



## Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document

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*Gut* 2002;51;1-9  
doi:10.1136/gut.51.suppl\_6.vi1

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## GUIDELINES

# Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document

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*Gut* 2002;51(Suppl VI):vi1–vi9

## 1.0 GUIDELINES

### 1.1 Development of guidelines

There is currently no clear national consensus for the optimal diagnosis and treatment of cholangiocarcinoma. The need for these guidelines was highlighted following the annual meeting of the British Association for the Study of the Liver (BASL) in September 2000. During their development these guidelines were presented at a BASL Liver Cancer Workshop in January 2001. They were also circulated to BASL members and the Liver Section of the British Society of Gastroenterology (BSG) Committee members, including gastroenterologists, hepatologists, gastroenterological surgeons, pathologists, radiologists, and epidemiologists for comments before the final consensus document was drawn up.

### 1.2 Strategy

The guidelines are based on comprehensive literature surveys including results from randomised controlled trials, systematic reviews and meta-analyses, and cohort, prospective, and retrospective studies. On issues where no significant study data were available, evidence was obtained from expert committee reports or opinions. Where possible, specific recommendations have been graded, based on the quality of evidence available (section 2.4).

### 1.3 Context and intent

These guidelines are intended to bring consistency and improvement in the patient's management from first suspicion of cholangiocarcinoma through to confirmation of the diagnosis and subsequent management. As stated in previous BSG guidelines, patient preferences must be sought and decisions made jointly by the patient and health carer, based on the risks and benefits of any intervention.

Furthermore, the guidelines should not necessarily be regarded as the standard of care for all patients. Individual cases must be managed on the basis of all clinical data available for that case. The guidelines are subject to change in light of future advances in scientific knowledge.

## 2.0 BACKGROUND

Mortality rates from intrahepatic cholangiocarcinoma have risen steeply and steadily over the past 30 years and since the mid 1990s more deaths have been coded annually in England and Wales as being due to this tumour than to hepatocellular carcinoma.<sup>1</sup> In 1997 and 1998 cholangiocarcinoma caused almost 1000 deaths/year in England and Wales (approximately equal numbers of men and women). The cause of this rise is unknown and does not appear to be explained simply by improvements in diagnosis or changes in coding practice.<sup>1</sup> The incidence of biliary cancers corresponds to mortality rates as the prognosis from these tumours is very poor.

### 2.1 Risk factors<sup>1,2</sup>

- Age (65% of patients are over 65 years old).

- Primary sclerosing cholangitis (PSC), with or without ulcerative colitis, is the commonest known predisposing factor for cholangiocarcinoma in the UK (lifetime risk 5–15%).
- Chronic intraductal gall stones.
- Bile duct adenoma and biliary papillomatosis.
- Caroli's disease (cystic dilatation of ducts, lifetime risk 7%).
- Choledochal cysts (about 5% will transform, risk increases with age).
- Thorotrast (a radiological agent no longer licensed for use, although the risk of cholangiocarcinoma lasts several decades).
- Smoking (increased risk in association with PSC).
- In SE Asia, where the tumour is quite common, the associated risk factors are:
  - liver flukes—*Opisthorchis viverrini* and *Clonorchis sinensis*,
  - chronic typhoid carriers—sixfold increased risk of all hepatobiliary malignancy.

### 2.2 Anatomical classification<sup>3–5</sup>

"Cholangiocarcinoma" originally referred only to primary tumours of the intrahepatic bile ducts and was not used for extrahepatic bile duct tumours but the term is now regarded as inclusive of intrahepatic, perihilar, and distal extrahepatic tumours of the bile ducts (fig 1).

- 20–25% are intrahepatic.
- 50–60% of all cases of cholangiocarcinoma are perihilar tumours (those involving the bifurcation of the ducts are "Klatskin" tumours).
- Most Klatskin tumours may have been coded as intrahepatic tumours for purposes of death certification.
- 20–25% are distal extrahepatic tumours.
- About 5% of tumours may be multifocal.

The extent of duct involvement by perihilar tumours may be classified as suggested by Bismuth:<sup>3</sup>

- type I: tumours below the confluence of the left and right hepatic ducts;
- type II: tumours reaching the confluence but not involving the left or right hepatic ducts;

Abbreviations: BASL, British Association for the Study of the Liver; BSG, British Society of Gastroenterology; PSC, primary sclerosing cholangitis; CEA, carcinoembryonic antigen; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, MR cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography; TNM, tumour-node-metastasis; LDH, lactate dehydrogenase; 5-FU, 5-fluorouracil.

