Update on Cholangiocarcinoma

Judy Wyatt
Belfast, June 2017

Update on Cholangiocarcinoma

- 1200 pa in England.
- Around 20% operable, around 10% 5 yr survival

Liver resections in Leeds, 12 years 2005-2017

Liver resections in Leeds, 12 years 2005-2017

Liver resections in Leeds, 12 years 2005-2017

Pub med “Cholangiocarcinoma + pathology” 1979 - 2015

Summary – update on cholangiocarcinoma

- Illustrate handling and reporting resection specimens
- Staging, prognostic factors
- Distinguish intrahepatic from perihilar CC
- New insights – stroma, cell of origin, molecular pathology

S8F

- Presented with painless jaundice and weight loss.
- MRI and CT – tumour in left lobe, cholangiocarcinoma
- Stenting right duct – relieved jaundice but caused pancreatitis
- Staging laparoscopy
CT portal venous phase,

Left lobe atrophy
Mass obstructing the ducts and stricture the left portal vein

Role of staging laparoscopy in the stratification of patients with perihilar cholangiocarcinoma

For radiologically occult disease
HES data 2010-2015

- Resectable? - 116/431 (27%) patients – of which
  - Laparoscopy: 31/114 (27%) had unresectable disease – 25 peritoneal, 6 locally advanced or liver mets
  - Laparotomy: 16/85 (19%) another 16 unresectable – 6 with peritoneal, 10 locally advanced, mets
- Sensitivity for peritoneal disease 71% (15/21)
- 69/116 (59%) had successful resection, 34% of all patients

Conclusion: staging laparoscopy was useful in determining radiologically occult disease


Left hepatectomy, segments 2,3,4. 344g attached duct 35mm, GB, nodes 25mm
Outside growing in or Inside growing out??

Intrahepatic growing edge is cellular

Dilated intrahepatic ducts

Most is desmoplastic

Right duct margin

Perineural infiltration

common hepatic duct

Cholangiocarcinoma, perihilar and extrahepatic ducts

Significant prognostic factors in 442 patients (75% perihilar), 1977-2005

<table>
<thead>
<tr>
<th>Variable</th>
<th>univariate</th>
<th>Relative risk</th>
<th>multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation</td>
<td>&lt;0.0001</td>
<td>1.73</td>
<td>0.0002</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>&lt;0.0001</td>
<td>1.38</td>
<td>0.0098</td>
</tr>
<tr>
<td>Venous invasion</td>
<td>&lt;0.0001</td>
<td>1.71</td>
<td>0.0067</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>&lt;0.0001</td>
<td>1.45</td>
<td>0.0038</td>
</tr>
<tr>
<td>pT stage</td>
<td>&lt;0.0001</td>
<td>1.61</td>
<td>0.0005</td>
</tr>
<tr>
<td>Nodal metastasis</td>
<td>&lt;0.0001</td>
<td>1.51</td>
<td>0.0034</td>
</tr>
</tbody>
</table>


Circumferential margin: transverse or longitudinal sections?

Serial transverse sections Give better sampling of circumferential margin

Longitudinal sections give extent of tumour infiltration along duct wall*

Circ. = π x diameter
10 slices = 31.4cm

10 slices = 18cm

Radical operation for hilar cholangiocarcinoma in comparable Eastern and Western centres: Outcome analysis and prognostic factors.

**Time after surgery (years)**

**Disease-specific survival (%)**

- **Hirosaki** (N=80)
- **Leeds** (N=103)

**Multivariate: predictive factors of survival, n=183:**
- LN p=0.002; Margin p=0.005; differentiation p=0.029; vascular invasion p=0.046

Kimura N et al, Surgery 2017 epub May 24

**Radical surgery for perihilar cholangiocarcinoma**

**Impact of resection margins.**

- **Hirosaki** (n=80)
  - 19% R1 resection
- **Leeds** (n=103)
  - 54% R1 resection

