The Management of Localized Bile Duct Cancer: Are there any Indications for Radiation Therapy?

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Disclosures

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• Research funding from Merck paid to institution
Outline: Cholangiocarcinoma Radiation Therapy

- Radiotherapy
- Cholangiocarcinoma (intrahepatic, extrahepatic)
- Perihilar cholangiocarcinoma (Klatskin’s Tumor)
- Adjuvant radiation therapy
- Selection of patients
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Strategies to Deliver Therapeutic Dose Radiation Therapy

- External beam radiotherapy (EBRT)
  - Conformal radiotherapy (CRT)
  - Intensity modulated radiation therapy (IMRT)
  - Stereotactic body radiation therapy (SBRT)
  - Proton radiation therapy
  - Heavy ion radiation therapy (Carbon ions)

- Brachytherapy
  - Interstitial
  - Interluminal

- Intra-operative RT (IORT)
  - Mobile electron unit

- Radioisotopes
  - Iodine 131 Lipiodol
  - Yttrium 90 microspheres
Many Advances in Radiation Therapy

→ improved outcomes for cholangiocarcinoma and other upper GI cancers

- SBRT, hypofractionation
- MR (and other image) guided RT
- Motion management
- Adaptive RT (personalized)
- Artificial intelligence/ automation
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Cholangiocarcinoma

- Most historical RT experience is with fractionated RT +/- brachytherapy
- SBRT/hypofractionation (without stents) may precipitate biliary obstruction, late strictures, if no stent

**Peripheral IHC most well suited for SBRT**

**Extra-hepatic better suited for standard or hyper-fractionation**

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**Biliary Tract Cancers**

- Right hepatic duct
- Left hepatic duct
- Common hepatic duct
- Cystic duct
- Common bile duct
- Gall bladder
- Pancreatic duct
- Duodenum
- Pancreas
- Sphincter of Oddi
- Bile

- Intrahepatic CCA
- Perihilar CCA
- Extrahepatic CCA

- N. America: 3 / 100,000
- Japan: 20 / 100,000
- Common: N India, E Europe, S America, Asia
Role of Radiation Therapy

- No level 1 evidence for radiation therapy (RT)
  - Single institution or multi-centre retrospective reviews
  - Large databases with limited patient details
  - No comparative, prospective trials
  - Heterogeneity (IHC, hilar, distal bile duct, gallbladder cancer)

- Unlike pancreatic cancer, extrahepatic cholangiocarcinoma has a dominant local-regional pattern of failure

- Conventional RT, hyperfractionated and hypofractionated RT appear to have less toxicity compared to SBRT

- Even without a proven survival benefit, there is rationale to maintain local control to preserve biliary function and quality of life

- When RT is used, recommendation is to sequence RT post systemic therapy

### Extrahepatic Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (95% CI)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery plus RT</td>
<td>16.00 (15.00–17.00)</td>
<td>701</td>
</tr>
<tr>
<td>Surgery</td>
<td>9.00 (9.00–11.00)</td>
<td>1372</td>
</tr>
<tr>
<td>RT</td>
<td>9.00 (9.00–10.00)</td>
<td>475</td>
</tr>
<tr>
<td>No surgery or RT</td>
<td>4.00 (3.00–4.00)</td>
<td>2210</td>
</tr>
</tbody>
</table>

### Intrahepatic Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (95% CI)</th>
<th>N</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery with radiation</td>
<td>11.00 (9.00–13.00)</td>
<td>286</td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>6.00 (5.00–6.00)</td>
<td>948</td>
<td></td>
</tr>
<tr>
<td>Radiation alone</td>
<td>7.00 (6.00–8.00)</td>
<td>396</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>3.00</td>
<td>2209</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

University of Michigan Conformal RT: unresectable

Patients

Metastases 47  Med survival 17.2 months
Intrahepatic cholangiocarcinoma 46  13.3 months
HCC 35  15.2 months

- 1.5 Gy bid (individualized, max 90Gy)
- Concurrent hepatic arterial FUdR

- Median tumor size 6 cm
- Local control at 2 years – 90%

Ben Josef et al., JCO, 2005
## SBRT as definitive therapy for cholangiocarcinoma.

