The Pathologies of the Intra- and Extra-hepatic biliary tree

Cholangiocarcinoma: Surgical Treatment

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U.O.C. Chirurgia generale e Trapianti d’Organo
Sapienza Università di Roma
Classification of cholangiocarcinomas

Less than 10% of all the hepato-biliary tumors

**INTRAHEPATIC (PERIPHERAL)**
- 20-30%

**Hilar**
- 60-70%

**Distal**
- 5-10%

**EXTRAHEPATIC**
Peripheral cholangiocarcinoma

20–30% of cholangiocarcinomas are intrahepatic mass; however, peripheral cholangiocarcinomas may also be polypoid or focally stenotic. Excluding the nodular intrahepatic type (60-70% of cases), about 3/4 of cholangiocarcinomas manifest as a focal stricture and 1/4 are polypoid or diffusely stenotic.
Peripheral cholangiocarcinoma

Staging systems

**UICC/AJCC Classification**

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Solitary tumour without vascular invasion</td>
</tr>
<tr>
<td>T2</td>
<td>Solitary tumour with vascular invasion or multiple tumours, none &gt;5 cm in the greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Multiple tumours &gt;5 cm or tumour involving a major branch of the portal or hepatic vein(s)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</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>T4</td>
<td>N0</td>
<td>M0</td>
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<tr>
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<td>Any T</td>
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<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Absence of nodal involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Presence of regional lymph-node involvement</td>
</tr>
<tr>
<td>M0</td>
<td>Absence of metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Presence of metastases</td>
</tr>
</tbody>
</table>

**LCSGJ Classification**

- MF: mass forming
- PI: periductal infiltrating
- IG: intraductal
- a) Papillary
- b) forming a thrombus
Radical surgery is the only therapeutic option that can ensure a long-term survival.

Factors related to patient survival:

- gross type (size, multifocality, vascular, serosal and biliary involvement)
- Local extent
- lymph-node involvement
- microscopic and molecular biological patterns
Curative resection (Ro) is the most effective treatment and the only therapy associated with prolonged disease-free survival.

No agreement on the indications for surgical resection

Ro only in patients with:
- single lesion
- negative lymph nodes
- resectable hepatic margins of $>1$ cm
- no gross intrahepatic biliary infiltration
Peripheral cholangiocarcinoma

Lymphadenectomy

The rational extent of radical lymphadenectomy not clearly defined. No consensus on the role of lymph-node dissection.

Incidence: 43–62%

Lymph-node involvement associated with unfavourable prognosis

long-term survival following aggressive surgical resection including lymph-node dissection
Peripheral cholangiocarcinoma

Results and survivals

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Morbidity (%)</th>
<th>30-Day mortality (%)</th>
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<tbody>
<tr>
<td>Valverde [7]</td>
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<td>Lang [1]</td>
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<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>N+ (%)</th>
<th>IM (%)</th>
<th>Median survival (months)</th>
<th>1-Year</th>
<th>3-Year</th>
<th>5-Year</th>
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<tr>
<td>Isa [23]</td>
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<td>Okabayashi [24]</td>
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<td>-</td>
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<td>Uenishi [25]</td>
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<td>33</td>
<td>36</td>
<td>18</td>
<td>61</td>
<td>40</td>
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National Database Italian Chapter of IHPBA
January ‘90 – May ’08: 16 centres

- Milano
  - Ospedale San Paolo
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  - San Raffaele

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- Palermo
  - ISMETT

Torino 24/9/2010

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Torino 24/9/2010
Enrolled patients: 434 (M/F: 234/191)
Age (mean): 63.9 year (range 29-84)
Joundice: 60 (13.8%)
Preoperative biliary drainage: 37 (61.6%)

<table>
<thead>
<tr>
<th>Mass-Forming</th>
<th>Periductal infiltrating</th>
<th>Intraductal</th>
<th>Mixed</th>
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<tbody>
<tr>
<td>341 (78.5%)</td>
<td>38 (8.7%)</td>
<td>5 (1.4%)</td>
<td>46 (10.5%)</td>
</tr>
</tbody>
</table>

Diameter (mean): 62 mm (range 10-250 mm)
Number (single/multiple): 293 / 140
Vascular invasion: 211 (48.6%)
Minor resection  
130 (29.9%)  
Wedges 17  
Segmentect 51  
Bi-segmentect 62