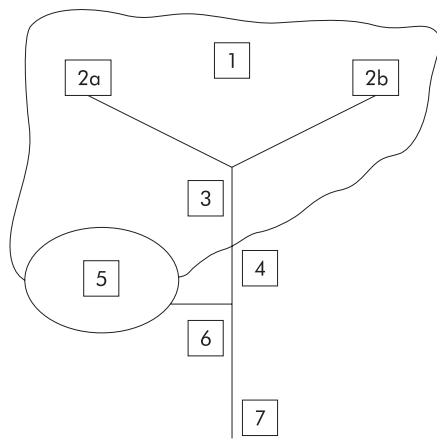


Figure 1 Schematic diagram for sites of cholangiocarcinoma. Intrahepatic cholangiocarcinoma (International Classification of Disease-9 codes (ICD-9) 155.1): 1=peripheral cholangiocarcinoma; 2a, b=right and left hepatic ducts; and 3=confluence of right and left hepatic ducts (perihilar, Klatskin tumours). Extrahepatic (ICD-9 156): 4=common hepatic duct; 5=gall bladder (ICD-9 156.0); 6=cystic duct; and 7=common bile duct.

- type III: tumours occluding the common hepatic duct and either the right (IIIa) or left (IIIb) hepatic duct;
- type IV: tumours that are multicentric or that involve the confluence and both the right and left hepatic ducts.

### 2.3 Pathology<sup>6-14</sup>

There are separate histological classifications of intrahepatic and extrahepatic cholangiocarcinomas. The WHO classifications are given below.

#### 2.3.1 WHO classification of carcinomas of the liver

- Hepatocellular carcinoma
- Combined hepatocellular cholangiocarcinoma
- Cholangiocarcinoma, intrahepatic
- Bile duct cystadenocarcinoma
- Undifferentiated carcinoma

#### 2.3.2 WHO classification of carcinomas of the extrahepatic bile ducts

- Carcinoma in situ
- Adenocarcinoma
- Papillary adenocarcinoma
- Adenocarcinoma, intestinal-type
- Mucinous adenocarcinoma
- Clear cell adenocarcinoma
- Signet ring cell carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma
- Small cell carcinoma (oat cell carcinoma)
- Undifferentiated carcinoma

#### 2.3.3 Histological grade

Most cholangiocarcinomas (95%) are *adenocarcinomas*. Adenocarcinomas are classified (1-4) according to the percentage of tumour that is composed of glandular tissue. Some types of adenocarcinoma are however not graded: carcinoma in situ, clear cell adenocarcinoma, and papillary adenocarcinoma. Signet ring cell carcinoma is given a grade of 3 and small cell carcinoma a grade of 4. Squamous cell carcinomas are graded according to the least differentiated areas. Most studies have

### Levels of evidence lead to subsequent **grading of recommendations** as:

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;  
D=level 5 evidence *or* inconsistent or inconclusive studies of any level.

demonstrated a relation between histological grade and post-operative outcome although stage is more important.

#### 2.3.4 Molecular diagnosis<sup>15</sup>

- Cholangiocarcinoma is often associated with inactivation of tumour suppressor genes—for example, p53, APC, Smad-4, *bcl-2*, and p16.
- Mutations in oncogenes have also been described—for example, *K-ras*, *c-myc*, *c-erbB-2*, and *c-neu*.
- Chromosomal aneuploidy has been reported in up to 25% of periampullary tumours.
- Although these mutations can lead to detectable phenotypic changes, the diagnostic or prognostic usefulness of these developments is unclear and molecular profiling does not, as yet, have an established clinical role in patients with cholangiocarcinoma.

#### 2.4 Levels of evidence<sup>16</sup>

Studies used as a basis for these guidelines are graded in relation to the quality of evidence according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001).<sup>16</sup> These are summarised in the appendix with explanatory notes, and have been reproduced with the permission of the Centre for Evidence-based Medicine.

