Embolotherapy for Cholangiocarcinoma: 2016 Update

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GEST 2016
Igor Lobko, M.D.

• No relevant financial relationship reported
Cholangiocarcinoma Embolization

- Recent Literature
- Ongoing Studies
- When is Embolization of Cholangiocarcinoma appropriate?
  - Patient Selection
  - Prognostic Factors
  - Does Size Matter?
  - Tumor Enhancement – What does it mean?
- Cholangiocarcinoma IR Therapies Algorithm
Cholangiocarcinoma

- Primary malignant neoplasm of the hepatobiliary system arising from the biliary ducts epithelia
- Second most common primary malignancy of the liver
- 2000-3000 new cases a year in USA, 1.67/100000
- More common in South East Asia:
  - China 0.97-7.5, Korea 7.1-8.75, Thailand 5.7-85/100000
- Usually diagnosed at advanced stage, have a poor prognosis
Literature Review
Trans arterial Therapies

Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma.

• 20 articles, 657 patients

• Median OS: Response Rate:
  - HAI – 22.8 months 56.9%
  - TARE – 13.9 months 27.4%
  - TACE – 12.4 months 17.3%
  - DEB-TACE – 12.3 months

• Toxicity: HAI - Highest

Boehm LM et al, J Surg Oncol. 2015 Feb
Trans-arterial embolization therapies for unresectable intrahepatic cholangiocarcinoma: a systematic review

• 20 studies eligible for review between 2000-2013 (929 patients)
• 4 studies with more than 50 patients
• 12 studies retrospective
• No Randomized Controlled Trials
• Radiological Response: complete – 10%, partial – 22%
• MOS: TARE - 12.5 months; TACE – 13 months
• 1 Year Survival TARE – 54.5% (40-61%); TACE – 53% (38-78%)
• Negative Predictive Factors: TARE - Large Tumor Burden, Multiplicity, PS > 2
  TACE - Hypovascularity, Extrahepatic Disease

Linda Yang et all, Gastrointest Oncol. 2015 Oct
Intra-arterial therapy for advanced intrahepatic Cholangiocarcinoma: a multi-institutional analysis

• Retrospective review 198 patients treated in 4 major centers
• Compared cTACE, DEB, TAE, TARE

Response: Complete or partial – 25.5%
Stable disease – 61.5%
Progression – 13%

Medial OS 13.2 months and did not differ between IAT
Similar Treatment Related Toxicities

Hyder O, Ann Surg Oncol. 2013 Nov
Treatment of unresectable intrahepatic cholangiocarcinoma with **yttrium-90 radioembolization**: A systematic review and pooled analysis

- 12 Studies, 298 patients:
  - 7 prospective and 5 retrospective studies
  - No randomized studies
  - Median OS 15.5 months
  - Radiological Tumor Response:
    - Partial – 28%
    - Stable – 54%
    - 7 patients down staged to surgery

D.P. Al-Adra et al, Eur J Surg Oncol. 2015 Jan
Radioembolization improves survival in intrahepatic cholangiocarcinoma: a SEER-Medicare population study

- Retrospective
- 585 patients: Chemotherapy 513 – 88%
  
  Chemotherapy + TARE 72 - 12%
- Median Overall Survival:
  
  Chemotherapy 811 days
  
  Chemotherapy + TARE 1043 days
- Combination therapy of ICC with chemotherapy and radioembolization results in a median 7.6 months of greater survival than chemotherapy alone.