Major resection  
220 (50.7%)  
R- hep 77  
L-hep 65  
Other 78

Extended resection  
84 (19.4%)  
Ext-R 65  
Ext-L 19

Median 31 months

% survival

0.0 0 12 24 36 48 60 72 84 96 108 120

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

% survival

Months

80% 45.6% 30.8%
Hilar cholangiocarcinoma arises from the extrahepatic bile ducts (right and left hepatic ducts at or near their junction) and is considered an extrahepatic carcinoma.
Hilar cholangiocarcinoma

Staging systems

**Bismuth-Corlette Classification**

- Type I: Neoplasm arises near the biliary confluence without involvement of the left and right biliary ducts
- Type II: Neoplasm arises at the biliary confluence with extension to left and right ducts
- Type IIIa: Neoplasm arises at the biliary confluence with extension to the right hepatic duct up to the second order ducts
- Type IIIb: Neoplasm arises at the biliary confluence with extension to left biliary duct up to the second order ducts
- Type IV: Neoplasm arises at the biliary confluence with bilateral extension to the second order biliary ducts

**UICC/AJCC Classification**

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<td></td>
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<td>M0</td>
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<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

- T: Carcinoma in situ
- T1: Tumour is confined to biliary duct
- T2: Tumour invades through entire biliary duct wall
- T3: Tumour invades liver, gallbladder, main branches of portal vein or hepatic artery (right or left)
- T4: Tumour invades portal vein trunk, proper hepatic artery or other surrounding organs (colon, stomach, duodenum)

- N0: No lymph-node metastases
- N1: Presence of regional lymph-node involvement
- M0: No metastases
- M1: Presence of metastases
Radical surgery is the only therapeutic option that can ensure a long-term survival.

Factors related to patient survival:

1) macroscopic aspect
2) local extent
3) lymph-node involvement
4) distant metastases
5) histological characteristics

Poorly differentiated tumor
Hilar cholangiocarcinoma
Resectable or not?

A standardised definition has not yet been agreed upon, especially between Japanese and Western authors

**Absolute contraindications**
- bilateral extension to the second order intrahepatic biliary radicles, distant metastases

**Not absolute contraindications**
- portal infiltration, lobar atrophy, adjacent extrahepatic organ invasion

**Extended lymphadenectomy?**
- not yet proved that it guarantees improvement in survival
Hilar cholangiocarcinoma

In presence of resectable tumour at preoperative studies, a decision must be made considering:

1) jaundice
2) concomitant presence of infection
3) extent of the tumour along the biliary tract
4) evaluation of remnant liver
In presence of jaundice without signs of infection and in absence of lobar atrophy, surgery can be directly performed.

In presence of cholangitis, preoperative biliary drainage (PTBD) is mandatory, preferably unilateral on the future remnant liver, bilateral or multiple if bilirubin level does not decrease or cholangitis persists.
Hilar cholangiocarcinoma

Lobar atrophy and future remnant liver

In presence of homolateral lobar atrophy, the atrophic lobe does not need draining, unless the patient presents signs of sepsis sustained by the undrained lobe.

When the volume of the future remnant liver is less than 30–40% of the total liver volume, it can prove useful to adopt the technique of portal vein embolisation (PVE).
## Volumetric evaluation: MeVis

<table>
<thead>
<tr>
<th>Territory</th>
<th>Volume (in ml)</th>
<th>(relative) (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>55</td>
<td>(3.5%)</td>
</tr>
<tr>
<td>II</td>
<td>135</td>
<td>(8.6%)</td>
</tr>
<tr>
<td>III</td>
<td>124</td>
<td>(7.9%)</td>
</tr>
<tr>
<td>IVa</td>
<td>132</td>
<td>(8.4%)</td>
</tr>
<tr>
<td>IVb</td>
<td>42</td>
<td>(2.7%)</td>
</tr>
<tr>
<td>V</td>
<td>113</td>
<td>(7.2%)</td>
</tr>
<tr>
<td>VI</td>
<td>252</td>
<td>(16.1%)</td>
</tr>
<tr>
<td>VII</td>
<td>266</td>
<td>(17.0%)</td>
</tr>
<tr>
<td>VIII</td>
<td>451</td>
<td>(28.7%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1569</strong></td>
<td>(100.0%)</td>
</tr>
</tbody>
</table>
Hilar cholangiocarcinoma

PVE

Low rate of complications, measurable hypertrophy of the non-embolized lobe.
PVE does not change long-term survival
Indications: still unclear because of the few data regarding the minimal hepatic volume required to tolerate surgery without serious complications.
In the literature, the yield of laparoscopy is variable: 20-40% of preoperatively misdiagnosed lesions are detected.