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Location</th>
<th>Number of patients</th>
<th>RT dose scheme ± Chemo-therapy</th>
<th>2 y local control</th>
<th>2 y/median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tse [68]</td>
<td>Phase I</td>
<td>Intra-hepatic</td>
<td>10</td>
<td>6 × 4–9 Gy No chemo</td>
<td>65% at 1 y</td>
<td>58% at 1 y 15 months</td>
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<td></td>
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<tr>
<td>Momm [65]</td>
<td>Retrospective</td>
<td>Perihilar</td>
<td>13</td>
<td>32–56 Gy in 3–4 Gy per fraction 6/13 Chemo</td>
<td>Not reported</td>
<td>67% 23.6 months</td>
</tr>
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</tr>
<tr>
<td>Kopek [64]</td>
<td>Retrospective</td>
<td>Intra-hepatic</td>
<td>1</td>
<td>3 × 15 Gy (at isocenter) No chemo</td>
<td>84% at 1 y</td>
<td>15% 10.6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perihilar</td>
<td>26</td>
<td></td>
<td></td>
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<tr>
<td>Polistina [66]</td>
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<tr>
<td>Barney [63]</td>
<td></td>
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<tr>
<td>Jung [62]</td>
<td>Retrospective</td>
<td>Extra-hepatic:</td>
<td>33</td>
<td>53 SBRT 30–60 Gy in 3–5 fractions 5 SBRT boost 1 × 15–18 Gy No chemo</td>
<td>72%</td>
<td>20% 10 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extra-hepatic:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymph nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahadevan [61]</td>
<td>Retrospective</td>
<td>Intra-hepatic</td>
<td>31</td>
<td>10–45 Gy in 3–5 fractions 18 chemo</td>
<td>79%</td>
<td>31% 17 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perihilar</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intra- + extra-hepatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tao [67]</td>
<td>Retrospective</td>
<td>Intra-hepatic</td>
<td>79</td>
<td>50.4–75 Gy in 15–30 fractions 75 chemo</td>
<td>BED ≤ 80.5 Gy 3y 45%</td>
<td>61% 30 months</td>
</tr>
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</tr>
</tbody>
</table>

### Increased risk of acute and late biliary toxicity post SBRT

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A. Méndez Romero, R.A. de Man / Best Practice & Research Clinical Gastroenterology 30 (2016) 603–616
IHC Retrospective Study: MD Anderson/MGH

- 79 inoperable IHC patients
  - Median size: 7.9 cm
  - 58% node positive
  - 20% metastatic disease
  - Child Pugh A 80%

- Doses assigned by proximity to critical structures
- Standard or modestly hypofractionated RT
- Median BED=80.5 Gy
  - 45 Gy covering PTV, up to 100 Gy to central GTV simultaneous boost
  - RT dose: 67.5 GyE (peripheral) and 58.05 GyE (central) in 15 fractions

- Median f/u: 24 months for all pts (range 4-133)

Tao and Crane JCO 2015
Local Control and Survival

RT dose only significant factor

- 48% pts had local PD
- LC significantly improved with higher doses (>95Gy BED)
- 3-yr LC 78% vs 45%

- Med survival 30 months
- OS also significantly improved
- 3-yr OS 73% vs 38%
- Median OS: not reached vs 27 mo.

