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 intended for use 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).1 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.
D: level 5 evidence or inconsistent or inconclusive evidence.

CC is the second commonest primary liver tumour worldwide, after hepatocellular carcinoma. 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.4-14 Since the mid-1990s, more deaths have been coded in England and Wales due to CC than to HCC.4 5 CC kills approximately 1500 people annually in the UK, with approximately equal numbers of men and women.

The cause of the rise in CC is unknown and is not explained by improvements in treatment. 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 rates may reflect misclassification of extrahepatic (ECC) tumours being incorrectly coded as intrahepatic instead of extrahepatic.3-12 The overall incidence and mortality from all CC, however, does appear to be increasing.12

There are several established risk factors for CC, but 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 West. In a study of 211 patients with PSC of whom 60% had inflammatory bowel disease (IBD), malignancies were the most frequent cause of death (44%).13 41% of patients developed colorectal cancer (CRC) and 15 (39%) 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 differences in patients with and without IBD.13 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.13

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### Guidelines

#### Table 1  Levels of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Therapy/prevention, aetiology/harm</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>DDx/symptom prevalence study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>SR (with homogeneity*) of randomised controlled trial (RCT)</td>
<td>SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; CDR‡ with 1b studies from different clinical centres</td>
<td>SR (with homogeneity*) of prospective cohort studies</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCT (with narrow CI)</td>
<td>Individual inception cohort study with ≥ 80% follow-up; CDR† validated in a single population</td>
<td>Validating† cohort study with good§ reference standards; or CDR† tested within one clinical centre</td>
<td>Prospective cohort study with good follow-up¶</td>
</tr>
<tr>
<td>1c</td>
<td>All or none**</td>
<td>All or none case-series</td>
<td>Absolute SpPins and SnNouts†</td>
<td>All or none case-series</td>
</tr>
<tr>
<td>2a</td>
<td>SR (with homogeneity*) of cohort studies</td>
<td>SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs</td>
<td>SR (with homogeneity*) of level &gt;2 diagnostic studies</td>
<td>SR (with homogeneity*) of 2b and better studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study (including low-quality RCT; eg. &lt; 20% follow-up)</td>
<td>Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR† or validated on</td>
<td>Exploratory† cohort study with good§ reference standards; CDR† after derivation, or validated only on</td>
<td>Retrospective cohort study, or poor follow-up</td>
</tr>
<tr>
<td>2c</td>
<td>‘Outcomes’ research; ecological studies</td>
<td>Ecological studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>SR (with homogeneity*) of case-control studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>Individual case-control study</td>
<td>Individual non-consecutive cohort study or very limited population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Case series (and poor quality cohort and case-control studies)§§</td>
<td>Case series or superseded reference standards</td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal or based on physiology, bench research or ‘first principles’</td>
<td>Expert opinion without explicit critical appraisal or based on physiology, bench research or ‘first principles’</td>
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<td></td>
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</table>

*Homogeneity means a systematic review (SR) that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all SRs with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant.
†CDR, Clinical Decision Rule (algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category).
§Validating studies test the quality of a specific diagnostic test based on prior evidence. An exploratory study collects information and trawls the data (eg, using a regression analysis) to find which factors are ‘significant’.

Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the ‘test’ is included in the ‘reference’, or where the ‘testing’ affects the ‘reference’) implies a level 4 study.

**Met when all patients died before the treatment became available but some now survive on it; or when some patients died before the treatment became available but none now die on it.
†††An ‘Absolute SpPin’: a diagnostic finding whose sensitivity is so high that a negative result rules out the condition.
§§Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into ‘derivation’ and ‘validation’ samples.

§§Poor quality cohort study: one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both exposed and unexposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. Poor quality case-control study: one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

### Other established risk factors for CC are summarised in Table 2.

#### Table 2  Established risk factors for cholangiocarcinoma (CC)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>References and details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65% of patients aged &gt;65 years</td>
</tr>
<tr>
<td>Chronic intraductal gallstones</td>
<td>Particularly in Asia where up to 10% of patients with hepatolithiasis (oriental cholangiohepatitis) develop intrahepatic CC.</td>
</tr>
<tr>
<td>Bile duct adenoma and biliary papillomatosis</td>
<td>Lifetime risk of CC of 6–30%; risk of CC increases with age, and the average age of CC detection is in the fourth decade, younger than sporadic CC.</td>
</tr>
<tr>
<td>Choleodochal (bile duct) cysts and Caroli’s disease (intrahepatic biliary cysts)</td>
<td>Radiological agent is no longer licensed for use, although risk of CC induced by Thorotrast lasts several decades.</td>
</tr>
<tr>
<td>Thorotrast</td>
<td>South-east Asia such as north-east Thailand where CC is relatively common.</td>
</tr>
<tr>
<td>Liver flukes (Opisthorchis viverrini and Clonorchis sinensis)</td>
<td>South-east Asia; sixfold increased risk of all hepatobiliary malignancy.</td>
</tr>
<tr>
<td>Chronic typhoid carriage</td>
<td></td>
</tr>
</tbody>
</table>

