Cholangiocellular carcinoma

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Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update

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ABSTRACT

The British Society of Gastroenterology guidelines on the management of cholangiocarcinoma were originally published in 2002. This is the first update since then and is based on a comprehensive review of the recent literature, including data from randomised controlled trials, systematic reviews, meta-analyses, cohort, prospective and retrospective studies.

BACKGROUND

Development of guidelines

These guidelines on the management of cholangiocarcinoma (CC) were originally published in 2002. This is the first update since then and is based on a comprehensive review of the recent literature. The recent European HepatoPancreatoBiliary Association Congress Conference on Cholangiocarcinoma guidelines have also been used as a source. Specific recommendations have been graded based on the quality of evidence available. In the absence of significant data, evidence was based on expert opinion. This manuscript has been developed with the support of The British Liver Trust and the UK cholangiocarcinoma charity, the Alan Monument Memorial Fund.

Introduction

These guidelines are intended to bring consistency and improvement in the management from first suspicion of CC through to diagnosis and subsequent treatment. As stated in other British Society of Gastroenterology guidelines, patient preferences must be sought and decisions made jointly by the patient and health professional, based on the risks and benefits of any intervention. A multidisciplinary team approach is recommended, and these often complex cases should be managed in specialist centres with the relevant experience. The guidelines should not necessarily be regarded as the standard of care for all patients. Each case must be managed on the basis of individual clinical data.

Levels of evidence

Studies used as a basis for these guidelines are graded according to the quality of evidence using the Oxford Centre for Evidence-based Medicine levels of evidence (table 1).3 Grading of recommendations is as follows:

A: consistent level 1 studies.
B: consistent level 2 or 3 studies or extrapolations from level 1 studies.
C: level 4 studies or extrapolations from level 2 or 3 studies.

A: level 5 evidence or inconsistent or inconclusive studies of any level.

EPIDEMIOLOGY

CC is the second commonest primary liver tumour worldwide, after hepatocellular carcinoma (HCC).2 4 5 Incidence and mortality rates for intrahepatic CC have risen steeply and steadily across the world over the past few decades with concomitant falls in extrahepatic CC rates.6 7 Since the mid-1990s, more deaths have been coded in England and Wales due to CC than to HCC.4 8 CC kills approximately 1500 people annually in the UK, with approximately equal numbers of men and women.5 7 The cause of the rise in CC is unknown and is not explained by improvements in diagnosis.9 10 12 There is debate as to whether the rise in intrahepatic CC represents a genuine increase in true parenchymal primary CC. Recent evidence from USA and UK data suggest that rising intrahepatic CC rates partly reflects misclassification of perilobular (“Klatskin”) tumours being incorrectly coded as intrahepatic instead of extrahepatic.11 The overall incidence and mortality from all CC, however, does appear to be increasing.12

Risk factors

Established risk factors

There are several established risk factors for CC, but these account for <30% of all cases.3 9–13 Most cases of CC are sporadic. Primary sclerosing cholangitis (PSC), with or without ulcerative colitis, is the commonest known predisposing factor for CC in the Western world (lifetime risk 5–3%).39 In a study of 211 patients with PSC of whom 80% had inflammatory bowel disease (IBD), malignancies were the most frequent cause of death (44%),39 41% of patients developed colorectal cancer (CRC) and 15 (8%) developed CC. Other malignancies included gall bladder cancer (GBC), n=2, pancreatic cancer (n=1), lymphoma (n=3), melanoma (n=1) and gastric cancer (n=1). Median interval between PSC diagnosis and CC was 2.5 years (range 0–9.8 years).

The estimated risk of CC after 10 years was 9% with no significant difference in patients with and without IBD.39 In patients with IBD the 10 and 20-year risks for CRC were 14% and 31%, respectively, significantly higher than for non-IBD patients (2% and 2%). CC, cholangitis and age at entry were independent risk factors for the combined endpoint of death or liver transplantation.39
Cholangiocarcinoma

- A slow growing malignancy of the biliary tract which tend to infiltrate locally and metastasize late

Incidence in CH (2009-2013):
- Gall Bladder/biliary tract cancer = 300/yr
- Hepatocellular cancer = 800/yr
- Pancreatic cancer = 1300/yr
- Colorectal cancer = 4200/yr

- Male/Female = 1:1
- Age: 60`s and 70`s
- incidence&mortality: CCC ↑, HCC↓
- Highest incidence: South-east Asia (liver flukes), Israel, native Americans (genetic factors?)