Hyun S. Kim, Minzhi Xing, SIR 2016 Annual Meeting
Yttrium-90 radioembolization for unresectable combined hepatocellular-cholangiocarcinoma

• Retrospective
• SIR Spheres 5 patients and Theraspheres 6 patients
• 11 patients
• Radiographic Response: Partial – 6
  Stable – 4
• Median OS: From 1st TARE – 9.4 months
  From Initial Diagnosis – 18 months
• Only Grade 1-2 toxicities observed

John D Louie, Daniel Sze, David S. Wang, SIR 2016 Annual Meeting
Summary of Published Data

Good News
• Embolotherapies for Cholangiocarcinoma Improve Survival
• Relatively Low Toxicities with Acceptable Safety Profile
• Similar results between different types of embolization

Bad News
• Low power studies due to small and heterogeneous samples
• Most studies based on retrospective data analysis
• No Randomized Trials
Current Studies Investigating Embolothersapies for Cholangiocarcinoma Treatment

• 6 - Ongoing Prospective Studies
• 2 – Dose Escalation Studies
• 2 - Safety and Feasibility
• 1 - International Cholangiocarcinoma Registry
• 2 - Randomized Trials

ClinicalTrials.gov
Yttrium Y 90 Glass Microspheres and Capecitabine in Treating Patients With Liver Cholangiocarcinoma or Liver Metastases, USA

- Prospective Dose Escalation Study
- Theraspheres
- Started March 2009, enrollment completed
- Estimated Study Completion Date December 2017
- 30 Patients
- Primary Outcome Measures:
  - Maximal tolerated dose of yttrium Y 90
  - Toxicity
  - Time to tumor progression
90Y Transarterial Radioembolization (TARE) Plus Gemcitabine and Cisplatin in Unresectable Intrahepatic Cholangiocarcinoma USA

- Prospective Dose Escalation Study
- SIR Spheres
- Start Date July 2015
- Estimated Completion Date August 2018
- 20 patients
- Primary Outcome Measure:
  Presence or absence of a dose limiting toxicity (DLT) of 90Y TARE in combination with gemcitabine and cisplatin
International Registry on Cholangiocarcinoma Treatment (CHOLANGIO), Italy

• Prospective Study
• DEB TACE with Doxorubicin
• Target number of patients 40
• Started July 2013
• Estimated Completion date August 2016
• Primary Outcome Measures:
  Tumor response
  Overall Survival
• Secondary Outcome Measures:
  Number adverse events
  Quality of life
Efficacy Study of Intra-hepatic Administration of Therasphere® in Association With Intravenous Chemotherapy to Treat Cholangiocarcinoma, France

• Prospective Safety/Efficacy Study
• Theraspheres
• Started September 2013
• Estimated Completion Date April 2018
• 41 Patient
• Primary Outcome Measure:

Radiological response rate to the treatment with the association of chemotherapy and radioembolization 3 months after TARE.
Selective Internal Radiotherapy (SIRT) Versus Transarterial Chemoembolization (TACE) for the Treatment of Cholangiocellular Carcinoma (CCC). Germany

- Randomized
- SIR Spheres
- Started February 2011
- Estimated Completion Date October 2016
- 24 Patients
- Primary Outcome Measures: Progression-free Survival (PFS)
- Secondary Outcome Measures: Overall Survival (OS) Time to Progression (TTP)
Drug-Eluting Bead, Irinotecan Therapy for Unresectable Intrahepatic Cholangiocarcinoma w/Concomitant Gemcitabine and Cisplatin (DELTIC), USA

- Randomized
- DEB TACE with Irinotecan
- Started July 2012
- Estimated Completion Date July 2016
- 48 Patients
- Primary Outcome Measures:
  Tumor response according to m-RECIST Criteria
- Secondary Outcome Measures:
  Hepatic Progression Free Survival
Future Research

• Prospective studies with pre-determined and standardized data assessment.

• Randomized controlled trials to assess efficacy of trans-arterial therapies in comparison with available systemic chemotherapies.

• Randomized controlled studies comparing different embolization therapies.

• Studies focused on determining the appropriateness of each specific embolization therapy.

• Pre treatment imaging as a tool for choosing the specific embolization therapy.

• Post treatment imaging in evaluation of the efficacy of different therapies.
When is cholangiocarcinoma embolization appropriate?