High accuracy in the identification of peritoneal and hepatic metastases, but low sensibility (even with ultrasound support): it does not allow identification of patients with local advanced disease or N+.

In advanced disease: its use could be helpful (high percentage of metastatic disease)
### Extrahepatic bile duct resections

<table>
<thead>
<tr>
<th>Common hepatic duct without obstruction of confluence</th>
<th>Extrahepatic bile duct alone</th>
</tr>
</thead>
</table>

#### Caudate resections

<table>
<thead>
<tr>
<th>Hepatic duct confluence and caudate branches</th>
<th>Independent caudate lobectomy</th>
</tr>
</thead>
</table>

#### Central resections

<table>
<thead>
<tr>
<th>Left medial (B4) segmental ducts</th>
<th>Left medial sectionectomy with caudate lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right anterior (B5,B8) segmental ducts</td>
<td>Right anterior sectionectomy with caudate lobectomy</td>
</tr>
<tr>
<td>Right anterior (B5,B8) and left medial (B4) segmental ducts</td>
<td>Central hepatic bisegmentectomy with caudate lobectomy</td>
</tr>
</tbody>
</table>

#### Right resections

<table>
<thead>
<tr>
<th>Right anterior (B5,B8) and posterior (B6,B7) segmental ducts</th>
<th>Right hepatectomy with caudate lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right anterior (B5,B8), posterior (B6,B7) and left medial (B4) segmental ducts</td>
<td>Right trisectionectomy with caudate lobectomy</td>
</tr>
</tbody>
</table>

#### Left resections

<table>
<thead>
<tr>
<th>Left lateral (B2,B3) and medial (B4) segmental ducts</th>
<th>Left hepatectomy with caudate lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lateral (B2,B3), medial (B4) and right anterior (B5,B8) segmental ducts</td>
<td>Left trisectionectomy with caudate lobectomy</td>
</tr>
</tbody>
</table>
National Database Italian Chapter of IHPBA
17 centres

- Patients resected: **440** (Jan 1992 - Dec 2007)
- Mean age: 64 years (*range* 30 – 95)
- M / F: 250/190
- Jaundice: 70% (304)
- Preoperative biliary drainage: 67% (294)
- Morbidity after preoperative biliary drainage: **22%**
- Right PVE: **8%** (37)
- 88 patients underwent staging laparoscopy
- *peritoneal carcinomatosis*: 1 patient (1.1%)
National Database Italian Chapter of IHPBA
Bismuth-Corlette Classification

Type 1  36 (8.2%)
Type 2  80 (18.2%)
Type 3  304 (69.1%)
Type 4  20 (4.5%)
Mortality: 38 (8.6%)
- after biliary resection 0 %
- after liver resection 10.1%

Morbidity: 191 (47.5%)
- after biliary resection 46.8%
- after liver resection 47.6%

Type of hepatectomy (376 patients)
Right hepatectomy 172 (45.8%)
Left hepatectomy 182 (48.4%)
Mesohepatectomy 22 (5.8%)

with caudectomy: 293 / 376 (78%)
Overall survival (440 cases)
Liver surgery

Experience of U.O.C. General Surgery and Organ Transplantation, Policlinico Umberto I

Liver resection: > 700 cases

Liver TX from CD: 517

Liver TX from LD: 9
Peripheral cholangiocarcinoma
Case history (Jan 2000-Oct 2010)

Hepatic resection (n = 390 patients)

- Metastases: 44%
- HCC: 26%
- Haemangioma: 12%
- Cholangiocarcinoma: 7%
- Idatid cyst: 6%
- LDLT: 2%
- Hepatic cyst: 1%
- Other: 2%