**Largest lymph node 25mm long**

3/5 nodes were +ve

**TNM staging for Intrahepatic Cholangiocarcinoma**


**TNM staging for Perihilar Cholangiocarcinoma**

<table>
<thead>
<tr>
<th>2002</th>
<th>2010</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTis</td>
<td>Carcinoma in situ</td>
<td>Inc. BilIN3</td>
</tr>
<tr>
<td>pT1</td>
<td>Single, no vascular inv.</td>
<td>pT1a single, &lt;5cm</td>
</tr>
<tr>
<td>pT2</td>
<td>Single with vascular inv.</td>
<td>pT1b single, &gt;5cm</td>
</tr>
<tr>
<td></td>
<td>Or multiple &lt;5cm</td>
<td>pT2a single with vascular invasion</td>
</tr>
<tr>
<td>pT3</td>
<td>Multiple ≥5cm or involves major branch of portal or hepatic vein</td>
<td>pT2b multiple v/- vascular invasion</td>
</tr>
<tr>
<td></td>
<td>Perforates visceral peritoneum or invades local extra-hepatic structures</td>
<td>pT3 vascular invasion or multiple</td>
</tr>
<tr>
<td>pT4</td>
<td>Direct invasion of adjacent organs other than GB or perforates visceral peritoneum</td>
<td>Perforates visceral peritoneum</td>
</tr>
<tr>
<td></td>
<td>Tumour with periductal growth pattern</td>
<td>Perforates visceral peritoneum</td>
</tr>
<tr>
<td>pN1</td>
<td>Regional nodes +ve</td>
<td>Regional nodes +ve</td>
</tr>
<tr>
<td></td>
<td>Sample 6 nodes</td>
<td>pN1 1-3 nodes +ve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pN2 &gt;3 nodes +ve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample 15 nodes</td>
</tr>
</tbody>
</table>

**Liver Cancer Study Group of Japan (1997)**


- **Mass forming – peripheral, large, sclerotic centre, cellular expansile margin**
- **Periductal infiltrating – arising from large ducts near hilum.**
- **Intraductal papillary – rare, good prognosis**
A novel approach to biliary tract pathology based on similarities to pancreatic counterparts: is the biliary tract an incomplete pancreas?

Biliary tree

pancreas

IgG4 related sclerosing cholangitis
Primary sclerosing cholangitis
Conventional cholangiocarcinoma
BILI 1-3
Invasive duct carcinoma
Intraductal papillary neoplasm - IPMN
Biliary cystic tumour with bile duct communication (cystic IPN)
Mucinous cystic neoplasm

Previously ‘cystadenoma’

AJCC Cancer staging manual 8th edition 2017:
Intrahepatic bile ducts

1. Anatomically, the intrahepatic bile ducts extend from the periphery of the liver to the second-order bile ducts.

2. Therefore, it may be difficult to distinguish central intrahepatic from hilar cholangiocarcinoma, particularly in the presence of a periductal infiltrating growth pattern.

Dichotomy in intrahepatic cholangiocarcinomas based on histological similarities to hilar cholangiocarcinoma.

47 cases of intrahepatic CC

21 perihilar type
26 peripheral type.

Staging - perihilar v intrahepatic

Two different types of cholangiocarcinoma

Outside growing in or Inside growing out??

Definition:
Perihilar - main lobar (left, right) ducts distal to segmental ducts and proximal to cystic duct.
needs to extend to 2nd order bile ducts

Dichotomy in intrahepatic cholangiocarcinomas based on histological similarities to hilar cholangiocarcinoma.

47 cases of intrahepatic CC – 21 perihilar type, 26 peripheral type.

Chronic liver disease
Mass forming
Perineural infiltration
BILI 1-3
pT1, pT4
Differences in p53, MUC5ac, SMAD4, BAP1, IDH

5 year survival

Perihilar = closely match ‘hilar’ CC in all of these

Akita M, Fujikura K, Ajiki T et al., Zen Y. Modern Pathology 2017 epub
More about stroma

- Cancer associated fibroblasts, signalling etc

CK19

SMA

Bile ducts and their stroma – non-neoplastic examples

Portal plate, extrahepatic biliary atresia

Ductal plate, biliary embryogenesis

Epithelial to mesenchymal transition and cancer invasiveness:
what can we learn from cholangiocarcinoma?