Tao and Crane JCO 2015
Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma


- Proton radiation: 58 Gy (central), 67.5 Gy (peripheral) in 15 fractions
- 92 patients (44 HCC, 37 IHC, 2 mixed)
- Median follow-up 19.5 months

- Local control at 2 years:
  - HCC 95%
  - IHC 94%

- Overall survival at 2 years:
  - HCC 63%
  - IHC 46%
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Mayo Transplant Protocol for Hilar tumors (Klatskin)

- Perihilar cholangiocarcinoma
  - 3 cm or less
  - Diagnosed by cytology (includes FISH), or CA19-9 >100 + mass + malignant appearing stricture
  - Node negative, no extrahepatic disease

- Staging by CT Liver, US, and bone scan, EUS nodal biopsy if indicated

- Neoadjuvant chemo (5Fu/Xeloda) + concurrent EBRT (45 Gy, 1.5 Gy bid)

- Intra-biliary brachytherapy boost (20-30 Gy LDR equivalent, now w HDR)
  - 4 Gy x 4, (1 cm depth, potentially tighter near bowel)

- Staging laparoscopy

- Continue maintenance chemotherapy until transplant
**Radiation Therapy**

**External beam RT**
- 4,500 cGy in 30 fractions (1.5 Gy given bid over 3 weeks)
  - Using MRI and CT liver fused to planning CT; target includes nodes
- PVI 5FU or Xeloda delivered concurrently

**Brachytherapy**
- Catheters placed endoscopically with cholangiogram to assist
- Original protocol utilized 20-30 Gy LDR equivalent (24-48 hrs)
- Most sites using HDR
  - 4 Gy x 4 (Mayo), or 5 Gy x 3 (CCF) over 2 days prescribed to 1 cm
Orthotopic Liver Transplant (OLT)

- Results:
  - 38 of 71 patients underwent OLT
    - No residual tumor in 16 of 38 explanted livers (42%)
  - 5 yr OS: 82% after OLT vs. 21% after resection (p = 0.022)
  - Recurrence at 5 years: 12% after OLT vs. 58% after resection.

- Updated results (Rosen, n=148)
  - 5 yr OS 55% (all pts)
  - 5 yrs OS 71% (transplanted)
Multi-centre series: Orthotopic Liver Transplant

- Analysis of 287 pts treated on pre-transplant protocols at 12 centers from 1993 – 2010
- Results:
  - 71 patients dropped off transplant list.
  - 117 (54%) of the explanted livers either had no tumor visible on pathology or grade was not attainable.
  - ITT survival at 5 yrs post transplant was 53%
  - ITT RFS at 5 years post transplant was 65%
- Caveat: 193 patients were from one center

Pathologic CR or non-cancer upfront?
Princess Margaret Hilar Cancer Protocol

- 45 Gy in 1.5 Gy twice daily to clinical target volume and nodes
- 75 Gy total in 1.5 Gy twice daily to primary tumor
- Gem/Cisplatin systemic therapy
- Goal: external beam RT: attempt to reduce late biliary toxicity
Princess Margaret Klatskin Protocol

- Medium survival from day 1: 18.8 months (including drop off)
- 11/18 patients dropped off
  - Metastases and/or nodes involved at laparotomy
- 56% survival post transplant (in transplanted patients)
- Audit revealed that some patients had tumors > 3 cm
- Protocol amended to:
  - Decrease delays to start of treatment
  - Strict inclusion criteria: tumors < 3 cm
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Extrahepatic cholangiocarcinoma: Outcomes after Adjuvant Radiation Therapy

