiocarcinoma

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Extended Left Hepatectomy for IHCC

- 55 Year-old Female
- Tumor size was 4.5cm and extended into the left bile duct and further to the level of the bifurcation.
Extended Left Hepatectomy for IHCC

- Infiltrating moderately differentiated adenocarcinoma, most consistent with cholangiocarcinoma of the left hepatic duct (T4N0M0)
- No evidence of disease after extended left hepatectomy for 11 years.

Intrahepatic Cholangiocarcinoma (ICCA)

1. MDACC Experience
2. Local Therapy (surgery and radiation)
3. Molecular Profiling
4. Non-surgical treatment option
**MDACC-BTC**

Oncology Referrals or New Cases/ Year

**IHCCA - MDACC over 18 Years**

Yamashita et al, *Cancer, Submitted*
ICCA – MDACC n=362
Local Therapy versus Systemic Therapy

Survival Improvement after Local Therapy

Yamashita et al, Cancer, Submitted

ICCA- MDACC n=207
Survival Improvement after Local Therapy

Survival Outcomes of ICC Has Improved for Local Therapy-Based Definitive Treatment, Which may be Attributable to Maintaining Control of Intrahepatic Disease, Reducing Occurrence of Death due to Liver Failure.

Yamashita et al, Cancer, Submitted
ICCA – MDACC n=362
Local Therapy Reduces Risk of Liver Failure

Multivariable Analysis Identified Local Therapy as a Sole Predictor of Death without Liver Failure (OR 4.1, \( P<0.001 \)).

Yamashita et al, *Cancer, Submitted*

Largest Molecular Profiling experience in BTC

<table>
<thead>
<tr>
<th>CGP Findings</th>
<th>IHCCA (n=412)</th>
<th>EHCCA (n=57)</th>
<th>GBCA (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GA/patient</td>
<td>3.6</td>
<td>4.4</td>
<td>4.0</td>
</tr>
<tr>
<td>CRGA/patient</td>
<td>2.0</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>ERBB2 Amplification</td>
<td>4%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>BRAF Substitutions</td>
<td>5%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>KRAS Substitutions</td>
<td>22%</td>
<td>42%</td>
<td>11%</td>
</tr>
<tr>
<td>PI3KCA Substitution</td>
<td>5%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>FGFR1-3 Fusions and Amplifications</td>
<td>11%</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td>CDKN2A/B Loss</td>
<td>27%</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>IDH1/2 Substitutions</td>
<td>20%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ARID1A Alterations</td>
<td>18%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>MET Amplification</td>
<td>2%</td>
<td>0</td>
<td>1%</td>
</tr>
</tbody>
</table>

Javle et al, *Clinical Science Symposium, ASCO 2015*
Overall Survival of Biliary Tract Cancer

![Graph showing overall survival rates for patients treated and not treated with FGFR targeted therapy.](image)

- Treatment with FGFR targeted (n=20)
- Not treated with FGFR targeted (n=34)

Jain, Shroff, Meric-Bernstam, et al (ASCO CSS 2016)

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Current Portfolio of Trials

- **First Line:** GAP (Gem, Abraxane, Cisp) [Shroff]
- **NRG1101:** Chemo – CRT/Chemo [Crane/Javle]
- **Phase 2 Ramucirumab second-line** [Shroff]
- **IDH1/2 Molecular Therapy** [Janku/Shroff]
- **FGFR targeted therapy BGJ398** [Javle]
- **Phase 2 Durvalumab + Tremi (CTLA4)** [Javle]
- **OLT Registry- for intrahepatic CCA** [Methodist]
- **Planned:** HAI with nano-oxaliplatin [IR]
Hilar Cholangiocarcinoma (HCCA)

1. Preop. imaging diagnosis
2. Extent of resection
3. Short-term outcome
4. Long-term outcome

Accurate Staging and Assessment of Resectability with 3-D Reformation

- High resolution thin slice CT
  (1.25 or 0.625 mm slice thickness)
- 3-Dimensional vascular reconstruction
- 3-Dimensional liver volumetry and PVE

Resectability could be predicted in 17/18 cases

Extended Right Hepatectomy for Klatskin tumor

Extensive Associated Resection

Vascular Resection and Caudate Lobe Resection
Is Ext Hepatectomy Safe?