#### Likely risk factors

Less established but likely risk factors for CC include cirrhosis of any cause and chronic viral hepatitis B or C. Recent cohort, population-based, case-control and observational studies from around the world suggest that obesity, diabetes, fatty liver disease, alcohol, smoking, IBD without PSC and polymorphisms of genes coding for carcinogen metabolism, ammation and biliary transporters may also be toxins other than Thorotrast have been linked to CC, including dioxins, nitrosamines and vinyl chloride. Includes all bile duct cancers Up to 20% of all CC are intrahepatic, according to published series,
whereas 50–60% are perihilar, involving the bifurcation of the ducts. Perihilar CC are a subset of extrahepatic CC.\textsuperscript{12} Up to 20\% of CC are distal extrahepatic tumours and 5\% of tumours are multifocal. Given the differences in their frequency, pathology and management, intrahepatic, perihilar and distal extrahepatic CC should be viewed as separate entities.\textsuperscript{12,17}

The extent of perihilar CC may be described by the Bismuth–Corlette classification (figure 1).\textsuperscript{20}

- **Type I**: below confluence of left and right hepatic ducts.
- **Type II**: reaching confluence but not involving left or right hepatic ducts.
- **Type III**: occluding common hepatic duct and either right (IIIa) or left (IIIb) hepatic duct.
- **Type IV**: multicentric or bilateral intrahepatic segmental involvement; or involving common hepatic ducts.

This classification does not take into account vascular encasement and distant metastases. A novel system for reporting perihilar CC was recently proposed based on tumour size, extent of disease in the main bile ducts, involvement of the hepatic artery and/or portal vein, lymph node involvement, distant metastases, volume of the putative remnant liver after resection and underlying liver disease.\textsuperscript{21} Although more complex than the Bismuth classification, the important aim of this system is to standardise the prospective reporting of perihilar CC and help identify factors relevant to the outcome across multiple centres.

**PATHOLOGY**

**Histological classifications**

There are separate histological classifications for intrahepatic and extrahepatic CC.

**Macroscopic features of intrahepatic CC**

Intrahepatic CCs are whiter and contain more desmoplastic stroma. They occur more commonly in non-cirrhotic livers than HCCs and are divided into four macroscopic types (table 4). The intraductal type carries the best prognosis and the periductal type carries the worst.

**Histological grade**

Over 90\% of CCs are adenocarcinomas and are classified according to the percentage of tumour composed of glandular tissue. Some types of adenocarcinoma are not graded (eg, carcinoma in situ, clear cell adenocarcinoma and papillary adenocarcinoma). Signet ring cell carcinoma is graded as 3 and small cell carcinoma as 4.

**Molecular diagnosis**

CC is often associated with inactivation of tumour suppressor genes, for example, p53, Smad-4, bcl-2 and p16.\textsuperscript{15,27–33} Mutations in oncogenes have also been described including K-ras, p53, c-erbB-2 and c-neu. Chromosomal aneuploidy has been reported in over 80\% of PSC-associated CC. Although mutations can lead to detectable phenotypic changes, molecular profiling in biliary cytology does not currently have an established diagnostic or collision' tumours in which separate CCs and HCCs are present in the same liver.

CCs are uncommon primary liver cancer accounting for 15\% of all CCs. These are divided into classical and stem cell types. The latter is divided into the typical subtype in which there are nests of mature-appearing hepatocytes with peripheral clusters of small cells with the phenotype of stem/progenitor cells; the intermediate cell subtype with tumour cells intermediate between hepatocytes and cholangiocytes; and the cholangiocellular type with tumour cells growing in an anastomosing pattern. In one series, 28\% of HCCs contained cells expressing biliary/progenitor cell markers cytokeratin (CK) 7 and intrahepatic CCs are usually smaller and often arise in chronic liver disease, mostly HCV infection.

Distinguishing intrahepatic CC from metastatic adenocarcinoma can be difficult. Accurate differentiation, particularly from foregut metastases (lung, oesophagus, stomach, pancreas), often cannot be made histologically. Other modalities, especially imaging, are essential. Immunohistochemistry panels including CK7, CK19, CK20, CDX-2, TTF-1, oestrogen/progesterone receptors and PSA, are usually positive in CCs and CK20 negative. In distinguishing HCC from CC, lack of mucin production and expression of HepPar-1, CD10 and other...
**DIAGNOSIS**

**Clinical features**

Perihilar or extrahepatic CCs typically present with features of biliary obstruction (jaundice, pale stool, dark urine and pruritus). Cholangitis is unusual without prior biliary instrumentation. CC is usually advanced at presentation, particularly with more proximal intrahepatic and perihilar tumours obstructing one duct. These often present with systemic manifestations of malignancy including malaise, fatigue and weight loss.

**Blood tests**

No blood tests are diagnostic for CC. Liver function tests often show an obstructive picture. Normal but may be markedly raised in acute obstruction or cholangitis. Prolonged biliary obstruction can cause a reduction in fat soluble vitamins and an increase in prothrombin time. In advanced disease, non-specific albumin, erythrocyte sedimentation rate, C-reactive protein and haemoglobin may be altered.

