Biliary tumors

E-AHPBA Postgraduate course, MUMC 2016

BILIARY TRACT TUMORS

Bas Groot Koerkamp, MD PhD
Erasmus MC
Department of Surgery
Division of HPB and Abdominal Transplant
Rotterdam, Netherlands
DISCLOSURE

• Nothing to disclose.
BILIARY TUMORS - OVERVIEW

• Biliary anatomical variations
• Classification
  • Intrahepatic cholangiocarcinoma
  • Perihilar cholangiocarcinoma
  • Gallbladder cancer
• Systemic therapy
• Intraductal Papillary Neoplasm of the Bile duct (IPNB)
• Gallbladder polyp
BILIARY ANATOMICAL VARIATIONS

A 57%
B 12%
C 20%
D 6%
E 3%
F 2%
BILIARY TUMORS - CLASSIFICATION

Gallbladder cancer
- Including cancer arising from cystic duct

Cholangiocarcinoma
- AJCC 6th edition: intra- vs extrahepatic
- AJCC 7th edition: intrahepatic, perihilar, distal
- Intrahepatic: proximal to second-order bile duct
- Distal: distal to origin cystic duct
- Perihilar: in between second-order bile duct and cystic duct
Biliary tumors

BILIARY TUMORS

- **intrahepatic**
  - IHC
  - PHC

- **perihilar**
  - PHC

- **distal**
  - dCCA

10%
50%
40%
INTRAHEPATIC - DIAGNOSIS

- Incidence 1:100,000, about 5,000 annually in EU; increasing
- RF similar to HCC: cirrhosis, viral hepatitis, alcohol, DM
- Symptoms: weight loss, malaise, abdominal discomfort
- Tumor markers: 50% CA19-9 >100
- CT: large irregular hypo-intense mass on non-contrast, peripheral enhancement in arterial phase, progressive enhancement in venous phase
- Subtypes: mass-forming (85%), intra-ductal, periductal
- Rule out metastatic disease (CRC, gastric, breast)
- Biopsy not required
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INTRAHEPATIC - STAGING

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (intraductal tumor)</td>
</tr>
<tr>
<td>T1</td>
<td>Solitary tumor without vascular invasion</td>
</tr>
<tr>
<td>T2a</td>
<td>Solitary tumor with vascular invasion</td>
</tr>
<tr>
<td>T2b</td>
<td>Multiple tumors, with or without vascular invasion</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with periductal invasion</td>
</tr>
</tbody>
</table>

ANATOMIC STAGE/PROGNOSTIC GROUPS

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
INTRAHEPATIC - RESECTION

Only if:
1. Complete resection feasible, considering liver function
2. Resection likely to improve survival
3. Acceptable mortality risk

Unfavorable risk factors:
• Multiple tumors – multifocal, intrahepatic mets, satellites
• Vascular invasion
• Perforation visceral peritoneum (T3=stage III)
• Nodal metastasis (N1=stage IV)
Biliary tumors

**INTRAHEPATIC - RESECTION**

- 30-40% resectable; 15% resected in SEER
- Staging laparoscopy uncertain benefit.
- 75% at least 4 segments resected
- 25% hepaticojejunostomy
- Lymphadenectomy of regional nodes recommended for prognostic value.
- No adjuvant therapy. Ongoing trials: e.g., ACTICCA.
Biliary tumors

INTRAHEPATIC - OUTCOMES

• Mortality 1-5% in high-volume center; higher if cirrhosis, extended resection, or biliary drainage and reconstruction.
• Median RFS 20 months; 60% intrahepatic only, 20% extrahepatic only, 20% both\(^1\)
• Median OS 30 months with 5-year OS 32%, averaged over large series\(^2\)
• Liver transplant: similar to HCC if solitary <2cm in cirrhotic\(^3\)
• Several prognostic scores outperform AJCC; additional postoperative poor prognostic factors are positive margin and poor tumor differentiation.
• Presence of multiple RF does not preclude 5-year OS.