The left hepatic duct
- Long
- Extrahepatic
- Present in 97%

Supeiority of Right-Sided Resection

- Wide surgical margin
  - Left hepatic duct is longer

- Complete resection of the caudate lobe
  - Right sided margin of caudate process is unclear

- Combined resection of the right hepatic artery
  - Right hepatic artery resection is likely more curative

- Combined resection and reconstruction of the portal vein
  - Left portal trunk is longer...

...But Small Remnant Liver

Postoperative Hepatic Insufficiency

MDACC and Torino, Italy

n=133, 15 deaths within 90 days = 11%
85% Preoperative biliary drainage with 41% of cholangitis

Major Complications n=73

Hepatic Insufficiency n=29

Death n=10

Ribero et al. JACS 2016
Various Perioperative Risk Factors

Biliary drainage 85%
- Positive culture of biliary stent at surgery 79%
- History of cholangitis prior to surgery 23%

Malnutrition
- Preoperative albumin <4.0 g/dL 56%

Combined vascular resection/reconstruction 11%

Postoperative Hepatic Insufficiency

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Preoperative cholangitis</td>
<td>.029</td>
<td>4.134 (1.327-12.877)</td>
</tr>
<tr>
<td>FLR volume &lt; 30%</td>
<td>.030</td>
<td>3.584 (1.23-10.10)</td>
</tr>
<tr>
<td>Albumin level &lt; 3.5 mg/dl</td>
<td>.015</td>
<td>4.404 (1.532-12.661)</td>
</tr>
<tr>
<td>Total Bilirubin &gt; 3 mg/dl</td>
<td>.165</td>
<td>4.386 (1.357-14.178)</td>
</tr>
</tbody>
</table>

Ribero et al JACS 2016
Postoperative Liver Failure

<table>
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<tr>
<th>Factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Preoperative cholangitis</td>
<td>.001</td>
<td>11.95 (1.35-105.88)</td>
</tr>
<tr>
<td>FLR volume &lt; 30%</td>
<td>.012</td>
<td>8.06 (1.426-45.454)</td>
</tr>
</tbody>
</table>

Ribero et al JACS 2016

Postoperative Outcome of Patients with < 30% FLR Volume

Ribero et al JACS 2016
Postoperative Outcome of Patients with $\geq 30\%$ FLR Volume

<table>
<thead>
<tr>
<th>Hepatic insufficiency</th>
<th>Liver failure death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative cholangitis</td>
<td>0.21/0.62</td>
</tr>
<tr>
<td>No preoperative cholangitis</td>
<td>0.09/0.62</td>
</tr>
</tbody>
</table>

Ribero et al. JACS 2016

Optimize Portal Vein Embolization (PVE)
MD Anderson Approach

Pre-PVE FLR (seg 1-3) 10% vs. Total Liver Volume
Post-PVE FLR (seg 1-3) 33% vs. Total Liver Volume

Transhepatic Ipsilateral Right Portal Vein Embolization Extended to Segment 4 Branches and Spherical Microspheres
Comparison of patients who did and did not develop preoperative cholangitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preoperative cholangitis (n=42)</th>
<th>No preoperative cholangitis (n=91)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice at diagnosis, n (%)</td>
<td>37 (88)</td>
<td>79 (87)</td>
<td>0.837</td>
</tr>
<tr>
<td>Preoperative biliary drainage, n (%)</td>
<td>40 (95)</td>
<td>58 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endoscopic retrograde biliary drainage</td>
<td>27 (64)</td>
<td>21 (36)</td>
<td>0.002</td>
</tr>
<tr>
<td>Percutaneous transhepatic biliary drainage</td>
<td>13 (33)</td>
<td>37 (64)</td>
<td></td>
</tr>
<tr>
<td>FLR volume &lt; 30%</td>
<td>21 (50)</td>
<td>29 (32)</td>
<td>0.045</td>
</tr>
<tr>
<td>Median total bilirubin, mg/dL (range)</td>
<td>1 (0.3–20.9)</td>
<td>3 (0.1–30.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall complications, n (%)</td>
<td>40 (95)</td>
<td>62 (68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major complications, n (%)</td>
<td>31 (74)</td>
<td>42 (46)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>14 (33)</td>
<td>15 (16)</td>
<td>0.029</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>10 (24)</td>
<td>5 (5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Liver failure</td>
<td>8 (19)</td>
<td>2 (2)</td>
<td>0.001</td>
</tr>
<tr>
<td>FLR, future liver remnant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Toronto Experience Similar Findings: Percutaneous Superior to Endoscopic Walter T J Vasc Interv Radiol 2013;24:113