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patient (n)</th>
<th>Treatment</th>
<th>5-y OS rate (%); median (mo)</th>
<th>5-y LRC rate (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tororoki et al., (20)</td>
<td>19</td>
<td>Surgery alone</td>
<td>13.5; 10</td>
<td>31.3</td>
<td>Proximal bile duct tumor</td>
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<tr>
<td></td>
<td>17</td>
<td>Surgery plus RT</td>
<td>33.9; 32</td>
<td>79.7</td>
<td></td>
</tr>
<tr>
<td>Gerhard et al., (24)</td>
<td>15</td>
<td>Surgery alone</td>
<td>11; 8</td>
<td>—</td>
<td>Proximal bile duct tumor</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>Surgery plus RT</td>
<td>24; 30</td>
<td>—</td>
<td></td>
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<tr>
<td>Serafini et al., (18)</td>
<td>28</td>
<td>Surgery alone</td>
<td>—; 29</td>
<td>—</td>
<td>Benefit only in distal tumors</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>Surgery plus CRT</td>
<td>—; 42</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Hughes et al., (14)</td>
<td>30</td>
<td>Surgery alone</td>
<td>27; 22</td>
<td>—</td>
<td>Distal bile duct tumor</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>Surgery plus CRT</td>
<td>35; 36.9</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Bhatia et al., (23)</td>
<td>30</td>
<td>Surgery alone</td>
<td>11; 19.2</td>
<td>—</td>
<td>Ampullary tumor</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Surgery plus CRT</td>
<td>48; 40.8</td>
<td>—</td>
<td>From ampullary to proximal bile duct tumor</td>
</tr>
<tr>
<td>Present study</td>
<td>53</td>
<td>Surgery alone</td>
<td>28.2; 27.9</td>
<td>44.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>115</td>
<td>Surgery plus CRT</td>
<td>36.5; 36.4</td>
<td>58.5</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: RT = radiotherapy; CRT = chemoradiotherapy; other abbreviations as in Table 2.*
SWOG S0809 study of Adjuvant Therapy

- Single arm phase II study
- Extrahepatic cholangiocarcinoma or gallbladder cancer
- Resected pT2-4, or node (+), or R1, M0
- Gem/Capecitabine x 4 followed by chemo-RT
- Benefit for R1 patients

Table 3. Pattern of First Relapse

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>EHCC</th>
<th>Distal (n = 38)</th>
<th>Hilar (n = 13)</th>
<th>GBCA (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Local only</td>
<td>3</td>
<td>8</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Local plus distant</td>
<td>5</td>
<td>13</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Distant only</td>
<td>11</td>
<td>29</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>50</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>NOTE. Three patients for whom complete data were not available were excluded. Abbreviations: EHCC, extranepatic cholangiocarcinoma; GBCA, gallbladder carcinoma.</td>
<td></td>
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</tr>
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</table>

- Local failure (LF) with RT: 11/51 (21%)
- Historical LF controls w surgery alone: (35-70%)
RT In BilCap Era?

Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline

Rachna T. Shroff, MD1; Erin B. Kennedy, MHSc2; Melinda Bachini3; Tanios Bekaii-Saab, MD4; Christopher Crane, MD5; Julien Edeline, MD, PhD6; Anthony El-Khoueiry, MD7; Mary Feng, MD8; Matthew H.G. Katz, MD9; John Primrose, MD10; Heloisa P. Soares, MD, PhD11; Juan Valle, MD12; and Shishir K. Maithel, MD13

- 6 months adjuvant capecitabine recommended
- Adjuvant chemo-RT recommended post capecitabine, for R1 extrahepatic or R1 gallbladder ca
- Need to consider goals of care, co-morbidities, competing risks, performance status
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How to select patients best suited for RT?

- Improved biomarkers needed for selection of patients for RT
- KRAS mutations predict for RT resistance in preclinical models
- Clinical data supports poor radiation responses if KRAS mutation, and improved local control if KRAS wild type
  - colon cancer, other solid malignancies
- Recommend including RT in ‘Batch’ trials that link mutations to treatment, in prospective studies
- Anatomical and patient considerations: liver function, enough planned spared liver, performance status, competing risks
Conclusions

- Need for higher level evidence for RT in cholangiocarcinoma
- The risk and significance of local failure provides rationale for RT
  - Longer fractionations (CRT, 15 fractions, 1.5 Gy bid) appear safer than SBRT
- Most cholangiocarcinomas are KRAS WT, suggesting better RT responsiveness compared to pancreatic cancer
- High dose RT can control unresectable IHC and should be considered post systemic therapy
- RT post surgery improves local control, especially for R1 resection
- Recommend systemic therapy prior to RT, if RT recommended
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