Bundesamt für Statistik, Neuchatel 2016
Tumours of the biliary tract

<table>
<thead>
<tr>
<th>Benign</th>
<th>Premalignant</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumours of intrahepatic bile ducts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile duct adenoma</td>
<td>Biliary intraepithelial neoplasia</td>
<td>Intrahepatic cholangiocarcinoma</td>
</tr>
<tr>
<td>Microcystic adenoma</td>
<td>Intraductal papillary neoplasm</td>
<td>Intraductal papillary neoplasm with associated invasive neoplasia</td>
</tr>
<tr>
<td>Biliary adenofibroma</td>
<td>Mucinous cystic neoplasm</td>
<td>Mucinous cystic neoplasm with associated invasive neoplasia</td>
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<table>
<thead>
<tr>
<th>Premalignant</th>
<th>Carcinoma</th>
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</thead>
<tbody>
<tr>
<td><strong>Tumours of extrahepatic bile ducts</strong></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Biliary intraepithelial neoplasia</td>
<td>Adenosquamous carcinoma</td>
</tr>
<tr>
<td>Intracystic (gall bladder) or intraductal (bile duct) papillary neoplasm</td>
<td>Intracystic (gall bladder) or intraductal (bile duct) papillary neoplasm + associated invasive neoplasia</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm</td>
<td>Mucinous cystic neoplasm with associated invasive neoplasia</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Undifferentiated carcinoma</td>
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</tbody>
</table>
Classification of Cholangiocarcinoma (CCA)

- iCCA (intrahepatic) 20%
- pCCA (perihilar) 80%
- dCCA (distal)
Cholangiocarcinoma - Etiology

1. Primary sclerosing cholangitis±ulcerative colitis (up to 35% lifetime risk)
2. Bile duct stones (esp. Hepatolithiasis)
3. Choledochal cysts, polycystic liver disease, Caroli sy.
4. Thorostrast exposure (thorium dioxide as rx contrast)
5. Liver flukes (raw fish w/ tiny worms: Clonorchis sinensis, Opisthorcis viverrini)
6. Chronic typhoid carriage
7. Obesity
8. Alcohol (esp. cirrhotic patients)
9. Genetic factors (p53, Smad-4, bcl-2, KRAS, HER2, SNP of COX2)
Biliary tract carcinomas - Diagnosis and Workup

Presentation: jaundice, Wt loss, anorexia, abdominal pain, fever, nausea, palpable mass

Risk factors (PSC, IBD)

Premalignant conditions

Lab tests (obstruction enzymes, CRP, CA19-9, CA-125, IgG4), US, CT (mets)

Bile duct cancer
- MRCP
- ERCP w/ cholangioscopy
- EUS/IDUS
- PET
- Cytological/Histological examinations

Gallbladder cancer
- EUS
- MRCP
- PET
- Cytological/Histological examinations

Ampullary cancer
- Endoscopy w/ biopsy
- MRCP
- EUS/IDUS
- PET
- Cytological/Histological examinations

Staging, differential diagnosis

Cholangiocarcinoma – intrahepatic disease

**Diagnosis**

1. Suspicious mass ± bile duct dilatation on CT, consider CTA reconstruction
2. Biopsy is essential DD: adenocarcinoma of the colon, pancreas or stomach are common primary sites (upper/lower endoscopy, chest CT)
3. Immunohistochemistry: CK7 positivity, CK20 negativity (CRC)

**Therapy**

1. Extent of surgical therapy is determined by the location, hepatic function, and underlying cirrhosis 5-yr-survival rate 30-40%
2. Anatomic resections have lowest recurrence rates. However, nonanatomic resection increases potential surgical candidates and improves survival.
3. Hepatic devascularization prior to resection is preferred
Bismuth-Corlette classification of perihilar tumours