\(^1\)Hyder, Surgery 2013;153:811
\(^2\)Groot Koerkamp, JSO 2014;110:585
\(^3\)Sapisochin, AnnSurg 2014;259:944
Biliary tumors

**Intrahepatic cholangiocarcinoma (iCCA)**

- **TNM stage I**
  - Single tumor
  - Resectable (30-40%)
    - Curative resection
    - Observation
    - 5-yr survival R0: 40%
    - 5-yr survival N1 and VI: 20%

- **TNM stage II**
  - Single or multinodular vascular invasion (VI)
  - Resectable (30-40%)
    - Curative resection
    - Enroll in studies of adjuvant therapy

- **TNM stage III**
  - Visceral peritoneum perforation, local hepatic invasion
  - Unresectable (60-70%)
    - Local-regional therapy*
    - RF/TACE: median survival 15 mo
    - Chemotherapy: median survival 12 mo

- **TNM stage IV**
  - Periductal invasion, N1, M1
  - Extrahepatic disease
    - Gemcitabin and cisplatin*

* Konstantinidis, Cancer 2016;122(5):758

Bridgewater, J. Hepatology 2014;60:1268
PERIHILAR - DIAGNOSIS

- Incidence 2:100,000, about 10,000 in EU
- Presentation: painless jaundice (80%)
- CT: small perihilar mass with biliary dilatation, PV involvement with atrophy
- Hilar nodes (N1) are stage IIIb
- Biliary extent: Bismuth classification
- PV and HA involvement
- Brush cytology has low yield
- Biopsy not required
### PERIHILAR - STAGING

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>T0</td>
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</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor invades beyond the wall of the bile duct to surrounding adipose tissue</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor invades adjacent hepatic parenchyma</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades unilateral branches of the portal vein or hepatic artery</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement</td>
</tr>
</tbody>
</table>

### ANATOMIC STAGE/PROGNOSTIC GROUPS

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2a-b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4</td>
<td>N0-1</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>
PERIHILAR – DRAINAGE, PVE

• Biliary drainage of future liver remnant (FLR) to decrease liver failure risk.
• EBD: more cholangitis, more interventions
• PTCD: risk of peritoneal seeding
• FLR>50%: consider resection without drainage\(^1\)
• FLR <40%: consider PVE, drawback: you have to commit to left- or right-sided resection

\(^1\)Wiggers, JACS 2016 Apr 2
PERIHILAR - RESECTION

- Staging laparoscopy: 25% mets
- Staging laparotomy: up to 50% unresectable
- Caudate lobectomy
- Hilar lymphadenectomy
- PV reconstruction may be necessary
- No-touch technique with default PV resection and reconstruction debated
- HA reconstruction debated; increased postoperative mortality and poor biology
PERIHILAR - OUTCOMES

- 90-day mortality 10% (mostly liver failure) in two nation-wide series.\textsuperscript{1,2} With ALPSS 40%.\textsuperscript{3}
- Risk score for 90-day mortality: preop cholangitis, FLR<30%, PV reconstruction, incomplete FLR drainage.
- Median RFS 26 months; recurrence plateau at 8 years.\textsuperscript{4}
- Only 18% initial isolated local recurrence.\textsuperscript{4}
- Median OS 38 months after resection in Western series.
- Liver transplant: median OS 60 months (65% PSC)
- RF: N1, R1, poor tumor differentiation
- Only N1 precludes survival beyond 7 years.
- Several prognostic models that outperform AJCC.\textsuperscript{5}

\textsuperscript{1}Nuzzo, Arch Surg 2012;147:26
\textsuperscript{2}Farges, BJS 2013;100:274
\textsuperscript{3}Serenari, HPB 2016;18:419
\textsuperscript{4}Groot Koerkamp, JACS 2015;221(6):1041
\textsuperscript{5}Groot Koerkamp, Ann Onc 2015;26(9):1930
Biliary tumors

GALLBLADDER CA - PRESENTATION

- Incidence 3 in 100,000; 15,000 in EU
- Higher in Chili, Northern India
- RF: chronic inflammation, stones (90%)
- 2/3 incidental: at path exam after lap chole for stones
- 1/3 symptomatic: presenting with RUQ pain, weight loss, and mass on CT
- 40% of symptomatic patients are jaundiced (Chilean perihilar)
- 60% in fundus, 30% body, 10% neck
GALLBLADDER CA - STAGING

- Diagnostic work-up: CT chest-abdomen-pelvis
- GB facing liver has no peritoneum
- lap chole dissection between muscularis and cystic plate: R1 unless T1a
- Incidental: find out whether GB perforation, site of tumor, T-stage, cystic duct margin
- DD: Xanthogranulomatous cholecystitis up to 16%
Biliary tumors

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<tr>
<td>T1</td>
<td>Tumor invades lamina propria or muscular layer (Figure 20.3)</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor invades lamina propria</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades muscular layer</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver (Figure 20.4)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NX</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes</td>
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<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
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</tr>
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</table>
# GALLBLADDER CA - INCIDENTAL

<table>
<thead>
<tr>
<th>T-stage</th>
<th>Number of patients</th>
<th>Percentage of all stages (%)</th>
<th>Residual disease - (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>8</td>
<td>8</td>
<td>38</td>
</tr>
<tr>
<td>T2</td>
<td>67</td>
<td>68</td>
<td>57</td>
</tr>
<tr>
<td>T3</td>
<td>22</td>
<td>22</td>
<td>77</td>
</tr>
<tr>
<td>All stages</td>
<td>97</td>
<td>100</td>
<td>59</td>
</tr>
</tbody>
</table>