**Serum tumour markers**

Carbohydrate antigen (CA) 19-9 and CA-125 are the most used serum tumour markers. Specificity is low and they are not helpful for monitoring disease progression. With other diagnostic modalities, CA19-9 is elevated in up to 85% of patients with CC with a sensitivity of 40% and predictive value (PPV) of 16%. CA19-9 elevation frequently occurs in PSC and other causes of non-malignant obstructive jaundice, but persistently raised levels of CA19-9 after decompression suggest malignancy. CA19-9 does not discriminate between CC, pancreatic or gastric malignancy and may also be elevated in severe hepatic injury from any cause. Furthermore, 10% of individuals lack Lewis blood group antigens and may not be useful in this context.

Novel potential tumour markers linked to CC include Mac-2BP, matrix metalloproteinase-7, insulin-like growth factor 1, interleukin 6, trypsinogen and MUCIN-5AC. None has yet been shown to be superior to CA19-9.

**Immunoglobulin (Ig) G4-associated cholangiopathy**

IgG4 cholangiopathy is an inflammatory disorder in which bile ducts are infiltrated with IgG4-positive lymphocytes. It should be considered in suspected cases of CC. A review of 53 such cases reported that most were men (85%), presented with obstructive jaundice (77%), were associated with autoimmune pancreatitis (92%), increased serum IgG4 levels (74%) and abundant IgG4-positive cells in bile duct biopsy specimens (88%).

Strictures of intrapancreatic bile ducts in 51% of cases, and proximal extrahepatic/intrahepatic ducts were involved in 49%. Following successful steroid therapy, relapse occurred in 53% of cases after steroid withdrawal. The presence of proximal extrahepatic/intrahepatic strictures was predictive of relapse. Steroid therapy normalised liver biochemistry in 61% and biliary stents should be excluded in suspected cases of CC by testing for IgG4 cholangiopathy.

**Imaging**

Imaging is the main diagnostic modality for CC.Appearances include an intrahepatic mass lesion with characteristics of...
a metastasis, a hilar stricture or distal bile duct obstruction, with or without a discernible mass. Differentiating between benign and malignant biliary strictures is challenging.

Ultrasonography

CC should be suspected when there is biliary ductal dilation, particularly with a related mass lesion and consistent clinical history. In suspected biliary obstruction, ultrasonography (US) is reliable for excluding gallstones but is operator-dependent and is insufficient alone for investigating suspected CC. For detecting advanced CC in patients with PSC, US offers specificity and negative predictive value of 90%, but sensitivity and PPV are only 50%.32–34 US may miss small tumours and cannot accurately de US may also detect tumour-induced compression or vascular thrombosis.

High resolution/spiral CT

Contrast CT has higher sensitivity for CC detection than US (up to 80%), providing good views of intrahepatic mass lesions, dilated intrahepatic ducts, localised lymphadenopathy and extrhepatic metastases. However, the extent of CC is often not well-defined.42 PSC and does not necessarily indicate metastatic disease.

MRI

Contrast MRI is the optimal imaging investigation for suspected CC.45–48 In addition to avoiding radiation, MRI delineates hepatobiliary anatomy, local extent of duct involvement by MR cholangiopancreatography (MRCP), parenchymal abnormalities including the presence of liver metastases and hilar vascular involvement (MR angiography). However, MRI is inferior to CT for detecting distant metastases, particularly in the lungs and bone.43–46

Cholangiography (MRCP, ERCP, PTC)

Cholangiography is essential for assessing the extent of bile duct involvement and resectability, avoiding risks of endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) and avoiding radiation. MRCP had superior sensitivity (96%), specificity (91%) compared with ERCP (80%, 75% and 78%, respectively) for differentiating between CC and benign strictures.37 A UK study comparing MRCP with ERCP in biliary obstruction predominantly relating to gallstone disease found in favour of MRCP with respect to cost-saving and quality of life. Similar studies on malignant biliary disease are lacking. ERCP and PTC allow bile sampling for cytology and stent insertion for relief of biliary obstruction. There is no clear evidence that PTC should generally be favoured over ERCP on the basis of the level of obstruction. Although ERCP is usually preferred above PTC, experience of and facilities for PTC should be available in treating centres for cases where ERCP has failed.