Guide to the extent of surgery required (aim: 5mm tumour-free margin)

Resection of segment 1 (metastases)
# Impact of Child’s Classification on surgery of CCA

<table>
<thead>
<tr>
<th>Class</th>
<th>Alb (g/dl)</th>
<th>Bil (µmol/l)</th>
<th>Prothrombin time (prolongation in sec.)</th>
<th>Ascites</th>
<th>Encephalopathy</th>
<th>Surgical Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&gt;3.5</td>
<td>&lt;34</td>
<td>&lt;4</td>
<td>none</td>
<td>0</td>
<td>5%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60% of the liver</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>2.8-3.5</td>
<td>34-50</td>
<td>4-6</td>
<td>Mild/Suppressed w/medication</td>
<td>Minimal</td>
<td>10-20%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wedge resection/RFA</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>&lt;2.8</td>
<td>&gt;50</td>
<td>&gt;6</td>
<td>Moderate/severe</td>
<td>Recurrent/Persistent</td>
<td>30-40%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No surgery</td>
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</table>
Cholangiocarcinoma – macroscopic types

• mass-forming (mainly in small intrahepatic bile ducts)
• periductal-infiltrating (worst prognosis)
• intraductal growth (least common, best prognosis)
• mixed
Cholangiocarcinoma – endoscopy aspects

Operable cases
• Preoperative biliary stenting in case of cholangitis, neoadjuvant chemotherapy, delayed surgery (plastic or covered SEMS)

Inoperable cases:
• Longer survival, less complications with biliary stenting
• If feasible, bilateral stenting is preferred (30-day mortality, risk of cholangitis), however may be challenging
• SEMS are superior to plastic stents (narrow delivery system with a wider diameter, fewer disfunction, greater patency, longer survival
  SEMS insertion if expected survival ≥(4)6 mo
• Covered vs uncovered SEMS: no difference in survival, covered stents longer time to obstruction, fewer interventions, however higher migration rate
• RFA and PDT w/ or w/o stenting: longer survival
Cholangiocarcinoma – Therapy and survival

Therapy
• Adjuvant chemotherapy with 5 FU-based regimen for all resectable tumors
• Palliative therapy with cisplatin+gemcitabine, consider radiotherapy
• Re-image all every 6 mo for 2 yr. Start workup over for a new mass

Survival

1. surgery + chemo/radiotherapy: 24-36 mo
2. stenting + chemo/radiotherapy: 12-18 mo
3. stenting only: few months

<table>
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<tr>
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<th>5-year relative survival</th>
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<tbody>
<tr>
<td>iCCA</td>
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</tr>
<tr>
<td>localized</td>
<td>15%</td>
</tr>
<tr>
<td>regional</td>
<td>6%</td>
</tr>
<tr>
<td>distant</td>
<td>2%</td>
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<table>
<thead>
<tr>
<th></th>
<th>5-year relative survival</th>
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<tbody>
<tr>
<td>dCCA</td>
<td></td>
</tr>
<tr>
<td>localized</td>
<td>30%</td>
</tr>
<tr>
<td>regional</td>
<td>24%</td>
</tr>
<tr>
<td>distant</td>
<td>2%</td>
</tr>
</tbody>
</table>
Gall Bladder Cancer

- predominantly in the elderly (6th decade)
- 1:3, male:female
- incidentally diagnosed at an early stage after cholecystectomy for cholelithiasis
- highest prevalence in Israel, Mexico, Chile, Japan, and Native American women
- risk factors
  - gallstones (10x risk if stone ≥ 3cm)
  - porcelain gallbladder/selective intramucosal calcifications
  - polyps (particularly ≥10 mm)
  - chronic typhoid
Gall Bladder Cancer – Therapy and survival

• If negative for metastasis: surgery + adjuvant chemo/radiation

• Biliary stenting + chemo/radiotherapy: 12-18 mo

• Survival:
  - T1 (cholecystectomy) 90%
  - T2 (radical cholecystectomy with nodal dissection, central hepatectomy, w or w/o bile duct excision) 70%
  - T3 (surgery + chemo/radiation) 20-50%

  Overall 5-year survival = 60%