## 3.0 DIAGNOSIS

### 3.1 Clinical features<sup>5 17</sup>

- Most common presenting clinical features of perihilar or extrahepatic tumours are those of biliary obstruction: jaundice, pale stool, dark urine, and pruritus.
- Right upper quadrant pain, fever, and rigors suggest cholangitis (this is unusual without drainage attempts).
- Cholangiocarcinoma usually presents after the disease is advanced. This is particularly true with more proximal intrahepatic and perihilar tumours obstructing one duct, which often present with systemic manifestations of malignancy, such as malaise, fatigue, and weight loss.
- Some cases are detected incidentally as a result of deranged liver function tests, or ultrasound scans performed for other indications.

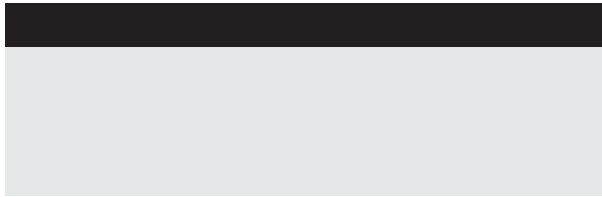
### 3.2 Blood tests<sup>5 17</sup>

There are no blood tests diagnostic for cholangiocarcinoma. Liver function tests often show an obstructive picture with raised:

- alkaline phosphatase
- bilirubin
- gamma glutamyl transpeptidase.

However, aminotransferases are frequently relatively normal but may be markedly raised in acute obstruction or cholangitis.

- Prolonged obstruction of the common bile or hepatic duct can cause a reduction in fat soluble vitamins (A, D, E, and K) and increase prothrombin time.



- Gall stones excluded.
- Often misses small perihilar, extrahepatic, and periaampullary tumours and not good at defining the extent of the tumour.
- Colour Doppler can detect tumour induced compression/

- With advanced disease, systemic non-specific markers of malignancy may be altered—for example, reduced albumin, haemoglobin, and lactate dehydrogenase (LDH).

### 3.2.1 Serum tumour markers<sup>5 18-20</sup> (evidence level 2b)

There are no tumour markers specific for cholangiocarcinoma. Overall, the sensitivity and specificity of tumour marker measurements are low but may be useful in conjunction with other diagnostic modalities where diagnostic doubt exists. There is no evidence that measurement of tumour markers is useful for monitoring tumour progression. CA 19-9, carcinoembryonic antigen (CEA), and CA-125 are currently the most widely used serum tumour markers.

#### CA 19-9

The value of CA 19-9 in patients with suspected cholangiocarcinoma is unclear. However:

- CA 19-9 is elevated in up to 85% of patients with cholangiocarcinoma;
- it has been reported that a CA 19-9 value greater than 100 U/ml has a sensitivity of 75% and specificity of 80% in patients with PSC;
- CA 19-9 elevation can occur in obstructive jaundice without malignancy but persistently raised levels of CA 19-9 after biliary decompression suggest malignancy;
- CA 19-9 does not discriminate between cholangiocarcinoma, pancreatic, or gastric malignancy and may also be elevated in severe hepatic injury from any cause;
- the value of CA 19-9 for detecting cholangiocarcinoma in patients without PSC is unknown;
- CA 19-9 may be useful for the differential diagnosis of cholangiocarcinoma but further studies are needed.

#### CEA

- Carcinoembryonic antigen (CEA) is raised in approximately 30% of patients with cholangiocarcinoma.
- CEA can also be elevated in inflammatory bowel disease, biliary obstruction, other tumours, and severe liver injury.

#### CA-125

- This is elevated in 40–50% of cholangiocarcinoma patients.
- It may signify the presence of peritoneal involvement but further studies are needed

#### Other serum tumour markers

Several other potential serum tumour markers have been linked to cholangiocarcinoma including CA-195, CA-242, DU-PAN-2, IL-6, and trypsinogen-2. Their clinical role is currently unclear.

### 3.3 Imaging<sup>5 17 21-31</sup>

#### 3.3.1 Ultrasonography (US)<sup>5 17 21</sup> (evidence level 4)

- Remains the firstline investigation for suspected biliary obstruction.
- Diagnosis should be suspected when intrahepatic, but not extrahepatic, ducts are dilated.
- Intrahepatic cholangiocarcinoma may be seen as a mass lesion but this is unusual.











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