Histology and cytology

Although positive histology and/or cytology findings are often difficult to obtain, they are essential for confirming a diagnosis of CC, particularly in patients not proceeding to resection, and for clinical trials. Tumours are usually adenocarcinomas and have prominent desmoplastic stroma. However, except in cases where there is co-existing biliary dysplasia, it may not be possible, even with immunohistochemistry, to differentiate between CC and metastatic tumour. Examples of this include intraductal papillary neoplasm with associated invasive neoplasia, and mucinous cystic neoplasm with associated invasive neoplasia.50–51

Standard cytology from brushings at ERCP/PTC is positive in >50% of CC cases, hence negative cytology findings do not exclude malignancy.52–55 Combining cytology with biopsy increases the positive yield to 40–70%. Applying fluorescence in situ hybridisation (FISH), which uses fluorescently-labelled DNA probes to detect aneuploidy in cells, reportedly confirmed cancer in 60% of patients in whom standard brush cytology was negative.56 A subsequent study confirmed the ability of FISH to improve the diagnostic accuracy in indeterminate biliary strictures, increasing the sensitivity of brush cytology from 21% to 40%

Including the presence of 9p21 deletion increased the city of FISH was 97% compared

Guidelines

In a study comparing CT plus MR versus positron emission tomography (PET)-CT, PET-CT exhibited no advantage for CC diagnosis but did have higher accuracy for detecting hepatic ne needle aspiration in potentially resectable tumours. However, this is not the case in most centres. Rates of tumour seeding are unclear, being reported as between 1:10 000 and 1:40 000, although this may be an underestimate.

In a prospective multicentre study, transpapillary cholangioscopy increased the ability to distinguish benign from malignant strictures compared with ERCP alone, and facilitated targeted biopsy.58 Cholangioscopy may be useful in experienced centres and further data are

Given the disappointing accuracy of current diagnostic techniques, interest in cholangioscopy has renewed following techn-
Guidelines

Staging

CC staging is based on the tumour-node-metastasis (TNM) system. The 7th edition of the TNM classification introduced a specific staging system for intrahepatic CC, separate from HCC, providing better prognostic information.22 23 The T category is based on the number of tumour nodules, vascular invasion and direct extension into extrahepatic tissues. Unlike HCC, tumour size is not considered important. A positive resection margin (non-R0 resection) is a very poor prognostic factor.

Although distant spread is late and uncommon in CC, comprehensive staging must be carried out to screen for metastatic disease. CT provides more accurate information for this purpose than MRI. At presentation, up to 50% of patients are lymph node-positive and 10% most centres consider a staging laparoscopy to exclude local metastatic disease in those considered resectable on imaging. Only approximately 50% of patients with perihilar CC who undergo laparotomy are ultimately suitable for curative resection. In a study of 175 patients with suspected perihilar CC who underwent staging laparoscopy during the past decade, the overall yield and accuracy of staging laparoscopy decreased compared with earlier reports, possibly due to improved imaging techniques during this time period. The benefit of staging laparoscopy in suspected CC are warranted.

Metastatic adenocarcinoma mimicking CC may arise from several organs, particularly the pancreas, stomach, breast, lung and colon. CC is different from adenocarcinoma, particularly if the pathological sample is obtained from outside the biliary tree. Thorough clinical assessment and other investigations are necessary to exclude a primary from elsewhere.

Recommendations

- Studies obtained for the initial diagnosis may also provide staging information. However, to rule out metastatic disease, contrast CT of the abdomen, chest and pelvis should be carried out on all patients, particularly if resection is being considered (Grade B).

Screening for CC in PSC

No benefit in screening for CC in PSC has been proven and there is no robust screening test. Nevertheless, most experts agree that early detection of CC in PSC is important to identify cases amenable to curative surgery and to avoid inappropriate liver transplantation.61–66 As well as an increased risk of CC, patients with PSC are also at increased risk of HCC; colorectal, gastric and pancreatic cancers; and malignant gall bladder polyps.62 64 66

Up to 50% of CCs are diagnosed within 2 years of PSC diagnosis and the subsequent risk of CC is approximately 1% per year.64–66 The severity of liver disease (Child–Pugh or Mayo score) does not appear to be a significant risk factor. Smoking, alcohol, duration of IBD if present, previous CRC/dysplasia and the HLA-DR4, DQ8 haplotype are reported risk factors for malignancy in PSC, but none has been validated as a predictive factor. A suggested algorithm for CC screening in PSC is given in figure 2. This is unproven and based on expert opinion. Regular investigations, including surveillance colonoscopies in patients with PSC and IBD and US for gall bladder lesions, are recommended in both the European Association for the Study of the Liver (EASL) and the American Association for the Study of

- Confirmatory histology and/or cytology at ERCP, laparoscopy or laparotomy should be obtained if at all possible (Grade C).
- However, due to the risk of tumour seeding, surgical assessment of resectability should be established prior to EUS-guided or percutaneous biopsy attempted (Recommendation Grade B).
- Laparoscopy may be considered to detect occult metastatic disease (Grade B).

Small retrospective studies have suggested that ursodeoxycholic acid (UDCA) may reduce the risk of colonic dysplasia and CRC. The United Kingdom National Institute for Health and Care Excellence recommends the use of UDCA in patients with PSC, at a dose of 20 mg/kg per day, and the subsequent risk of CC is approximately 1% per year.64–66

Survival on local clearance (R0 or R1 status), vascular invasion and lymph node metastases. R0 resection and well-differentiated tumour grading are independently associated with improved survival and lymph node involvement (occurring in 50% at presentation) is 67 68 72 73. Peritoneal dissemination (20% at presentation) are contraindications to surgical resection. In a multivariate analysis, post-resection prognosis correlated most strongly with clinical stage.

