Cholangiocarcinoma

GI Practice Guideline

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This guideline is a statement of consensus of the GI Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.
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Background/Incidence

- Rare (<400 cases/yr in Canada). Most pts >65.
- Risk factors PSC, choledochal cysts, Caroli's disease, pyogenic cholangiohepatitis e.g clonorchis and Oriental cholangiohepatitis, environmental agents (thorium, radon, nitrosamines, dioxin, asbestos).
- 10% intrahepatic; perihilar and distal extrahepatic (25%) more common. 10% diffuse.
## Staging

**TMN Classification for Extrahepatic Bile Duct Tumors**

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to the bile duct histologically</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades beyond the wall of the bile duct</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis N0 M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3 N0 M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1-3 N1 M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4 Any M M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4 Any M M1</td>
</tr>
</tbody>
</table>


*Hilar, celiac, periduodenal, peripancreatic, and superior mesenteric nodes*
Treatment – Resectable

- Criteria for resection vary; minimal requirements:
  - Absence of N2 nodal metastases or distant liver metastases
  - Absence of invasion of the portal vein or main hepatic artery (although some centers support en bloc resection with vascular reconstruction)
  - Absence of extrahepatic adjacent organ invasion
  - Absence of disseminated disease

Treatment – Potentially Resectable

- Neoadjuvant therapy: one small retrospective series suggests benefit
  - McMasters et al, Am J Surg 1997 Dec;174(6):605-8: Three out of 9 pts with preop chemoradiation (5FU) had pCR and all were R0 resections compared to 54% of 31 pts without preop treatment.
    - ongoing trial through NCI: Registry Study of Neoadjuvant Chemoradiation & Transplant for Cholangiocarcinoma Patients
  - Portal vein embolisation to induce hypertrophy – inconsistent results to date; not universally recommended
    - Preoperative percutaneous portal vein embolization: evaluation of adverse events in 188 patients. Di Stefano DR; de Baere T; Denys A; Hakime A; Gorin G; Gillet M; Saric J; Trillaud H; Petit P; Bartoli JM; Elias D; Delpero JR SO Radiology 2005 Feb;234(2):625-30
Treatment – Adjuvant Therapy

- Adjuvant therapy after R0 resection – predominantly retrospective series, usually including gallbladder and/or peri-ampullary and/or pancreatic neoplasm.

- Chemotherapy: Randomized trial (Japan) negative using MMC/5FU; Takada et al Cancer 2002 Oct 15;95(8):1685-95 [5YS 41 vs 28%, NS].


- Chemoradiotherapy: Conflicting retrospective single – arm series (most include R1 and R0 resections). Randomized trial which also included pancreatic cancers: minimal positive effect (trend towards better 2 YS 67 vs 63%), Klinkenbijl et al, Ann Surg 1999 Dec;230(6):776-82.

- Adjuvant therapy after R1 resection - some retrospective series suggest benefit to radiation. No data found specifically for cholangiocarcinoma with R1 resection except

- Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. AU Todoroki T; Ohara K; Kawamoto T; Koike N; Yoshida S; Kashiwagi H; Otsuka M; Fukao K SO Int J Radiat Oncol Biol Phys 2000 Feb 1;46(3):581-7. 5YS 34 vs 13 % (47 pts)
  - Mix of Intraoperative and Postoperative radiation

- Observation or clinical trial or chemoradiotherapy (for R1 disease) are acceptable options

- ongoing trial through NCI Capecitabine vs observation for R0 or R1 resection
Treatment – Palliative Therapy

- Median survival 7-12 months
- Supportive care, chemoradiation, trial, or systemic chemotherapy are all valid options
- 14 ongoing trials registered at NCI (e.g. Gemcitabine/oxaliplatin/capecitabine, erlotinib, hyperthermia...)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>RR(%)</th>
<th>Median Survival (months)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU</td>
<td>0-34</td>
<td>~6</td>
<td>34% if interferon added</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>20</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Epirubicin 60mg/m² q21d + Cisplatin 50mg/m² q21d + Fluorouracil 200mg/m² daily continuous infusion</td>
<td>19-40</td>
<td>9-12</td>
<td>Used at LRCP. Less toxic then 5FU-Etop.-LV</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>13-60</td>
<td>~8</td>
<td>Unclear if 5FU adds benefit</td>
</tr>
<tr>
<td>Gem / Cisplatin</td>
<td>28-35</td>
<td>9-11</td>
<td></td>
</tr>
<tr>
<td>Gem / Oxaliplatin</td>
<td></td>
<td>15</td>
<td>In good PS pts</td>
</tr>
<tr>
<td>Gem / Capecitabine</td>
<td></td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

Reference

Decision Tree

Presentation
Biliary mass          Jaundice

Required Work-up

• Confirm diagnosis preoperatively, if possible.
• Consider baseline serum CEA together with CA19-9 (sensitivity/specificity for diagnosis determined by cutoff values used and biliary tract diseases e.g. PSC, cholangitis, etc.)
• CT abdomen/pelvis, CXR

• Absence of N2 nodal metastases or distant liver metastases, absence of invasion of the portal vein or main hepatic artery, absence of extrahepatic adjacent organ invasion, absence of disseminated disease

Surgical Assessment

Unresectable/Palliative intent

Ensure biliary drainage (stent bypass, percutaneous drain)

Palliative therapy

• Local therapy
  • Consider ablation (RFA, cryotherapy)
  • Consider chemoradiation or radiation + brachytherapy

• Systemic therapy
  • Trial
  • BSC
  • Consider palliative chemotherapy

Resectable/Curative intent

Surgery

LRCP referral MO + RO

Incomplete resection

R0 resection

Observation or trial
Authors, Contact Information

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