27 cases
Peripheral cholangiocarcinoma: 27 cases

13 left hepatectomies (B2, B3)
7 right hepatectomies (B5, B6, B7, B8)
2 right trisectionectomies (B 4, B5, B6, B7, B8)
3 segmentectomies (B 5 and B6)
1 trisegmentectomy (B6, B7, B8)
1 central hepatic bisegmentectomy (B4, B5, B8)
Extrahepatic cholangiocarcinoma
Case history (Jan 2000-Sep 2010)

15 cases

Hilar: 10

Distal: 5

4 hepaticojejunostomies
2 Right hepatectomies (B5, B6, B7, B8 + B1)
3 left hepatectomies (B2 B3 + B1)
1 central hepatic bisegmentectomy (B4, B5, B8 + B1)

4 DCP
Peripheral cholangiocarcinoma
Liver transplantation

No data in literature on results of adjuvant and neoadjuvant treatments in transplantation.

Transplantation does not represent a treatment option for peripheral cholangiocarcinoma. Its use must be restricted to clinical trials.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Institution</th>
<th>N</th>
<th>1-Year Survival</th>
<th>3-Year Survival</th>
<th>5-Year Survival</th>
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<tr>
<td>O’Grady [4]</td>
<td>1988</td>
<td>King’s College</td>
<td>13</td>
<td>38</td>
<td>10</td>
<td>10</td>
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</tr>
<tr>
<td>Pichlmayr (2) [9]</td>
<td>1995</td>
<td>Hannover</td>
<td>18</td>
<td>13.9</td>
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<td>Yokoyama [10]</td>
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<td>42</td>
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<td>Becker N [13]</td>
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<td>280</td>
<td>74</td>
<td>-</td>
<td>38</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

*Nationwide follow-up survey
Hilar cholangiocarcinoma
Liver transplantation

Increased surgical radicality, curative intent
Indications not clearly defined in the literature

Early studies: 3-year survival: 20%; recurrence rate: 57%

Liver transplantation + pancreatoduodenectomy: 14% of postoperative mortality; 4-year survival: 30%
(Neuhaus et al.)

Cluster transplantation (liver, pancreas, duodenum): 18% of postoperative mortality; 5-year survival of 9.1% (Starzl et al.)
Adjuvant and neoadjuvant treatments

Adjuvant 5-FU chemotherapy with external radiotherapy; median survival of 16.7 months (Iwatsuki et al.)

University of Nebraska protocol: neoadjuvant treatment with iridium-192 + 5-FU chemotherapy. Excluded patients: 35%. After transplantation: mortality rate 27%; 3-year survival 45%; recurrence 18%.

Mayo Clinic protocol: neoadjuvant external and intraluminal (Ir-192) radiation therapy + 5-FU or capecitabine chemotherapy. Excluded patients: 39%. After transplantation: 5-year survival 76%; recurrence 17%.

At present, studies are limited; only adjuvant aggressive treatment seems to significantly improve long-term outcome.
# Hilar cholangiocarcinoma

Liver transplantation: long-term survivals

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Institution</th>
<th>Patients</th>
<th>1-year</th>
<th>Survival 3-year</th>
<th>5-year</th>
<th>1-year</th>
<th>DFS 3-year</th>
<th>5-year</th>
</tr>
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*, Cluster transplantation; **, Liver transplantation + pancreatoduodenectomy; ***, Neoadjuvant radiotherapy + chemotherapy; DFS, Disease-free survival
Liver transplantation for cholangiocarcinoma: case history

- 69% Cholangiocarcinoma
- 29% Other
- 2% HCC

526 cases

4 peripheral CC
6 hilar CC
Conclusions: peripheral cholangiocarcinoma

- Higher survival rates after curative hepatectomy are obtained in high volume centres.
- Ro resection is still the most important factor for long term survival.
- No standardized criteria have been recognized for the selection of patients eligible for resection.
- The role of limphadenectomy is still unclear.
- For the moment, no protocols of liver transplantation are on the way for the treatment of this tumor.
Conclusions: hilar cholangiocarcinoma

- Operative risk for this tumor is higher than that of liver resection for other diseases.
- The best results are related to aggressive surgical policy.
- Effective complementary therapies are strongly needed.
- Protocols composed by neoadjuvant therapies and liver transplantation seem to give excellent results in a very selected population of patients.
- Organ shortage represents the bigger limit to the expansion of this approach.