Resection, which should be guided by medical risk rather than age, involves a major operative procedure and requires appropriate surgical and anaesthetic experience. Surgical treatment depends on the site and extent of bile duct involvement by tumour. Intrahepatic CCs are usually treated by resection of the involved segments or lobe of the liver. Distal CCs are managed by pancreaticoduodenectomy, as with ampullary or pancreatic head cancers. Major hepatectomy for hilar CCs carries a considerable risk of hepatic insufficiency if there is a small future liver remnant. Portal vein embolisation of the liver lobe to be removed is a safe method for increasing the future liver remnant and permits potentially curative hepatic resection to be carried out.74–76

Liver transplantation for CC

Historically, liver transplantation for CC was associated with rapid recurrence of disease and poor survival rates; around 10% for intrahepatic CC and 25% for extrahepatic CC.77 78 Recent studies, however, have reported 5-year survivals of over 70% in patients carefully selected by their response to pre-transplant
chemoradiation. CC and most of the published data so far have been from a single centre in the USA. However, a recent study analysed data from 12 transplant centres in the USA. Each had treated at least three patients with perihilar CC using varying protocols of neoadjuvant chemoradiation followed by liver transplantation between 1993 and 2010. Two hundred and eighty-seven patients were treated and 71 dropped out before transplantation. The overall intent-to-treat survival rate was 53% 5 years after treatment and the post-transplant recurrence-free survival rate was 65%. Patients with tumour mass disease or with a prior malignancy had significantly lower survival times. Although most patients (n centre, the other 11 centres had similar survival times.

Surgical resection with palliative rather than curative intent is unproven. Symptoms from biliary obstruction in irresectable disease may be palliated by biliary stenting rather than a surgical bypass. Stent placement resulting in adequate biliary drainage improves survival. Surgical bypass has not been demonstrated to be superior to stenting. Close liaison between oncological, surgical and radiological specialities is important. Surgical resection specimens should be reported systematically, for example, according to Royal College of Pathologists’ guideline report should include the following:

- a. Cytology
- b. Histology
- c. Extent of invasion (according to the TNM system)
- d. Perineural invasion: this is common and has prognostic implications

These must be adequately sampled because local recurrence is related to involvement of the margins. This is particularly important because extrahepatic CC may be multifocal in up to 50% of cases.

To stage lymph nodes accurately, the node groups must be specifically identified. Peripancreatic nodes located along the body and tail of the pancreas are considered sites of distant metastasis.

Additional pathological findings
These must be noted if present (e.g., carcinoma in situ, sclerosing cholangitis).

Metastases
Metastases to other organs or structures should be reported.

Biliary decompression and stents
Stenting prior to surgery
Preoperative biliary drainage is controversial. It has been associated with bacteriobilia and fungal colonisation, higher

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**Figure 2** Suggested algorithm for cholangiocarcinoma screening in primary sclerosing cholangitis (Recommendation Grade D). AFP, alpha-fetoprotein; CC, cholangiocarcinoma; CRC, colorectal carcinoma; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FISH, fluorescence in situ hybridisation; FNA, fine-needle aspiration; IBD, inflammatory bowel disease; MDT, multidisciplinary team; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis; US, ultrasonography.

**Recommendations**

- For perihilar CC, the Bismuth classification is a guide to the extent of surgery required (aim is tumour-free margin of >5 mm). Surgical treatment is principally as follows (Grade B):
  - For types I and II: en bloc resection of the extrahepatic bile ducts and gall bladder, regional lymphadenectomy and Roux-en-Y hepaticojejunostomy.
  - For type III: as above plus right or left hepatectomy.
  - For type IV: not usually resectable but extended right or left hepatectomy may be feasible, dependent on biliary anatomy.
- Segment 1 of the liver may preferentially harbour metastatic disease from hilar CC and removal should be considered with stages II–IV.
- Intrahepatic CCs are managed by segmental or lobe resection.
- Distal CCs are treated by pancreato-duodenectomy.
- Increasing data suggest that liver transplantation for CC can be successful in rigorously selected patients undergoing neoadjuvant therapy in highly specialised centres.

Adjuvant therapy for resectable tumours
There is no current evidence to support the use of adjuvant chemotherapy or radiotherapy. Appropriate trials are needed to address this issue. The largest trial currently accruing is the BILCAP trial.