• Patient Selection
• “To Be or Not to Be”
  OR
  Failure vs Success
  - Does Size Matter?
  - Can preprocedure imaging predict the outcome?
  - Can favorable IR therapy be chosen prospectively?
Prognostic Factors for ICC Survival

- **R0 Resection**: Achieved – 63%
  - 5 Year Survival – 40-63%
  - Local Recurrence – 62%
- Lympho-Vascular Invasion
- Intrahepatic Invasion
- Metastases: 50-75%
- Lymph Nodes Metastases: 30-50% of all patient,
  - 25% tumor < 3cm
- Multifocal Tumors
Patient Selection

- No Other Local Therapies Possible:
  - Poor Surgical Candidates
  - Multiple Bilobar Masses
  - Gross Vascular Invasion
  - Unfavorable Location for Ablation
  - Large Size: Too Big for Ablation or when Surgical Resection would live insufficient amount of functioning liver
- Metastatic disease
Correlation between Tumor Size and Aggressive Futures

- 443 Patients Surgical Resections for ICC
- Perineural Invasion and Regional Lymph Node Metastases are independent risks for microvascular invasion in tumors > 5cm

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<tr>
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<th>&lt; 3cm</th>
<th>3-5cm</th>
<th>5-7cm</th>
<th>7-15cm</th>
<th>&gt; 15cm</th>
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<tbody>
<tr>
<td>Microscopic Vascular</td>
<td>3.6%</td>
<td>24.7%</td>
<td>38.3%</td>
<td>32.9%</td>
<td>55.6%</td>
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<tr>
<td>Invasion</td>
<td></td>
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<tr>
<td>High Tumor Grade</td>
<td>9.7%</td>
<td>19.8%</td>
<td>24.2%</td>
<td>21.1%</td>
<td>31.6%</td>
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The incidence of multiple tumors, vascular invasion, and poorly undifferentiated tumors increased with tumor size (all $P < .005$)
Tumor Size and Possibility of Curative Resection

- Curative Resection/5 year Survival – 10%  
- The 5-year survival rate of 15 patients who had ICC measuring ≤2 cm in greatest dimension without lymph node metastasis or vascular invasion was 100%

1. Spolverato G. Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? Cancer. 2015 Nov 15

Ablation vs Embolization for Treatment of Cholangiocarcinoma Using Size Criteria

• Ablations should be reserved for favorably located tumors < 3 cm, may be even < 2 cm.
• Tumors > 3 cm should be treated with Embolotherapies.
• Even for small tumors, 2-3cm, ablations combined with embolization may improve outcomes.
Tumor Enhancement as Prognostic Factor in Therapy Selection

- 42 patients undergone hepatectomy
- Microvascular Density (MVD) compared with tumor enhancement on CT: 24 < 16HU > 18.

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<th>Low Attenuation Hypo-group-24</th>
<th>Higher Attenuation Hyper-group-18</th>
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<tr>
<td>Size &lt;5/&gt;5cm</td>
<td>7/17</td>
<td>14/4</td>
</tr>
<tr>
<td>Histologic Differentiation Well/Moderately/Poorly</td>
<td>2/15/7</td>
<td>8/6/4</td>
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<td>2 years tumor recurrence</td>
<td>14</td>
<td>4</td>
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<td>Survival: 1-3-5 year</td>
<td>49 – 17 – 17%</td>
<td>78-69-69%</td>
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Nanashima A, *Intrahepatic cholangiocarcinoma: relationship between tumor imaging enhancement by measuring attenuation and clinicopathologic characteristics.* Abdom Imaging. 2013 Aug,
Cholangiocarcinoma

- < 2cm: Ablation
- 2-3 cm: Ablation +/- Embolization
- > 3cm: Embolization

- Hypervascular: TAE
- Hypovascular: TACE, TARE

- Metastatic Disease
- Multiple Tumors
- High Grade
- Gross Vascular Invasion
Embolotherapy for Cholangiocarcinoma: 2016 Update Summary

• Embolotherapy for Cholangiocarcinoma works and improves survival
• Low Toxicities
• High rate of aggressive futures make embolotherapy a preferable modality for treatment of unresectable cholangiocarcinomas
• Mass size correlates with presence of lymphovascular invasion and tumor differentiation
• Cholangiocarcinoma enhancement correlates with tumor grade and patients survival
• More and better quality research needed.