Ribero et al JACS 2016

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**Evolution of Surgical Treatment for Perihilar Cholangiocarcinoma**

*A Single-Center 34-Year Review of 574 Consecutive Resections*

<table>
<thead>
<tr>
<th>Time Period (%)</th>
<th>Total (%)</th>
<th>Earlier Period</th>
<th>Later Period</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients resected</td>
<td>574</td>
<td>72</td>
<td>116</td>
<td>168</td>
<td>218</td>
</tr>
<tr>
<td>Resectability</td>
<td>574/754 (76.1)</td>
<td>72/93 (77.4)</td>
<td>116/148 (78.4)</td>
<td>168/216 (77.8)</td>
<td>218/297 (73.4)</td>
</tr>
<tr>
<td>Type of hepatectomy*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1,2,3,4,5,6,7,8</td>
<td>43 (7.5)</td>
<td>5 (6.9)</td>
<td>11 (9.5)</td>
<td>4 (2.4)</td>
<td>23 (10.6)</td>
</tr>
<tr>
<td>S1,2,3,4,5,6,7</td>
<td>177 (30.8)</td>
<td>17 (23.6)</td>
<td>40 (34.5)</td>
<td>53 (31.5)</td>
<td>67 (30.7)</td>
</tr>
<tr>
<td>S1,2,3,4,5,6,7,8</td>
<td>110 (19.2)</td>
<td>4 (5.6)</td>
<td>12 (10.3)</td>
<td>29 (17.3)</td>
<td>65 (29.8)</td>
</tr>
<tr>
<td>S1,2,3,4,5,6,7,8,9</td>
<td>187 (32.6)</td>
<td>27 (37.5)</td>
<td>35 (30.2)</td>
<td>68 (40.5)</td>
<td>57 (26.1)</td>
</tr>
<tr>
<td>S1,2,3,4,5,6,7,8,9,10</td>
<td>38 (6.6)</td>
<td>11 (15.1)</td>
<td>10 (8.4)</td>
<td>11 (6.5)</td>
<td>4 (1.8)</td>
</tr>
</tbody>
</table>

*Hepatectomy includes coupled resection, transsection, and lobectomy.*

The incidence of left hepatic trisectionectomy gradually increased, reaching approximately 30% in the last 5-year period. Perioperative mortality steadily decreased 1.4% (2006-2010).

Nagino et al *Ann Surg* 2013
Evolution of Surgical Treatment for Perihilar Cholangiocarcinoma
A Single-Center 34-Year Review of 574 Consecutive Resections

Survival for 574 resected patients according to the time periods. (Log-rank test)

The selection of extended procedures may have contributed to the improved outcome (other factors immunonutrition, preconditioning, surgical technique, nasobiliary drainage)

Nagino et al Ann Surg 2013
Six Steps to Improve Outcome of HCCA

1. Precise imaging study
2. Portal vein embolization
3. Biliary drainage
4. Bile replacement
5. Early enteral feeding
6. Perioperative synbiotics

Conclusion

- Multimodality treatment contributes to improved survival in patients with intrahepatic cholangiocarcinoma
- Specific cut-offs for PVE in hilar cholangiocarcinoma with or without cholangitis may be needed
- Additional techniques to further improve regeneration and accurately measure function should be developed
- Optimize preoperative drainage with percutaneous transhepatic catheters may reduce the risk of preoperative cholangitis