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rates of postoperative sepsis, wound infection, longer hospital stay and increased cost. A meta-analysis of preoperative biliary drainage for obstructive jaundice included four trials (n=235) comparing PTC-biliary drainage with direct surgery and one trial (n=85) comparing preoperative endoscopic drainage with direct surgery. Overall, there were no significant differences in mortality, morbidity or complications between the preoperative biliary drainage and the direct surgery groups. One of the included studies found that preoperative endoscopic biliary drainage prolonged hospital stay and increased cost. However, the overall strength of evidence was deemed low due to the poor quality of the included trials. A multicentre randomised trial comparing preoperative biliary drainage with surgery alone for patients with pancreatic cancer and obstructive jaundice included 206 patients; 106 were randomly assigned to undergo preoperative biliary drainage for 4 weeks by surgery, and 96 to surgery alone within 1 week of diagnosis. The rates of serious complications were 39% in the early surgery group and 74% in the biliary drainage group (RR in the early surgery group 0.54, p<0.001). Length of hospital stay did not differ between the groups. Although most of the data relate to obstructive jaundice from cancers other than CC, on current evidence the routine use of preoperative biliary drainage cannot be recommended. In patients who are severely malnourished or have acute supplicative cholangitis and in whom early surgery is planned, preoperative drainage may be beneﬁcial. Rigorously designed randomised controlled trials (RCTs) with appropriate sample sizes are required with respect to CC.

**Recommendation**

**Routine biliary drainage before assessing resectability or preoperatively should be avoided except for certain situations such as acute cholangitis, with modiﬁcation of antibiotic prophylaxis according to patient characteristics and local microbiological specialist advice (Grade B).**

**Stents for palliation of jaundice**

Most patients with CC have unresectable disease. In such patients, a study from the USA found that endoscopic stenting cost signiﬁcantly less and was associated with longer survival than surgical treatment (19 vs 16.5 months), suggesting that endoscopic stenting is the procedure of choice for palliative biliary drainage. Most initially inserted stents are plastic. Stents of diameter ≥10Fr usually remain patent for approximately 3 months. Narrower stents have lower patency rates and should not be used routinely. Covered removable self-expanding metal stents (SEMS) may also be used and some specialists prefer SEMS in patients who are candidates for neoadjuvant therapies.

Biliary drainage by the percutaneous route can be effective, particularly for high strictures involving segmental ducts. A multicentre retrospective Korean study of 85 patients with newly diagnosed advanced hilar CC who did not undergo surgery, chemotherapy or radiotherapy compared percutaneous versus endoscopic SEMS insertion. Successful biliary decompression was signiﬁcantly higher in the percutaneous group than in the endoscopic group (93% vs 77%, p=0.049). Procedure-related complications, median survival and stent patency duration were similar in both groups.

**Bilateral versus unilateral stents in hilar CC/advanced malignant biliary strictures**

Bilateral versus unilateral stent insertion for hilar strictures is controversial. Early small studies reported that 30-day mortality and cholangitis were lower in patients who underwent bilateral compared with unilateral drainage for hilar strictures. Failure to drain opacified lobes is associated with a poorer outcome. Post-stent cholangitis can be reduced by minimising the amount of contrast injected. Careful imaging with MRCP to plan endoscopic stent placement in complex hilar tumours may guide optimum stent placement. In particular, non-atrophic areas of the liver with a likelihood of providing viable bile ducts should not be used routinely. If contemplated, it should be performed in expert centres.

Most patients with malignant biliary obstruction treated by plastic stents will require at least one stent change. Metal stents have a relatively narrow delivery system (8Fr) with a wider diameter on deployment (10 mm). SEMS are also available that are 8 mm on deployment, which may help in stent selection, depending on the anatomical conﬁguration. The patency rates of metal stents are signiﬁcantly greater than those of plastic stents (up to 12 months vs 3 months). Metal stents are associated with fewer ERCPs, a shorter hospital stay and fewer complications than plastic stents in patients who survive more than 6 months. A retrospective study of unresectable hilar CC in the USA found that SEMS were more cost-effective than plastic stents for other forms of treatment. Other studies have also found that metal stents are more cost-effective in patients surviving more than 4 months. Plastic stents may be satisfactory for patients with more indolent disease.

Disadvantages of uncovered metal stents include being diﬃcult to remove endoscopically and potentially making surgery more technically challenging. Metal stents should not be deployed for biliary strictures prior to a multidisciplinary team decision on resectability. Tumour growth through the mesh of metal stents may lead to further problems with biliary obstruction and sepsis. This may be overcome by inserting plastic stents through the lumen of the metal stent, or placement of a further mesh metal stent where technically possible.

Covered biliary metal stents have recently been developed to prevent tumour ingrowth. A prospective RCT comparing covered and uncovered stents in irresectable malignant distal biliary obstruction found no diﬀerence in survival but a longer time to obstruction in the group with covered stents, who overall had fewer interventions and lower costs. Patency was higher in pancreatic cancer and in lymphadenopathy-associated obstruction compared with biliary malignancy, but numbers of the latter were small. Another RCT demonstrated improved survival in patients with extrabiliary CC who percutaneously received a covered (243 days) compared with an uncovered stent (180 days), with comparable cost and complication rates. The incidence of stent dysfunction was signiﬁcantly lower in the covered stent group. The largest study so far in this area was a multicentre unblinded RCT of 400 patients with unresectable
distal malignant biliary obstruction. Patients were randomised to ERCP with insertion of a covered or uncovered metal (nitinol) stent.106 There were no significant differences in stent patency time, patient survival time or complication rates between covered and uncovered metal stents. However, covered stents migrated significantly more often than uncovered stents and tumour ingrowth was more frequent with uncovered stents.106

Complications of stenting
Complications of stents include complications of endoscopy and sedation. Following palliative stenting, patients can die from recurrent sepsis, biliary obstruction and stent occlusion, as well as disease progression. Acute cholecystitis from covered stents is another recognised complication.