Metastasisation requires 4 steps:
- Reducing cell-cell contacts, rearrange cytoskeletal architecture in favour of a motile phenotype
- Impair integrity of basement membrane and invade surrounding stroma – cross-talk with mesenchymal and inflammatory cells which in turn support their invasiveness
- Disseminate through vascular channels
- Engraftment at distant sites

Epithelial-to-mesenchymal transition transcription factors in cancer-associated fibroblasts (CAF)

- EMT transcription factors (EMT-TF) Snail, Twist, ZEB – essential metastasis and chemoresistance-promoting molecules.
- Expressed in both cholangiocarcinoma and cancer associated fibroblasts
- TGFβ and IL6 important in CC, induce Twist1, activates CAF.
- CAF expressing EMT-TFs promote expression of these factors in adjacent tumour cells. Stromal expansion precedes tumour expression.
- Microenvironment changes stimulate EMT-TF expression in tumour cells that sustains stemness, increases tumour cell motility and chemoresistance.

Expression pattern of cancer-associated fibroblasts and its clinical relevance in intrahepatic cholangiocarcinoma

- ‘Immature’ fibroblasts – plump, SMA+ve, Associated with LN mets, late stage,
- Independent factor for poor survival

Alpha-smooth muscle actin-positive fibroblasts (CAF) promote biliary cell proliferation and correlate with poor survival in cholangiocarcinoma (CC).

- High expression of alpha-SMA in cholangiocarcinoma (CC) fibroblasts had a statistically significant correlation with larger tumour size (P=0.009) and shorter survival time (P=0.013).
- Bilary epithelial cells and CC cell lines - CC fibroblasts have proliferative effects which may directly effect tumour promotion and progression of bilary epithelial cells.
Periductal infiltrating:

Peripheral mass forming

Origin of cholangiocarcinoma

- Perihilar – ducts with peribiliary glands
  - ? Originate from cells in peribiliary glands
- Peripheral – from small ducts/progenitor cells /canals of Hering
- Molecular for Intrahepatic CC

Intra-biliary hepatic metastasis of colorectal carcinoma mimicking primary cholangiocarcinoma

71M painless jaundice
50 years after rectosigmoid pT1N0
Liver resection for metastasis 4 years ago

MRI: 1.4cm intraductal mass at hepatic hilum

Pathology – papillary tumour colonising duct
Also conventional CRC mets

CK7 - CK20+ CDX2+
Can also be papillary – do IHC

Dong et al. Case reports in Pathology 2016

Treatment trials

Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study.

Post-Surgery Capecitabine 'Should Become Standard of Care' in Biliary Tract Cancers

J Clin Oncol 35, 2017 (suppl: abstr 4006) June 4, 2017

- 447 participants were randomised to Cape (n = 223) or Obs (n = 224)
  - from 44 UK sites between 2006-2014
  - R1 38%, N1 54%
- Median survival 53 months v 36 months (p=0.028)

Others:

- ACTICCA-1 – adjuvant gemcitabine and cisplatin after resection
- ABC-06 – 5FU and oxaliplatin in advanced biliary tract cancers

Dataset for liver cancer resections – 2nd 2010

- New proformas for intrahepatic cholangiocarcinoma,
  - Mass forming, periductal infiltrating
  - Different histological patterns
  - New staging
- Already 32 pages instead of 23

Dataset for liver cancer resection specimens - 3rd ed 2017 – in progress....

Minor revision for change in TNM staging.
Summary – update on cholangiocarcinoma

- Illustrate handling and reporting resection specimens
- Staging, prognostic factors
- Distinguish intrahepatic from perihilar CC
- New insights – stroma, cell of origin, molecular pathology

The end.

Thanks to –
- Colleagues in Leeds – Darren Treanor, Olorunda Rotimi
- Hepatobiliary MDT team

UK Liver Pathology Group –
- To promote excellence in liver histopathology services in the UK and Ireland, across all levels of specialisation, through professional collaboration in education, quality assurance and research.
- http://www.virtualpathology.leeds.ac.uk/eqa/specialist/liver/