- MSK, 1998-2009
- n=135 re-exploration
- 61% recurrent disease
- No recurrent disease: median DFS 8 years, 10-year OS 60%
- Recurrent disease: median DFS 1 year, 10-year OS 15%

→ benefit of resection appears small

Pawlik, JGS 2007;11(11)1478
Butte, JACS 2014;219(3):416
GALLBLADDER CA - RESECTION

- Staging laparoscopy for peritoneal or intrahepatic mets.
- Consider sampling aortocaval or celiac nodes (N2, stage IV).
- 2-3 cm wedge resection of segment IVb and V en-bloc with gallbladder with lymphadenectomy of the hepatoduodenal ligament.
- En-bloc resection of colon or duodenum if adherent to tumor: 50% has tumor involvement at final path (T3, stage III).
- Extrahepatic bile duct resection if cystic duct margin involved.
Biliary tumors

GALLBLADDER CA – DON'T...

• Don't resect patients with M1 or N2 disease.
• Don't resect patients with HA or PV involvement (T4, stage 4).
• Don't resect patients with GBC presenting with jaundice: no survivors beyond 2 years.¹
• Don't perform a routine extrahepatic bile duct resection to clear possible microscopic disease.²
• Don't perform an extended liver resection for (occult) satellites or intrahepatic mets.
• Don't perform an extended lymphadenectomy.
• Don't perform port-sites resections for incidental GBC: disfiguring without survival benefit.

²Wiggers, HPB 2013
GALLBLADDER CA - OUTCOMES

- Postoperative mortality 1%
- Median OS without treatment: 5 months
- Only 16% complete resection (SEER)
- Median DFS: 1 year
- 85% of initial recurrence is distant (peritoneum, liver, lung)
- RF for recurrence: N1, R1, moderate/poor differentiation
- Other poor prognostic factors: bile spillage, jaundice, T2 on hepatic side (vs peritoneal side)
- Only 1 prognostic model for benefit adjuvant (chemo)rad.

Wang, JCO 2011;29(35):4627
http://skynet.ohsu.edu/nomograms/
SYSTEMIC TREATMENT

• ABC-02: the only phase 3 RCT for biliary tumors
• ICC, PHC, GBC, or ampullary cancer
• locally advanced/metastatic/recurrent
• n=420, mostly WHO 0/1
• gemcitabine +/- cisplatin
• Superior median OS in gem-cis group: 12 vs 8 months.
• Similar HR for all (extent of) disease subgroups
• Challenge: get patients requiring biliary drainage and recurring cholangitis to chemotherapy
• No RCT in adjuvant setting: ACTICCA is recruiting

Valle, NEJM 2010;362:14
IPNB

- Intraductal papillary neoplasm of the bile duct
- Intraductal growth (vs nodular-sclerosing)
- Precursor is exophytic (vs flat biliary dysplasia)
- 2010 – first appearance in WHO classification
- intrahepatic, perihilar, or distal
- 10% of bile duct tumors
- 75% invasive component at resection
- Diagnostic work-up and treatment as cholangiocarcinoma

Rocha, Hepatology 2012;56:1352
GALLBLADDER POLYP

- 5% healthy adults has gallbladder polyp of wall thickening.
- If polyps <12mm: no GBC\(^1\)
- If polyp >20mm: 59% GBC\(^2\)
- Guidelines: resect polyp if >10mm
- Exception: PSC, resect if >5mm
- Staging: CT, consider EUS to determine invasiveness
- Treatment: cholecystectomy, or en-bloc liver resection if concern invasion
- Avoid gallbladder perforation (1/3 in lap chole)
- Follow-up <10mm: 3 large series no GBC

\(^1\)Kozuka, Cancer 1982;50(10):2226
\(^2\)Konstantinidis, JGS 2012;16(3):549
TAKE HOME MESSAGES

• Scrutinise imaging before and after surgery.
• Know and anticipate biliary and vascular variants.
• A biopsy is rarely needed prior to surgery: imaging determines management, biopsy peritoneal seeding, brush false-negative.
• Perform a quick staging laparoscopy in all patients with biliary tumors.
• Criteria for resection: complete resection is feasible, likely to improve survival, and acceptable postoperative mortality.
• Biliary tumors should only be treated in a tertiary referral center. Don't do a perihilar cholangio as your first case.
SELECTED REVIEW'S

- Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. – J Hep 2014;60:1268