Photodynamic therapy
In an early prospective open-label trial, 39 patients with unresectable CC were randomised to stenting alone or stenting and photodynamic therapy (PDT). Cantly higher median survival (493 days vs 98 days), further evaluated in the larger UK Photostent-02 trial in which 92 patients with histologically or cytologically con tract cancer (BTC) were randomised to receive either PDT plus stenting or stenting alone. for PDT plus stenting and 8.5 months for stenting alone (HR 1.8, p=0.027). Nine patients (20%) in the PDT/stenting arm and 19 (41%) in the stenting alone arm received subsequent chemotherapy. Although overall survival was signi improved among those who had chemotherapy compared with those who did not (11.1 vs 4.8 months, p this only reduced the PDT/stenting HR from 1.8 to 1.6, suggesting that failure to receive subsequent chemotherapy did not completely explain the excess risk from PDT.

Recommendations
► Initial stent insertion for biliary obstruction should be plastic or covered SEMS, particularly if the diagnosis and resectability are undecided (Grade C).
► If the initial plastic stent becomes blocked, replacement with a metal stent is favoured if the estimated survival is expected to be >4 months (Grade B).
► Covered stents cannot be recommended for routine use based on current evidence (Grade B).
► Surgical bypass should be reconsidered in patients with a good estimated life expectancy where stenting has failed (Grade C).
► Photodynamic therapy cannot be recommended for routine use based on the most recent data (Grade A).

Oncological approaches
Given that most patients present with unresectable disease and at least half have lymph node metastases, oncological approaches could potentially have a beneficial impact on many patients.109–116 As a general guide from trial data, patients who are relatively fit and are not deteriorating rapidly should be treated early in the course of their disease rather than waiting for clinical progression. The performance status (PS) is a major prognostic factor. Patients should have a WHO or ECOG PS of 0 or 1 after optimisation of biliary drainage. Even achieving stable disease in patients on therapy correlates with length and quality of life. This is particularly important because of the frequent difficulty in confirming objective radiological responses, particularly in the perihilar area. Good symptom control is paramount and requires multidisciplinary team input and, for many patients, palliative care is immediately appropriate.

Chemotherapy
Locally advanced or metastatic inoperable CC and GBC (Evidence level 1a)
Until recently, chemotherapy for CC had poor results and studies were small and disparate. In 2010, a new standard of care in unresectable BTC was established with the reporting of the ABC-02 is the largest randomised phase III study reported in BTC to date. Four hundred and ten patients with locally advanced or metastatic CC, or gall bladder or ampullary cancer were randomised to receive 24 weeks of either cisplatin plus gemcitabine (CisGem).

After a median follow-up of 8.2 months, the median overall survival was 11.7 months for the 204) and 8.1 months for the Gem group 0.001). The median progression-free survival was 8.0 months for the CisGem group 0.001). Patients in the cantly improved tumour control 0.049). Overall toxicity was similar between the arms, with a slight excess in clinically non-signifi cant haematological toxicities for the CisGem group.117 The small proportion of patients with PS 2 in this study did not gain a survival advantage. Similarly, there was no clear advantage for the small subset of patients with ampullary cancer. However, patients with GBC (about 30% of the total cohort and well-balanced between the arms) derived as much benefit as the cacy of CisGem has been validated in the Japanese equivalent of the ABC-02 study, which reported

An investigation in the USA comparing direct medical costs, patient time costs and quality-adjusted life years in BTC found CisGem treatment to be cost-effective.

There are encouraging reports of several patients being successfully downsized with neoadjuvant chemotherapy and converted to operability in phase II studies, with occasional long-term survivors. Regimens combining chemotherapy with newer targeted biological agents are now being tested.

There is currently no evidence to support postoperative adjuvant therapy for CC outside a trial setting. A phase III RCT evaluated postoperative adjuvant therapy with mitomycin C and 5-fluo rouracil versus surgery alone in resected pancreatobiliary carcinoma.116 A significant survival benefit for patients with GBC was found. However, the trial was underpowered to show a survival advantage in CC and there was no significant survival advantage for patients with BTC overall. The UK NCRI BILCAP study is currently accruing and compares postoperative capecitabine monotherapy with observation alone. The trial is expected to report in 2014.112

Radiotherapy
External beam radiotherapy and chemoradiation
There is currently no evidence to support the routine use of radiotherapy postoperatively or for unresectable disease. Radiotherapy may have important palliative value—for example, for
localised metastases or uncontrolled bleeding.\textsuperscript{109–112} The role of chemoradiation remains to be established in RCTs.

Local radiation techniques: intraoperative or intraductal brachytherapy

A small non-randomised retrospective study of metal stent insertion combined with external beam radiotherapy versus stent insertion alone showed a longer survival in the combination group (10.6 vs 6.4 months) and also longer stent patency (9.8 vs 3.7 months).\textsuperscript{109} However, overall patency rates were shorter than previously reported for metal stents. A large epidemiological retrospective study of 17\% of 3839 patients with intrahepatic CC (on the USA SEER database) demonstrated a small survival benefit for radiotherapy plus surgery compared with radiotherapy alone (11 vs 7 months).

Similar study in 4758 patients with extrahepatic CC suggested that palliative radiotherapy prolonged survival; however, the benefit associated with surgery and/or radiotherapy was not significant after controlling for potential confounders.

A small prospective randomised study of perihilar CC, 21 patients with percutaneous stenting followed by intraluminal Ir-192 brachytherapy and external radiotherapy were compared with 21 patients with stenting only. The combination group had a significantly improved mean survival compared with the group with stenting alone (388 vs 296 days).

Operative radiotherapy or brachytherapy is unproven and has not been shown to be superior to standard chemotherapy; chemoradiation or stenting alone.

Recurrent bile duct cancer

The prognosis for any treated patient with progressing, recurring or relapsing bile duct cancer is poor. Further treatment depends on several factors including prior treatment, site of recurrence, specific symptoms and PS. Relief of recurrent jaundice usually improves quality of life. Clinical trials should be considered if appropriate.

Locoregional therapies

Recent literature suggests an emerging role for locoregional therapies in intrahepatic CC, including trans catheter arterial chemoembolisation, radiofrequency ablation and transarterial hepatic yttrium-90 ((90)Y) radioembolisation, which have previously been successfully used for the treatment of HCC and colorectal liver metastases.

Transcatheter arterial chemoembolisation (TACE)

In a retrospective matched series of transcatheter arterial chemoembolization (TACE, n alone (n=83) for unresectable intrahepatic CC, survival was significantly improved in the TACE group (median 12.2 vs 3.5 months, p<0.001). Toxicities were significantly higher in the TACE group but no patients died within 30 days following TACE.\textsuperscript{117} In another retrospective analysis of 114 patients with intrahepatic CC who underwent curative resection, adjuvant TACE was given in 57 cases. In patients with poor prognostic factors (tumour size >5 cm, TNM stage III/IV), 3- and 5-year survival rates were 34\% and 14\% in the adjuvant TACE group compared with 0\% and 0\% in the non-TACE group, respectively (p<0.001). TACE had no effect on survival in patients without poor prognostic factors.\textsuperscript{118}

Radiofrequency ablation

Several recent small studies have suggested that percutaneous US-guided thermal ablation for unresectable intrahepatic CC is safe and potentially effective, particularly for primary and relatively smaller tumours.\textsuperscript{120–124} In a Chinese study, 18 patients (8 primary and 10 recurrent cases after resection) with 25 intrahepatic CC nodules underwent US-guided thermal ablation with curative intention.\textsuperscript{120} Complete ablation was achieved in 23 (92\%) nodules (diameter 0.7–4.3 cm) and incomplete ablation was found in the remaining two tumours which were larger (6–7 cm). There were no treatment-associated deaths. Overall survival rates at 36 and 60 months were 30\% and 30\%, respectively. The patient source (primary or recurrent case, p=0.001) and the number of nodules (p=0.038) were significant prognostic factors for recurrence-free survival. Survival rates for primary intrahepatic CC at 56 and 60 months were 65\% and 29\%, respectively. Median overall survival was 22 months and time-to-progression (TTP) was 9.8 months. Survival and TTP were significantly prolonged in patients with ECOG 0 versus ECOG 1 or 2 (median overall survival 29.4, 10 and 5.1 months, respectively; TTP 17.5, 6.9 and 2.4 months, respectively). Tumour burden and tumour size (tumour size >5 cm, TNM stage III/IV), 3- and 5-year survival rates were 30\% and 30\%, respectively. The emerging data for locoregional therapies in unresectable CC are encouraging, but larger studies are required to determine further data on specific disease subsets such as perihilar CC are warranted to identify the best treatment combination options for different subcategories of CC (Grade B).

Gemcitabine and Cisplatin combination chemotherapy is recommended for locally advanced or metastatic unresectable CC.

Further data on specific disease subsets such as perihilar CC are warranted to identify the best treatment combination options for different subcategories of CC (Grade B). All operable patients should be offered adjuvant treatment trials. Similarly, all patients who have inoperable tumours or who are operable but have not been rendered disease-free, or those patients with recurrences should be actively encouraged to participate in chemotherapy and/or radiotherapy.

2 after adequate drainage and appropriate treatment of intercurrent sepsis should be considered for locoregional therapies such as radioembolisation and TACE need prospective randomised data to assess their true value.

REVISION OF GUIDELINES

We recommend that these guidelines are regularly audited and we request feedback from all users. These guidelines should be revised in the light of new evidence that is likely to improve management.

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